



Health Santé  
Canada Canada

Healthy Environments and Consumer Safety  
Santé environnementale et sécurité des consommateurs



## STATUS DECISION Procedures

- ☺ Receiving request.
- ☺ Verifying if listed in the CDSA
- ☺ Verifying if in the list of controlled or non-controlled substances

If not listed anywhere,

- ☺ Compiling as much information to be able to class the substance in the controlled or non-controlled status decision (previous status, Merk index, Internet)
- ☺ Adding the name of the substance to the list of controlled or non-controlled substances
- ☺ Sending an E-mail to Richard Laing, Health Canada, for his approval

When approved by R.L.,

- ☺ Completing a status decision sheet and attaching all the documents to support the decision
- ☺ Preparing a blue sheet for the Director's signature

When approved by the Director,

- ☺ Indicating the date approved in the list of controlled or non-controlled substances.
- ☺ Informing the applicant of the status (E-mail, copy of the approved sheet, letter, etc.)
- ☺ P.A. original with documentation in the file for controlled (9010-6-18) or non-controlled substances (9010-6-17)

E

001

6 2004

Mark Kozlowski

2004-10-06 02:14 PM

To: EHC Library/HC-SC/GC/CA@HWC

cc:

Subject: Article request

Mark Kozlowski

957-1083

74010

3503B

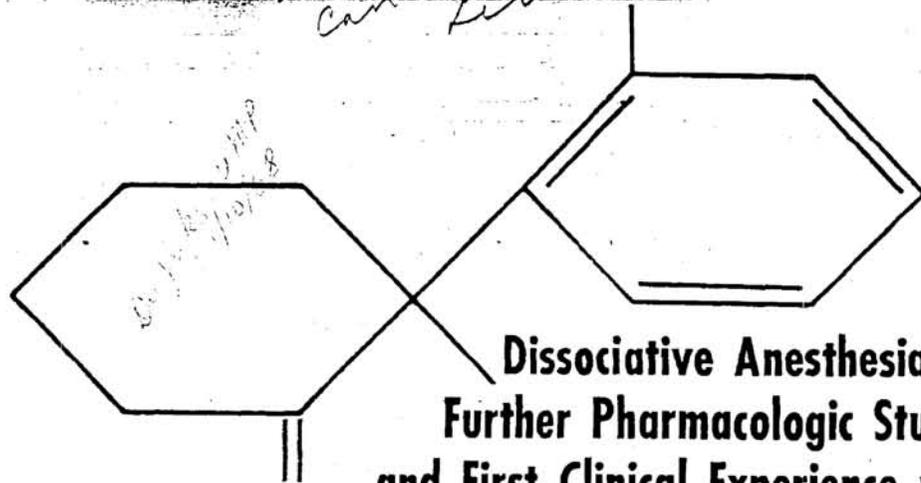
Corssen G, Domino EF: Dissociative anesthesia: further  
pharmacologic studies and first clinical experience with  
the phencyclidine derivative CI-581. Anesth Analg 1966;  
45(1): 29-40.

S

JANUARY-FEBRUARY, 1966

problem." The sedating, and not an sphygmomanom; that satisfactory l at levels of sys- us (believer and onsider safe. The rich could be sub- ysis showed that al where the sys- wed to fall below

E le, D. M., Jr.: Com- Use of "Controlled Arch. Surg. 67:549,



## Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581

GUENTER CORSEN, M.D.  
EDWARD F. DOMINO, M.D.  
Ann Arbor, Michigan\*

**T**HERE IS A definite need for safe and potent intravenously administered anesthetics of short duration which combine analgesic and sleep-producing effects without significant cardiovascular and respiratory depression. Recently, a number of compounds related to phenylcyclohexylamine have aroused clinical interest because they appear to approach such requirements. Phencyclidine hydrochloride was the prototype of this group of agents. After preliminary laboratory studies<sup>1</sup> its clinical usefulness as an anesthetic was investigated by Greifenstein and associates.<sup>2</sup>

The intravenously administered drug was shown to produce an adequate anesthetic state in most subjects, but its undesirable and occasionally long-lasting psychotomimetic activity during the postanesthetic phase precluded its widespread clinical acceptance.

Continued search for a more suitable derivative of phencyclidine with similar analgesic action but shorter duration and lesser psychotomimetic action led McCarthy and Chen<sup>3</sup> to investigate the pharmacologic properties of a large series of compounds of which 2-(0-chlorophenyl)-2-methylaminocyclohexanone HCl (CI-581) was shown to have some advantages. The structural formula of this compound in comparison to phencyclidine is shown in figure 1.

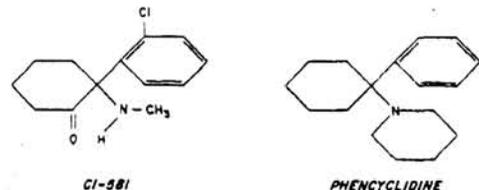


FIG. 1. Structural formulae of CI-581 and phencyclidine.

CI-581 is a white crystalline substance with a melting point of 259° C. It is soluble in water to 20 per cent as a clear, colorless solution. A 10 per cent aqueous solution has a pH of 3.5. In animals the agent was found to be somewhat weaker than phencyclidine on the basis of mg. per kg. body weight. However, when given in doses approximately 5 times as large as phencyclidine, CI-581 produced similar analgesia and anesthesia, with shorter and therefore more controllable duration of action. Immobilization and/or general anesthesia could be produced in a broad range of dosages.

Of particular interest was the fact that the depressant effect of CI-581 on the central nervous system was more specific than that of phencyclidine; even large doses did not produce the convulsions seen with the latter agent. From these laboratory studies, it was expected that CI-581 would be more suitable than its parent drug for clinical anesthesia.

\*Departments of Anesthesiology and Pharmacology, The University of Michigan Medical Center, Ann Arbor, Michigan.

Read at the 39th Congress of the International Anesthesia Research Society, March 28-April 1, 1965, Washington, D.C.

This copy is to be used solely for the purpose of research or private study. Any other use or further reproduction may require the authorization of the copyright owner.

Cette copie ne doit servir qu'à des fins d'études privées ou de recherche. Pour tout autre usage ou reproduction additionnelle, l'autorisation du titulaire du droit d'auteur pourrait être exigée.

Studies in human volunteers<sup>4</sup> confirmed these promising findings and stimulated our interest in further pharmacologic studies and in gaining clinical experience with this new product.

**METHODS**

**Human Pharmacologic Studies** — Ten male volunteers from a prison population served as subjects. Arterial blood pressure recordings were obtained in 2 of the subjects by inserting a cannula into the brachial artery. The cannula was connected to a Statham P23 pressure transducer and the blood pressure recorded on an Offner polygraph. Arterial pO<sub>2</sub>, pCO<sub>2</sub>, and pH were also determined before injection, and 1, 3, and 10 minutes after completion of the injection.

Respiratory volume measurements (tidal and minute volume) were recorded using a Wright ventimeter connected to a rubber face mask, as well as with the Fleisch pneumotachograph, which was connected to an Offner polygraph.

Continuous electrocardiographic (ECG) recordings (lead II) were obtained for all 10 volunteers.

Continuous electroencephalographic (EEG) recordings (10-20 International System) from F<sub>3</sub>, C<sub>3</sub>, P<sub>3</sub>, and O<sub>1</sub> to both ears as reference<sup>6</sup> were carried out with 6 volunteers, from the start of the intravenous injection until the subject had awakened or alpha rhythm returned. In addition, alterations in sensory input were studied in another 6 volunteer subjects, using visual stimulation by a flash of light directed into the eyes of the

subjects, and recording evoked responses from scalp electrodes. Employing averaging technics as previously described,<sup>6</sup> such visually evoked responses were measured before, during, and after CI-581 induced anesthesia.

**Clinical Studies**—A total of 130 patients (71 males), ranging in age from 6 weeks to 86 years, were anesthetized with CI-581 for a total of 133 surgical procedures (table 1). Twenty-nine patients were 2 years old or under, and 12 patients were 66 or over. Seventy-three patients were in good general health (physical state 1), 36 suffered from minor systemic disorders (physical state 2), and 18 suffered from major systemic disease (physical states 3 and 4). Three patients underwent emergency procedures.

Vital signs such as respiratory rate, heart rate, and systolic/diastolic blood pressures (inflatable cuff) were monitored at 1 to 3-minute intervals.

During certain operative procedures, such as direct-current electroshock treatment for cardioversion, intravenous succinylcholine and supplemental oxygen were used.

CI-581 was used in a 10 mg. per ml. concentration intravenously or 25 mg. per ml. intramuscularly. Intravenous injections were made in a vein at the dorsum of the hand, using a 21-gauge scalp-vein needle. The needle remained in place until completion of surgery in order to facilitate the administration of supplemental drugs when needed. The speed of intravenous injection ranged from less than 15 (5 patients) to 60 seconds (30 patients), and in the remainder was given over a 15 to 30-second period.

Dissociative Anest.

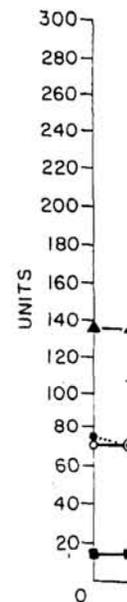


FIG. 2. Et

The intramuscular and intravenous approaches being injected quadrant of the

In 14 patients prior to anesthesia. The matocrit, blood rect, total, E and urinalysis albumin, sugar

**Pharmacology**

**Circulation**—pressor response (0.45 mg. per premedicated was administered od of 30 seconds the brachial pressures. A 1 tolic and diastolic Pulse rate was tory rate decreased of loss of of 1 mg. per l duration of u pressure and l Gradually the control levels.

**ABOUT THE AUTHORS**

★ GUENTER CORSSSEN, M.D. is Professor in the Department of Anesthesiology at the University of Michigan Medical Center, Ann Arbor, Michigan. He received his M.D. degree from the University of Hamburg, Germany, and took residency training in anesthesiology at the University of Texas Medical Branch, Galveston, Texas.



Dr. Corssen

★ EDWARD F. DOMINO, M.D. is Professor of Pharmacology at the University of Michigan in Ann Arbor. He received the B.S., M.S. and M.D. degrees from the University of Illinois in Urbana, and served a rotating internship at Presbyterian Hospital in Chicago, Illinois.

evoked respiratory response by employing averaging procedures, as described previously, such as visualized before, induced anesthesia.

of 130 patients: from 6 weeks to 1 with CI-581 for procedures (table 1). The 2 years old or 66 or over. Seven in good general 36 suffered from physical state 2), systemic disease. Three patients procedures.

respiratory rate, heart rate, blood pressures monitored at 1 to 3-

procedures, such as atropine treatment for succinylcholine were used.

0.5 mg. per ml. concentration or 25 mg. per ml. intramuscular injections were given in the palm of the hand, vein needle. The patient until completion of anesthesia to facilitate the administration of drugs when needed. Intravenous injection (5 patients) to 60 seconds in the remainder 30-second period.



Dr. Corssen  
University of Oregon  
degrees from  
at Presby-

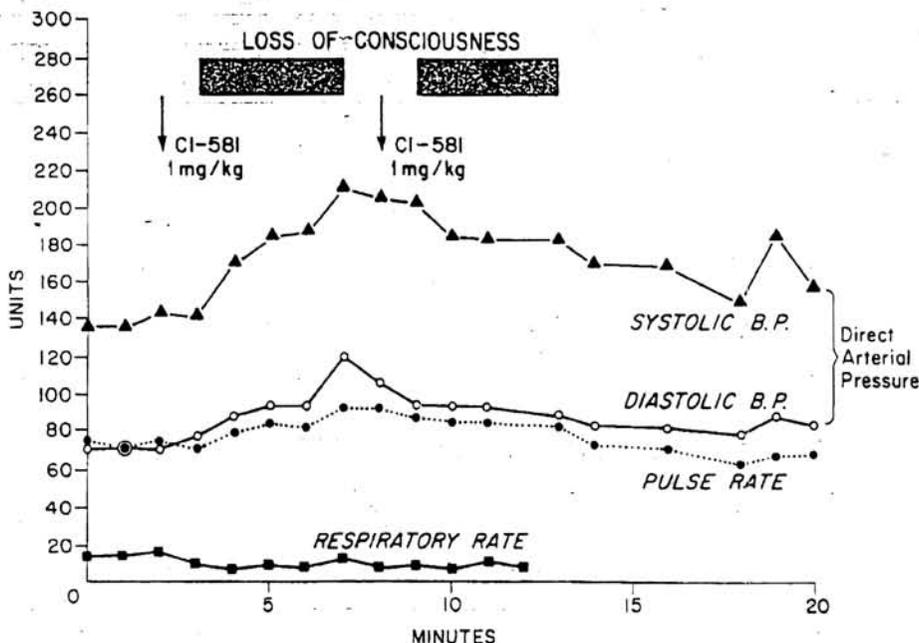


FIG. 2. Effects of CI-581 anesthesia on vital signs in an unmedicated human volunteer.

The intramuscular route was chosen for infants and small children when the intravenous approach appeared difficult, the drug being injected into the right or left outer quadrant of the buttocks.

In 14 patients, laboratory tests were carried out prior to and 1 to 3 days following anesthesia. These included hemoglobin, hematocrit, blood urea nitrogen, bilirubin (direct, total), SGOT, cephalin flocculation, and urinalysis (color, specific gravity, pH, albumin, sugar, leukocytes).

**RESULTS**

**Pharmacology Studies**

**Circulation**—Figure 2 illustrates the vasopressor response to a dose of 1 mg. per kg. (0.45 mg. per pound) of CI-581 in an unmedicated human volunteer. The drug was administered intravenously over a period of 30 seconds. A catheter was placed in the brachial artery to record direct arterial pressures. A marked increase in both systolic and diastolic blood pressure was noted. Pulse rate was increased and the respiratory rate decreased slightly during the period of loss of consciousness. A second dose of 1 mg. per kg. produced about the same duration of unconsciousness, while blood pressure and heart rate were still elevated. Gradually these values returned toward control levels.

**Respiration**—As seen in figure 3, CI-581 caused transient depression in minute volume, which started shortly after completion of injection and lasted from 1 to 3 minutes. Depression was most marked within the first minute after completion of drug injection. Considerable variability in the amount of respiratory depression was observed. In 1 subject the minute volume decreased to 30 per cent of control for 1 minute. When an unobstructed airway was maintained, these

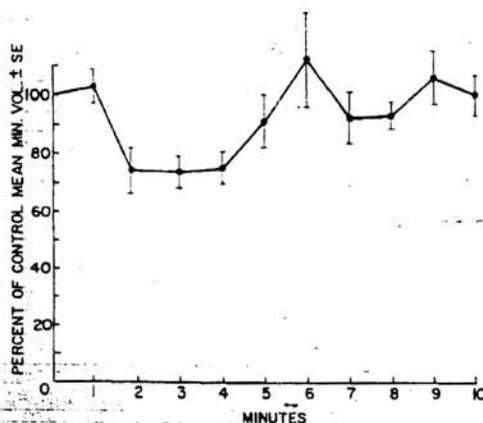


FIG. 3. Alteration of per cent mean respiratory minute volume following intravenous CI-581 (0.45 mg. per lb.) in 6 unmedicated human volunteers.

**CI-581:  
PROCEDURE:**

General surge  
Orthopedics  
Urology  
Ophthalmology  
Otolaryngology  
Oral surgery  
Cardiology (c  
Others

Total

the subject was  
trates the depr  
the increase in  
heart rate 3 n  
When the subj  
ness, the second  
ducing coma a  
cially in the fr  
Thirty-two mir  
was awake, alth  
partially retur  
(panel D).

Visually Evo  
ing anesthesia i  
was characteris  
in figure 5. The  
pecially promin  
came markedly  
the period of u  
ing emergence  
subject establis  
investigators. T  
the occipital ar  
of the faster  $\alpha$   
3). presence of  
cortical afterdis  
in harmony wi  
rhythm.

Clinical Stua  
tients in relativ  
vices (table 1)  
gery, patients ur  
age of abscess,  
rectal or sigmoid  
ures included  
and manipulat  
ogy group incl  
the bladder or  
chidectomy. Op  
cluded tonome  
fundoscopy, ren  
cauterization of  
logic procedure  
probing of tear  
removal of papill

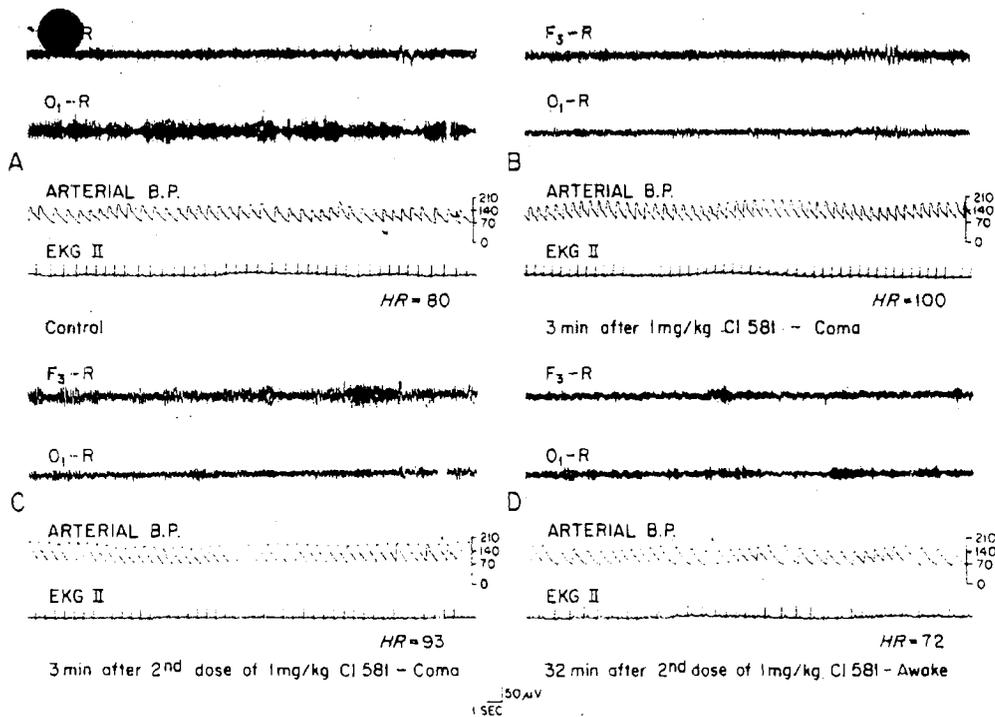


FIG. 4. Alterations of EEG and ECG recordings and arterial blood pressure in an unpremedicated human volunteer given CI-581 in 2 intravenous doses, 6 minutes apart.

changes were less marked. The transient drug-induced decrease in ventilatory exchange was not reflected in the arterial  $pO_2$ ,  $pCO_2$ , or pH values, which remained within physiologic limits.

In conclusion, although CI-581 causes respiratory depression, it is transient and not of clinical significance under these circumstances.

Electroencephalogram—CI-581 depressed the *alpha* rhythm and induced *theta* activity in the EEG (fig. 4). This subject received 2 doses (1 mg./kg. each) of CI-581. In panel A, before the drug was given, EEG *alpha* activity was normal, particularly in the occipital ( $O_1$ ) area. Direct arterial blood pressure and ECG lead II recordings were within normal limits. Within 1 minute after administration of the first dose of CI-581,

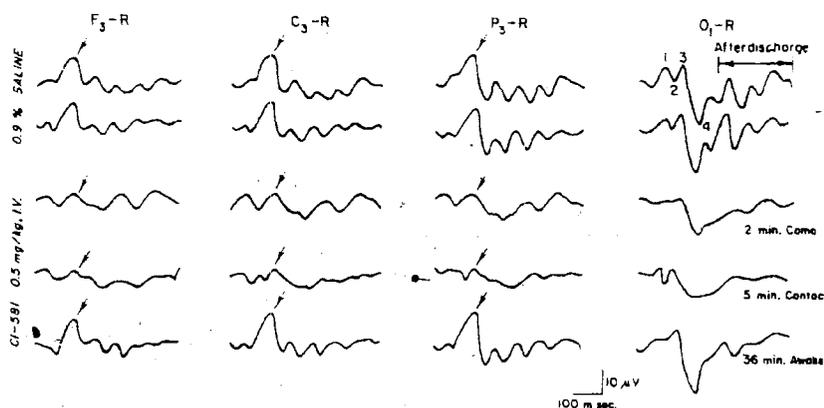
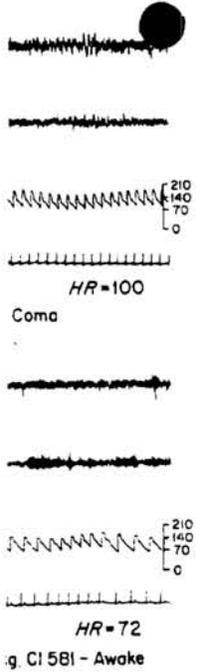
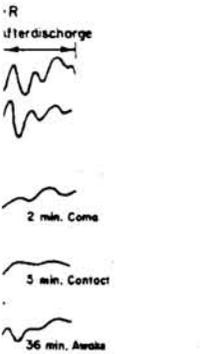


FIG. 5. Effects of CI-581 on visually evoked responses in an unpremedicated human volunteer, recorded from various brain areas.



an unpremedicated

CI-581 depressed *theta* activity (subject reached) of CI-581. When drug was given, EEG showed *theta* activity, particularly in frontal area. Rectal arterial blood pressure and heart rate recordings were made 1 minute after first dose of CI-581,



ated human

**Table 1**  
**CI-581: DISTRIBUTION OF 133 PROCEDURES TO DIFFERENT SERVICES**

General surgery	7
Orthopedics	17
Urology	48
Ophthalmology	31
Otolaryngology	8
Oral surgery	8
Cardiology (cardioversion)	9
Others	5
<b>Total</b>	<b>133</b>

the subject was unconscious. Panel B illustrates the depression of *alpha* rhythm and the increase in arterial blood pressure and heart rate 3 minutes after drug injection. When the subject had regained consciousness, the second dose was administered, producing coma again and *theta* activity, especially in the frontal ( $F_3$ ) area (panel C). Thirty-two minutes afterwards the subject was awake, although *alpha* rhythm had only partially returned toward control levels (panel D).

**Visually Evoked Response (VER)**—During anesthesia induced by CI-581, the VER was characteristically altered, as illustrated in figure 5. The vertex waves (arrows), especially prominent in  $F_3$ ,  $C_3$ , and  $P_3$ , became markedly depressed not only during the period of unconsciousness but also during emergence from anesthesia when the subject established verbal contact with the investigators. The potentials recorded from the occipital areas ( $O_1$ ) showed depression of the faster components (waves 1, 2, and 3), presence of wave 4, and depression of cortical afterdischarge. The latter effect is in harmony with the depression of *alpha* rhythm.

**Clinical Studies**—The distribution of patients in relation to different surgical services (table 1) includes, under general surgery, patients undergoing incision and drainage of abscess; skin graft, and removal of rectal or sigmoid polyps. Orthopedic procedures included close reduction of fractures and manipulation of frozen joints. The urology group included cystoscopy, biopsy of the bladder or prostate, meatotomy, and orchidectomy. Ophthalmologic procedures included tonometry, gonioscopy, goniotomy, funduscopy, removal of corneal sutures, and cauterization of corneal ulcer. Otolaryngologic procedures included myringotomy, probing of tear duct, tongue biopsy, and removal of papillomas from the vocal cords.

Oral surgical procedures included extraction of teeth and incision and drainage of sub-mandibular abscess. Nine patients undergoing cardioversion with the aid of direct current electroshock had previously undergone cardiac surgery for the correction of acquired valve defects, and were now experiencing atrial flutter or fibrillation. Other surgical manipulations included pneumoencephalogram and spinal tap with cerebral spinal pressure measurements in uncooperative children.

The average duration of the 133 surgical procedures was 10 minutes and 48 seconds. The longest procedure lasted 45 minutes (skin graft in a child 11 months old, with third-degree burns over 30 per cent of the body).

Preanesthetic medications consisted of conventional combinations of barbiturates or opiates with belladonna drugs. Two patients received no preanesthetic agents; a group of 30 patients, including mostly infants and children, received belladonna drugs only; 37 patients received chlorpromazine, alone or in combination with barbiturates or opiates.

Dosages of CI-581 used are shown in table 2. In 93 procedures, a single intravenous injection provided a duration of anesthesia sufficient to complete the surgical manipulation. In 7 instances, a second intravenous injection, consisting of  $\frac{1}{4}$  to  $\frac{1}{2}$  the initial dose, was administered to prolong anesthesia. A third injection was necessary in 9 cases, a fourth in 1 case, and a fifth in 2 cases.

Adequate anesthesia was established in 123, or 91.8 per cent, of the procedures. Analgesia also was adequate in most instances; 5 patients, however, required supplementation with nitrous oxide-oxygen

**Table 2**  
**CI-581: DOSAGES USED IN 133 INTRAVENOUS AND INTRAMUSCULAR INJECTIONS**

<b>A. Intravenous (initial dosage)</b>	
<0.50 mg. per pound of body weight	18
0.50	57
0.75	24
1.00	13
<b>Total</b>	<b>112</b>
<b>B. Intramuscular</b>	
2.50 mg. per pound of body weight	1
3.00	4
4.00 to 5.00	16
<b>Total</b>	<b>21</b>

2) mixtures. In 3 instances, skeletal muscle relaxation was inadequate, and in 2 instances there were movements of the eyeballs during ophthalmoscopic procedures.

**Dosage**—In the initial human pharmacologic studies, CI-581 was shown to produce anesthesia in doses of 1.0 to 2.0 mg. per kg. of body weight. Because the weight in clinical patients is usually expressed in pounds, the mg. per pound basis for dosage was used in this series. It was found that the optimal intravenous anesthetic dose in adults ranged from 0.5 to 0.75 mg. per pound. In infants and children the dose needed to be increased to 1 mg. per pound for a satisfactory anesthetic state. When the intramuscular route was chosen for infants and children, 4 to 5 mg. per pound proved adequate.

**Anesthesia**—Surgical anesthesia was established about 30 seconds after completion of the intravenous injection and 5 to 8 minutes after the intramuscular injection. With the intravenous administration, anesthesia lasted 5 to 8 minutes, and with the intramuscular, 20 to 30 minutes, depending on age and physical state of the patient. As a rule, in young and middle-aged adults the duration of anesthesia was shorter than in the elderly or the very young.

At the onset of anesthesia in adult patients, a slight decrease in respiratory rate and depth was frequently recorded, lasting from 30 to 60 seconds, after which the respiratory exchange was normal. In infants and children there was either no change in respiration or a slight increase in respiratory rate and/or depth. Usually patients maintained an adequate airway so that there was no need for other support.

**Changes in Circulation**—Administration of CI-581 resulted in an increase in arterial pressures in the majority of adult patients. In some subjects the increase was alarming, while in others receiving the same dose, it was barely perceptible. It was noted that the greatest increases in arterial pressure occurred when the speed of intravenous injection was fast (10 to 30 seconds).

Rapidity with which the drug is administered may play a role in the degree of the vasopressor response obtained. However, it should be noted that some volunteers still showed a significant increase in arterial blood pressure even when the drug was given as an intravenous infusion over a 5-minute period. Some of the variations in blood pressure response to CI-581 in 3 different patients are illustrated in figures 6, 7, and 8.

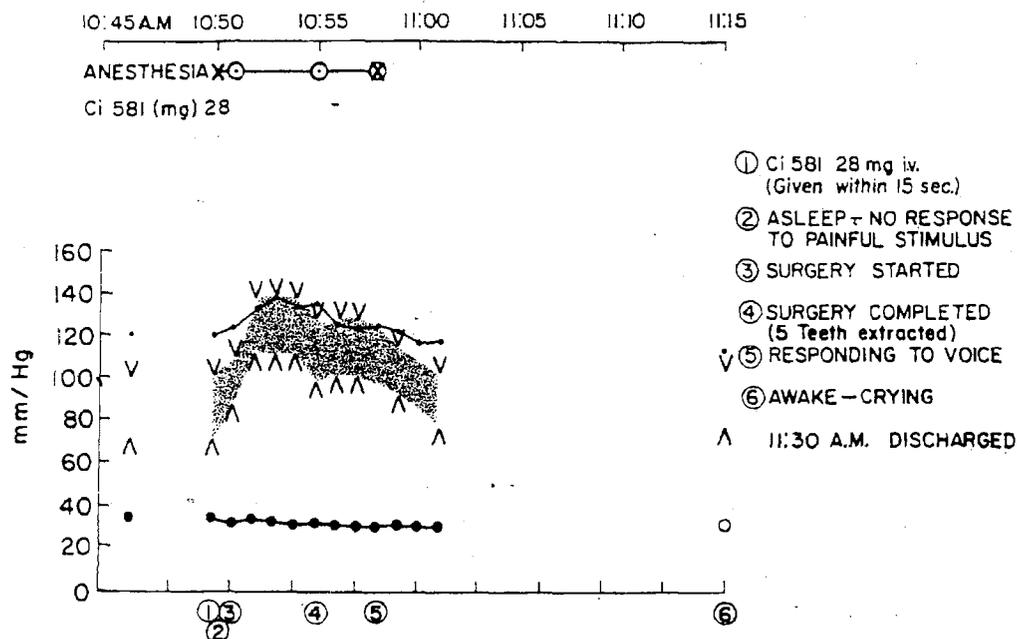


Fig. 6. Two-year-old white boy, 28 pounds. Preanesthetic medication: scopolamine hydrobromide, 0.2 mg. at 9:50 a.m. Surgical procedure: teeth extraction. Anesthesia: CI-581 intravenously. The intravenous injection was given within 15 seconds.

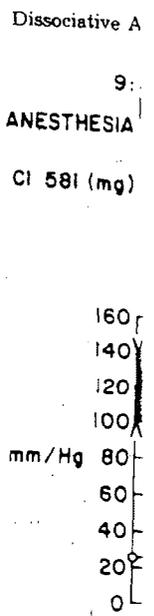


Fig. 7. Five-medication: pt myringotomy, within 60 sec

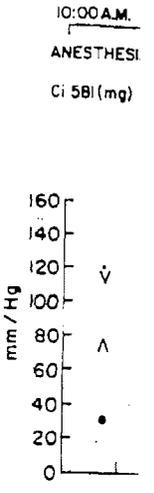


Fig. 8. Five-medication: pt myringotomy, within 60 sec

Figure 6 is a boy of CI-581 intravenously, marked increase in blood pressure after the injection return toward anesthesia

nesia in adult patients. A marked increase in respiratory rate was recorded, lasting for a period of 15 to 20 minutes after which the respiratory rate returned to normal. In infants there was no change in respiratory rate. In children there was a decrease in respiratory rate in patients mainly because of so that there was a decrease in respiratory rate.

1.—Administration of CI-581 in adult patients. An increase in arterial blood pressure was alarming, but the same dose, if administered over a 5-minute period, resulted in a decrease in arterial pressure (within 15 seconds).

The drug is administered in the degree of the anesthesia desired. However, in some volunteers still an increase in arterial blood pressure was noted after the drug was given over a 5-minute period. Variations in blood pressure of CI-581 in 3 different patients (figures 6, 7, and 8).

CI-581 28 mg iv. (in 15 sec.)  
 ASLEEP - NO RESPONSE TO PAINFUL STIMULUS  
 SURGERY STARTED  
 SURGERY COMPLETED (Teeth extracted)  
 RESPONDING TO VOICE  
 AWAKE - CRYING  
 3:30 A.M. DISCHARGED

scopolamine hydrobromide, administered intravenously. The intra-

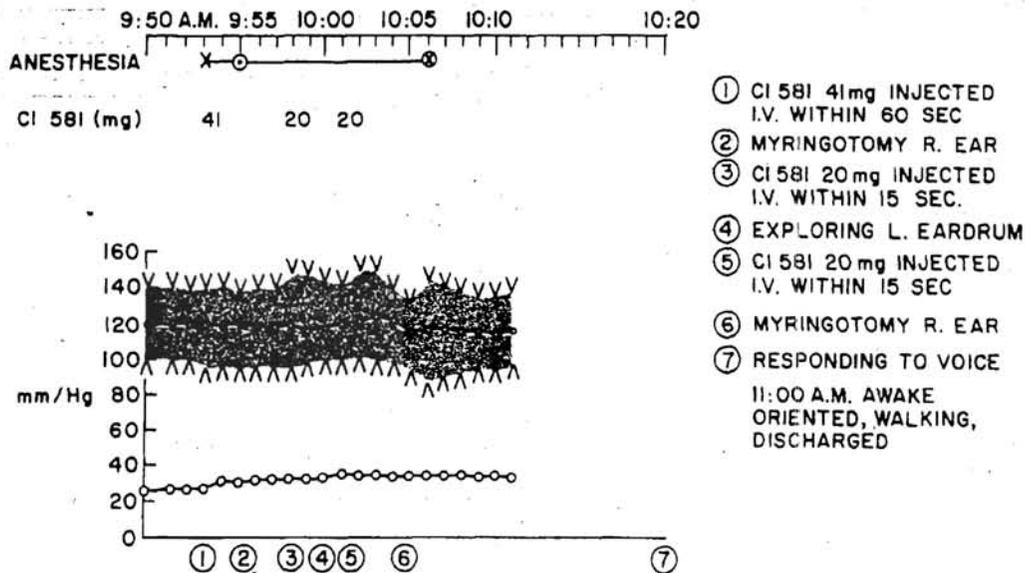


Fig. 7. Five-year-old white boy, 41 pounds, bilateral chronic otitis media, cleft palate. Preanesthetic medication: pentobarbital, 25 mg., scopolamine, 0.2 mg. at 8:55 a.m. Surgical procedure: bilateral myringotomy, insertion of myringal tubes. Anesthesia: CI-581 intravenously. The CI-581 was injected within 60 seconds.

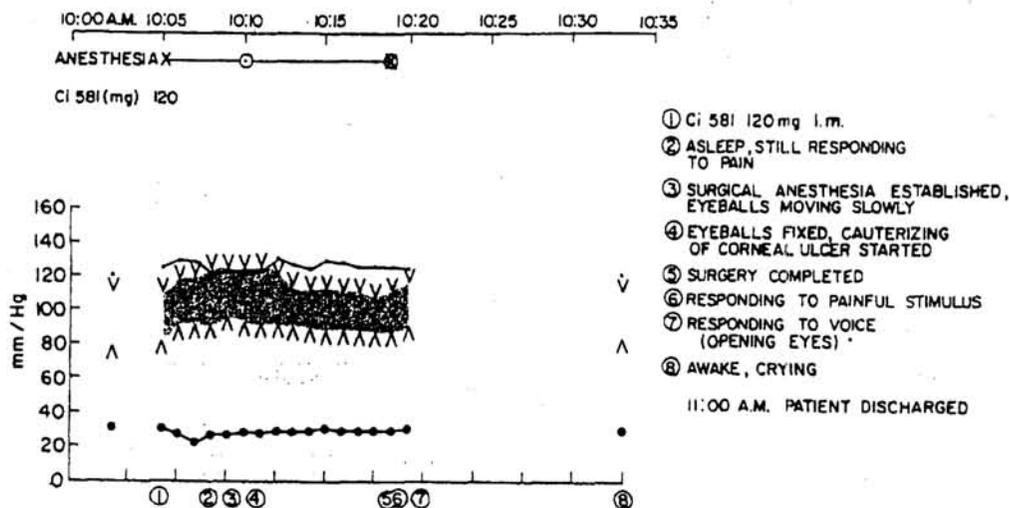


Fig. 8. Fifteen-month-old white girl, 30 pounds. Preanesthetic medication: pentobarbital, 30 mg., scopolamine, 0.2 mg. intravenously at 9:30 a.m. Surgical procedure: cauterization of corneal ulcer. Anesthesia: CI-581 intramuscularly.

Figure 6 shows the effect in a 2-year-old boy of CI-581 (1 mg./lb.) administered intravenously, given within 15 seconds. A marked increase in both systolic and diastolic blood pressure was noted immediately after the injection, with gradual decline and return toward preinjection levels at the end of anesthesia.

Figure 7 illustrates the anesthesia record of a 5-year-old boy who received CI-581 (1 mg./lb.) administered intravenously over a 60-second period. Note the even course of the systolic and diastolic pressure values recorded throughout anesthesia in this patient.

Figure 8 illustrates the anesthesia record

A 15-month-old girl to whom the drug was administered intramuscularly. At a dose of 4 mg. per pound, no significant effect on arterial blood pressure was observed.

Of particular interest was the observation that protective reflexes—pharyngeal, laryngeal, eyelid, and corneal—were present during the entire course of anesthesia. During surgery around and inside the mouth there was no need for an endotracheal tube to insure unobstructed airway. The achilles tendon and patellar reflexes were usually enhanced. In some instances the jaw muscles appeared to be more tense.

Recovery — In 92 patients, 2 endpoints were recorded to evaluate the speed of post-anesthetic recovery: (1) time in minutes, monitored from completion of surgery until first verbal contact was established; and (2) patient orientation as to person, time, and place. An average of 6 minutes elapsed until the patient responded to verbal commands. The average time from completion of surgery until orientation was 11 minutes. Full recovery usually occurred within 30 to 60 minutes. In 38 infants and small children such information could not be obtained.

Nausea and vomiting were virtually absent. One 5-year-old boy with chronic otitis media vomited once following bilateral myringotomy. At the time of emesis he was awake and was able to clear his throat spontaneously.

Skeletal muscle tone of the extremities and the masseter muscles was usually increased, although it was not necessary to administer muscle relaxants except where complete muscle paralysis was required, as in patients undergoing electroshock treatment or repositioning of dislocated joints. As a rule, abdominal muscles were relaxed. No grand mal convulsions were noted after CI-581. Muscle twitching involving facial and neck muscles occurred in an 8-year-old Negro girl following multiple extractions of teeth. This phenomenon lasted approximately 20 seconds and subsided spontaneously.

Some of the adult patients had vivid dreams or frank hallucinations during the awakening phase. Some described the dreams as amusing and pleasant, others considered them frightening. As a rule, such dreaming episodes lasted from 5 to 15 minutes, after which the patient promptly returned to reality and became clear and coordinated. The dreams frequently involved outer space.

Two patients, both middle-aged, showed signs of schizoid behavior during awakening. Both experienced traveling in outer space and thought that they had died and were flying to hell. In 1 patient this episode lasted only a few minutes; in the other, restlessness and agitation during the dreaming stage extended to 40 minutes, after which it abruptly subsided. Eight other adult patients showed signs of experiencing vivid dreams during awakening. In 3 instances the intravenous administration of 60 to 80 mg. of thiamylal sodium appeared to stop the restlessness; all 3 patients awoke several minutes later without any further signs of psychic disturbance.

Clinical Laboratory Data—In none of the patients studied was there any indication of an adverse effect of the drug on organ function. The various tests to detect possible toxic actions on hepatic or renal function showed values within normal limits. One patient, a 4-year-old boy with a history of total alopecia and ataxia of unknown etiology, underwent pneumoencephalography and had an elevated SGOT value before receiving CI-581. The SGOT value remained elevated when checked 24 hours after administration of the drug.

#### DISCUSSION

There seems to be little doubt that the phencyclidine derivative CI-581 is a powerful analgesic and anesthetic with an unusual spectrum of pharmacologic effectiveness. Of particular importance seems to be the significant difference in anesthetic or comatose state induced by this drug as compared to that established by conventional anesthetic agents or hypnotic drugs. Instead of sedative and hypnotic effects, CI-581 appears to produce a state resembling catalepsy.

As has been pointed out, phencyclidine-related drugs alter the reactivity of the central nervous system to various sensory impulses but do not produce true sensory blockade. This was borne out by reports of some patients and subjects who, during recovery from CI-581, felt as though they were in outer space, or had no arms or legs. The fact that in these individuals the motor reflexes were intact and frequently hyperactive may serve as additional evidence that the drug does not block primary sensory input at spinal or brainstem levels.

These and previous studies recording visual and somesthetic evoked potentials appear to indicate that sensory input may reach cortical receiving areas but fail to be

Dissociative

perceived because the presence in pulses resu fore suggest CI-581 be c

If we ac as to how c rence of 1 such condit tients respc state. The patient app this respec appears to verbal or tr be exposed. the early p observed th confusion, c ing the awa tempts of v room to arc asking ques Under such ly awakeni the various motion a c anxiety, co ness.

This was in a 21-ye from CI-58 gone surger perirectal a ly being ar by differen day of the thought she her from ai had difficul the heads c "made out answer the quately, she cry. As so no further e calm, and a out any fu chotic beha

In this r Cohen and deprivation tomimetic studies usir

Psychoto from CI-58 coma-prodt

JANUARY-FEBRUARY, 1966

de-aged, started  
uring awakening.  
g in outer space  
d died and were  
this episode last-  
he other, restless-  
g the dreaming  
es, after which it  
other adult pa-  
xperiencing vivid  
In 3 instances the  
of 60 to 80 mg.  
ared to stop the  
ts awoke several  
further signs of

a—In none of the  
any indication of  
ug on organ func-  
o detect possible  
or renal function  
ial limits. One pa-  
with a history of  
of unknown eti-  
encephalography  
T value before re-  
T value remained  
4 hours after ad-

ON

le doubt that the  
CI-581 is a power-  
ic with an unusual  
c effectiveness. Of  
ms to be the sig-  
hestic or comatose  
ig as compared to  
entional anesthetic  
. Instead of seda-  
CI-581 appears to  
ig catalepsy.

out, phencyclidine-  
activity of the cen-  
arious sensory im-  
luce true sensory  
e out by reports of  
ts who, during re-  
s though they were  
arms or legs. The  
huals the motor re-  
quently hyperactive  
evidence that the  
nary sensory input  
vels.

udies recording vis-  
ked potentials ap-  
ensory input may  
areas but fail to be

perceived in some of the association areas because these are depressed. This interference in proper association of afferent impulses results in "dissociation." It is therefore suggested that the state induced by CI-581 be called "dissociative anesthesia."

If we accept this term, a question arises as to how often one could expect the occurrence of psychotomimetic activity under such conditions. Undoubtedly, different patients respond differently to the dissociative state. The basic psychic disposition of the patient appears to be an important factor in this respect. Equally important, however, appears to be the amount of stimulation, verbal or tactile, to which the patient may be exposed at emergence from anesthesia. In the early phase of the clinical study it was observed that, in adults, signs of agitation, confusion, or even psychotic behavior during the awakening period coincided with attempts of various persons in the operating room to arouse the patient by continuously asking questions or applying painful stimuli. Under such conditions, the patient, suddenly awakening, seemed unable to associate the various afferent impulses, which set in motion a chain of reactions including fear, anxiety, confusion, agitation, and restlessness.

This was particularly well demonstrated in a 21-year-old Negro girl who emerged from CI-581 anesthesia after having undergone surgery for incision and drainage of a perirectal abscess. She remembered distinctly being aroused by continuous questioning by different persons about her name, the day of the week, her age, and so on. She thought she saw 6 doctors at once staring at her from above and asking questions. She had difficulty with vision, and remembered the heads of the doctors as appearing to be "made out of wood." Since she could not answer the questions promptly and adequately, she became frightened and began to cry. As soon as she was in her room with no further exposure to questions, she became calm, and awakened shortly afterward without any further sign of confusion or psychotic behavior.

In this regard, it should be recalled that Cohen and associates<sup>8</sup> reported that sensory deprivation decreased markedly the psychotomimetic effects of phencyclidine. Similar studies using CI-581 would be helpful.

Psychotomimetic effects during emergence from CI-581 can easily be controlled by coma-producing drugs. For example, small

intravenous doses of thiamylal (60 to 80 mg.) have proved satisfactory. However, it should be our aim to prevent rather than to treat postanesthetic drug-induced psychic disturbances. Further exploration of the effectiveness of premedication with antipsychotic drugs to suppress or eliminate such psychomotor activity may prove of value, although our preliminary experience with small doses of chlorpromazine have been disappointing.

There is some question about the use of scopolamine as a preanesthetic medication, in view of its own psychotomimetic effects, especially when given in large doses. Whether it should be omitted as a preanesthetic medication in favor of atropine deserves further investigation.

Variations in the use of small therapeutic doses of preanesthetic agents, including chlorpromazine, barbiturates, opiates, and belladonna derivatives, have failed to change materially the hypertensive and psychotomimetic effects of CI-581. A more gradual rate of injection of the drug into the circulation might reduce vasopressor activity. In our series this possibility was suggested by the observation that intramuscular injections did not result in any significant rise in blood pressure. Whether the critical variable was that children rather than adults were involved, or whether it was the speed of absorption, is still to be determined.

"Dissociative" anesthesia as produced by CI-581 and other cyclohexylamines seems to provide excellent "somatoanalgesia" involving extremities and the skeleton, but may be insufficient to protect against visceral pain. This observation was made in several patients undergoing urologic procedures to correct urethral strictures or for increased tone of the urinary sphincter. Repeated supplementary intravenous dosages were frequently necessary for adequate analgesia in these cases.

Inadequate or transient analgesia of only 1 to 3-minute duration was recorded in some patients during the early phase of the study when the drug was given in insufficient amounts. Nitrous oxide-oxygen mixtures had to be administered as a supplement in these instances to provide appropriate conditions for surgical manipulation. With intravenous dosages of CI-581 ranging from 0.5 to 0.75 mg. per pound of body weight in adults and 1.0 mg. per pound in children and infants, this complication was brought under control.

Of particular advantage appeared to be

intramuscular approach in very young patients. Profound analgesia of prolonged duration (20 to 30 minutes) resulted from intramuscular injections of 4 to 5 mg. per pound without any detectable effect on respiratory or circulatory mechanisms. Supplemental intramuscular doses were administered in 3 patients for reinforcement or prolongation of anesthesia.

As compared to intravenous, recovery from intramuscular injections was slightly prolonged, ranging from 30 to 90 minutes depending on individual variability. The efficiency and safety of this mode of administration of CI-581 in infants and children for carrying out prolonged and painful procedures such as extensive skin grafts for severe burns was clearly evident. The advisability of administering subanesthetic intramuscular doses for performing frequent burn-dressing changes in patients of all ages is now being investigated. The usefulness of CI-581 administered by intravenous drip for analgesia, supplemented by nitrous oxide-oxygen mixtures, as recommended by Chodoff<sup>9</sup> for the anesthetic management of patients for delivery, also deserves further study. The amnesic effect of nitrous oxide should materially reduce the incidence of emergence delirium or hallucinations.

Amnesia for the entire surgical and anesthetic procedure appears to be another desirable feature of the drug. However, many adults had distinct recollections of the awakening phase, especially when this was marked by vivid dreams or hallucinations.

In 3 adult patients with asthma, anesthesia induced and maintained with CI-581 as the sole anesthetic was smooth and uneventful. No signs of bronchial or bronchiolar spasm were detectable. The sympathomimetic action of the drug, possibly counteracting bronchial constrictive tendencies, may be beneficial in this type of patient.

CI-581 is well tolerated by the tissues. In no instance was there any local reaction to the intravenous or intramuscular injection.

**SUMMARY**

A new type of anesthetic agent, CI-581, a derivative of phencyclidine has been investigated. Pharmacologic details that supplement an earlier report are presented, and our first experiences with the drug in clinical cases are reported.

The compound produces profound analgesia associated with a peculiar state of alt-

ered consciousness ("dissociation"). Analgesia and unconsciousness are produced within 30 seconds following intravenous administration of the drug or, in children and infants, within 5 to 8 minutes following intramuscular injection. Duration of anesthetic action ranges from 5 to 30 minutes, according to the mode of administration, and can be prolonged by repetition of intravenous or intramuscular dosages.

Respiratory function is slightly but transiently reduced at the onset of anesthesia and returns to normal values within 1 to 3 minutes. In adults, intravenous administration sometimes elevates both systolic and diastolic blood pressures to undesirable levels, but slowing the speed of such injection may help to reduce the severity of this vasopressor action. Intramuscular administration in children seems not to be associated with hypertensive effects.

During emergence from dissociative anesthesia, the adult patient may go through a phase of vivid dreaming, with or without psychomotor activity, manifested by confusion, irrational behavior, and hallucinations. Such psychic aberrations, which have not been observed in infants and children, are transient and appear to be controllable by avoiding early verbal or tactile stimulation of the patient, thus preventing fear and anxiety reactions. Small amounts of short-acting barbiturates administered intravenously can effectively control the psychotomimetic response.

CI-581 does not exert any discernible toxic effects on organs, and it is well tolerated by the human tissues, no local reactions to injections having been recorded. The drug has been useful in the anesthetic management of patients undergoing short-lasting surgical procedures, especially those accompanied by severe pain, such as incision and drainage of abscesses, closed reduction of fractured bones, and manipulation of frozen joints. In pediatric patients, it has been for skin grafting in severe burn patients, myringotomy, probing of tear ducts, and various short-lasting ophthalmologic and oral surgical procedures.

CI-581 appears to be a potent anesthetic agent with a fast onset of action and limited duration. While its unusual effectiveness and safety in the anesthetic management of infants and children appears clearly evident, its future place in anesthesia for patients of all ages will depend largely on the results of further clinical exploration of the agent

and, partic  
vasopressor)

The aut/  
Lane and  
Company,  
help in ca  
studies and

Generi  
This  
Chl

1. Chen, G  
B.: The Ph  
Pipiridine H  
1959.

2. Greifens  
and Gajewsk  
Hexyl Amine  
283 (Septeml

3. McCart  
Anesthetic A  
aminocyclohe  
Monkey. Fe

4. Dominic  
Human Phar  
clidine Deriv

5. Jasper,  
tem of the Ir  
Clin. Neurop

6. Corsse  
Evoked Resp  
ing Cerebral  
Anesthesiolo

7. Domino  
(Sernyl), a  
Pharmacolog  
303, 1964.

8. Cohen,  
Gottlieb, J. :  
privation. C

9. Chodoff

F. E  
D  
Universi

The com  
of its actio  
clidine. Th  
sation and  
species an  
be general  
ever, poss  
ferentiate  
esthetics,

ciation") . . . s are produced y intravenous ad , in children and ites following ination of anesthet- 30 minutes, ac- ministration, and titution of intrave- ages.

slightly but tran- set of anesthesia ues within 1 to 3 enous administra- both systolic and 3 undesirable lev- of such injection erity of this vaso- cular administra- : to be associated

dissociative anes- nay go through a with or without ifested by confu- nd hallucinations, which have not and children, are e controllable by actile stimulation venting fear and amounts of short- inistered intrave- trol the psychoto-

y discernible toxic ; well tolerated by al reactions to in- orded. The drug nesthetic manage- oing short-lasting ally those accom- ch as incision and osed reduction of ipulation of frozen its, it has been for n patients, myrin- ducts, and various gic and oral sur-

potent anesthetic action and limited usual effectiveness tic management of ars clearly evident, esia for patients of ely on the results ation of the agent.

and, particularly, methods for preventing its vasopressor and psychotomimetic effects.

**ACKNOWLEDGMENT**

The authors are indebted to Drs. A. Z. Lane and E. L. Holmes, Parke, Davis and Company, Detroit, Michigan, for valuable help in carrying out the human volunteer studies and for generous supply of CI-581.

**Generic and Trade Names of Drugs**  
Thiamylal—Surital  
Chlorpromazine—Thorazine

**REFERENCES**

1. Chen, G., Ensor, C. R., Russel, D. and Bohner, B.: The Pharmacology of 1-(1-phenylcyclohexyl) PIPRIDINE HCl. *J. Pharmacol. Exp. Ther.* 127:241, 1959.
2. Greifenstein, F. E., DeVault, M., Yoshitake, J. and Gajewski, J. E.: A Study of a 1-Aryl Cyclo Hexyl Amine for Anesthesia. *Anesth. & Analg.* 37: 283 (September-October) 1958.
3. McCarthy, D. A. and Chen, G. M.: General Anesthetic Action of 2-(0-chlorophenyl) 2-methylaminocyclohexanone HCl (CI-581) in the Rhesus Monkey. *Fed. Proc.* 24:268, 1965.
4. Domino, E. F.; Chodoff, P. and Corssen, G.: Human Pharmacologic Effects of CI-581, a Phencyclidine Derivative. *J. Clin. Pharmacol.* 6:279, 1965.
5. Jasper, H. H.: The Ten-Twenty Electrode System of the International Federation. *Electroenceph. Clin. Neurophysiol.* 10:371, 1958.
6. Corssen, G. and Domino, E. F.: Visually Evoked Responses in Man: A Method for Measuring Cerebral Effects of Preanesthetic Medication. *Anesthesiology* 25:330, 1964.
7. Domino, E. F.: Neurobiology of Phencyclidine (Sernyl), a Drug with an Unusual Spectrum of Pharmacological Activity. *Int. Rev. Neurobiol.* 6: 303, 1964.
8. Cohen, B., Luby, E. D., Rosenbaum, G. and Gottlieb, J. S.: Combined Sernyl and Sensory Deprivation. *Compr. Psychiat.* 1:345, 1960.
9. Chodoff, P.: Personal communication.

**DISCUSSION**

F. E. GREIFENSTEIN, M.D.  
Division of Anesthesiology  
University of Arkansas Medical Center  
Little Rock, Arkansas

The compound CI-581 resembles in many of its actions another of this group, phencyclidine. These analogues produce loss of sensation and consciousness in most vertebrate species and may therefore be considered to be general anesthetic agents. They do, however, possess certain properties which differentiate them from the commonly used anesthetics, and some of these were brought

to light during investigations of phencyclidine. These differences may include (a) maintenance of adequate ventilation with transient or minimal respiratory depression at most; (b) maintenance of adequate circulation with frequent increases in blood pressure and heart rate; (3) failure to significantly abolish muscle tone; (d) failure of the eyes to close, but rather to remain open with some degree of lateral nystagmus; (e) clonic convulsions with higher doses; and (f) predominantly stimulant, rather than depressant effects, in some species of animals. These observations were made initially with phencyclidine but apparently also hold true, at least in part, for CI-581.

In the laboratory animal, CI-581 produces an elevation, sometimes marked, in blood pressure. The same effect has been seen in man with rapid injection of the drug, but can be reduced if a longer time is taken for injection.

The effect on respiration, following continuous infusion in the laboratory animal, is one of a reduced tidal volume with an increase in rate and a general tendency to maintain a normal minute volume. In man, a transient decrease in both rate and amplitude of breathing is seen, with rate decreasing more than depth.

Obviously both areas need much more study. The electrocardiogram in the dog shows no change except a slight slowing of the heart rate. Laboratory studies and those in man on liver and kidney function, electrolytes, and blood showed no significant change.

An interesting fact is that CI-581, like phencyclidine, will not produce a rapidly developing tolerance. Repeated daily doses in laboratory animals produced no increase in anesthesia time. I think Dr. Corssen has been able to demonstrate this very well by repeated administrations in man during the course of a single anesthetic. The lack of cumulative effect or sensitization is important when one is dealing with such a short-acting agent and where repeated injections may be necessary.

One of the great disadvantages of this group of compounds, and of phencyclidine particularly, was the high incidence of dissociative phenomena that occur following emergence from anesthesia. These reactions, severe enough to be categorized as "hallucinatory" in some instances, were seen in about 40 per cent of patients anesthetized

phencyclidine and were frequently of long duration.

Similar phenomena have been observed following the use of CI-581 but here they are of short duration and mild in character, perhaps no more marked than some "emergence reactions" following inhalational anesthesia. In almost all cases these can be ablated by small doses of short-acting barbiturates. Perhaps these effects will not be deterrent to the use of CI-581. In many short-term procedures, this dissociative effect was completely lacking.

Any new drug must be carefully evaluated and, finally, its area of usefulness, if any, delineated. Assuming that CI-581 shows clinical promise, wherein might it find applicability? One area of usefulness might be its use as the sole anesthetic in short procedures. Dr. Corssen has demonstrated its use in the outpatient clinic for such procedures and his results would warrant continued investigation in this field. Based on his preliminary observations, perhaps CI-581 might be of particular value in short-term pediatric surgery where little or no muscle relaxation is necessary.

A second usefulness might be the use of CI-581 as an agent for induction of anesthesia. Its apparent lack of effect in decreasing blood pressure, and to a lesser degree on ventilation, may offer some advantages over

induction of anesthesia with the thiobarbiturates.

A third area of usefulness may be in combination with nitrous oxide for superficial surgical procedures or nitrous oxide plus relaxant drugs for intra-abdominal or intrathoracic surgery. Several years ago we used phencyclidine in this manner with fairly good results in long procedures and experienced no real difficulty with the dissociative reactions. Since CI-581 apparently possesses a greater margin of safety than phencyclidine, and shows no cumulative effect, it may be of greater efficacy as an anesthetic. Repeated doses can apparently be given with relative impunity, or perhaps a continuous infusion technic employed.

CI-581 closely resembles phencyclidine in almost all of its actions; its effect on respiration, circulation, the excellent degree of analgesia, and the postoperative dissociation resemble those of phencyclidine. Its chief difference, and perhaps herein lies its advantage, is a shortening or compression of all these actions. The short duration of action and the rapidity with which CI-581 is metabolized, and its apparently greater margin of safety, may contribute to its clinical adaptability. This entire group of compounds is certainly interesting to the pharmacologist, and CI-581 may be equally interesting, and more importantly, useful to the anesthesiologist.

### SOCIAL SECURITY STATUS

Doctors who want to know more about their status under the Social Security system can generally get the answers through a single visit or telephone call. The Social Security Administration says physicians can save time by taking their specific questions directly to the nearest agency office. Inquiries addressed to other sources, the agency points out, will usually result in only generalized review of the law.

H  
  
JER  
V.  
  
THE EFFECTS OF RENAL FAILURE ON THE CLARIFICATION OF PROXIMAL TUBULES IN FURTHER COMMUNICATIONS

In a previous communication we measured tubular filtration rate in anesthetized rats. That group of rats that group of direct transport mechanism effects of a significant could not be all observation maximal rate p-aminohippuric acid crease in blood

Because halothane with nitrous oxide effects on renal clearance of halothane

Surgical patients (A.S.A.) indicated

\*Departments of Indiana.

This study was a Public Health

# ANESTHESIA

FIFTH EDITION

**Volume 1**

Edited by

**Ronald D. Miller, M.D.**

Professor and Chairman of Anesthesia and Perioperative Care  
Professor of Cellular and Molecular Pharmacology  
Department of Anesthesia  
University of California, San Francisco  
School of Medicine  
San Francisco, California

*Atlas of Regional Anesthesia Procedures illustrated by Gwenn Afton-Bird, M.S.*



CHURCHILL LIVINGSTONE

*A Division of Harcourt Brace & Company*

Philadelphia London Toronto Montreal Sydney Tokyo Edinburgh

cal or tissue irritant properties, and there are no known organotoxicities. Like all benzodiazepines, it appears to have a high safety margin, probably higher than those of agonists, because it does not produce prominent CNS depression. Unless it is found that benzodiazepine reversal in patients who have a long-term history of benzodiazepine use causes withdrawal reactions, including seizures, there is no current contraindication for the use of flumazenil. An important caution is that resedation could occur because of the relatively short half-life of the drug.

## PHENCYCLIDINES (KETAMINE)

### History

Phencyclidine was the first drug of its class to be used for anesthesia. It was synthesized by Maddox and introduced into clinical use in 1958 by Greifenstein et al.<sup>114</sup> and in 1959 by Johnstone et al.<sup>115</sup> Although phencyclidine proved useful as an anesthetic, it produced unacceptably high adverse psychologic effects (hallucinations and delirium) in the postanesthetic recovery period. Cyclohexamine, a congener of phencyclidine, was tried clinically in 1959 by Lear and coworkers,<sup>116</sup> but it was found to be less efficacious than phencyclidine in terms of analgesia and yet to have as many adverse psychotomimetic effects. Neither of these drugs is used clinically today, although phencyclidine is available for illicit recreational use. Ketamine (Ketalar) was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino.<sup>117</sup> It was chosen from among 200 phencyclidine derivatives and proved to be the most promising in laboratory animal testing. Ketamine was released for clinical use in 1970 and is still used in a variety of clinical settings. Ketamine is different from most other anesthetic induction agents because it has significant analgesic effect. It usually does not depress the cardiovascular and respiratory systems,<sup>118,119</sup> but it does possess some of the worrisome adverse psychologic effects found with the other phencyclidines.

### Physicochemical Characteristics

Ketamine (Fig. 9-12) has a molecular weight of 238 kd, is partially water soluble, and forms a white crystalline salt

with a negative log of the acid ionization constant ( $pK_a$ ) of 7.5.<sup>118,119</sup> It has a lipid solubility five to ten times that of thiopental.<sup>120</sup> Ketamine is prepared in a slightly acidic (pH 3.5-5.5) solution and comes in concentrations of 10-, 50-, and 100-mg ketamine base per milliliter of sodium chloride solution containing the preservative benzethonium chloride. The ketamine molecule contains a chiral center and therefore occurs as two resolvable optical isomers or enantiomers (11-12), the commercial preparation being a racemic mixture of both isomers [S-(+) and R-(-)] in equal amounts.<sup>118</sup>

### Metabolism

Ketamine is metabolized by the hepatic microsomal enzymes responsible for most drug detoxification. The major pathway involves *N*-demethylation to form norketamine (metabolite 1), which is then hydroxylated to hydroxynorketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in the urine.<sup>118,119,121</sup> The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite 1) has been shown to have significantly less (between 20 and 30%) activity than the parent compound.<sup>122-124</sup> Little is known about the activity of the other metabolites, but it is probable that ketamine is the major active drug.

### Pharmacokinetics

The pharmacokinetics of ketamine have not been as well studied as those of many other intravenous anesthetics. Ketamine pharmacokinetics have been examined after bolus administration of anesthetizing doses (2 to 2.5 mg/kg),<sup>125</sup> following a subanesthetic dose (0.25 mg/kg)<sup>125,126</sup> and after continuous infusion (steady-state plasma level  $\approx$  2,000 ng/mL).<sup>127</sup> Regardless of the dose, ketamine plasma disappearance can be described by a two-compartment model. Table 9-3 contains the pharmacokinetic values from bolus administration studies.<sup>125</sup> Of note is the rapid distribution reflected in the relatively brief slow distribution half-life of 11 to 16 minutes (Fig. 9-13). The high lipid solubility of ketamine is reflected in its relatively large volume of distribution, nearly 3 L/kg. Clearance is also relatively high, ranging from 890 to 1,227 mL/min, which accounts for the relatively short elimination half-life of 2 to 3 hours. The mean total

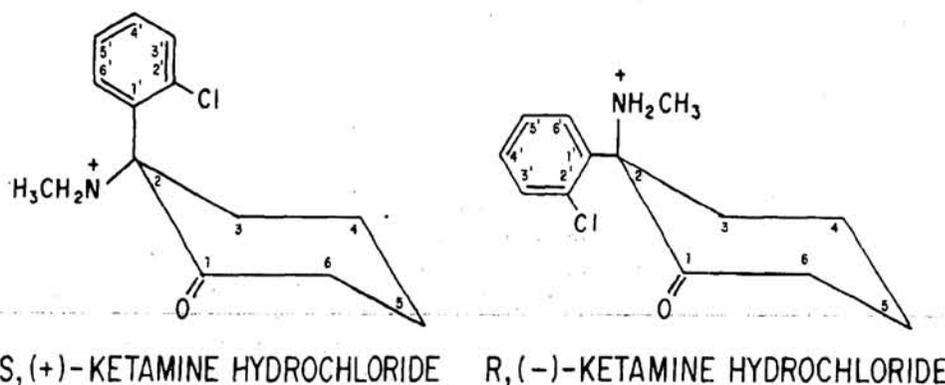
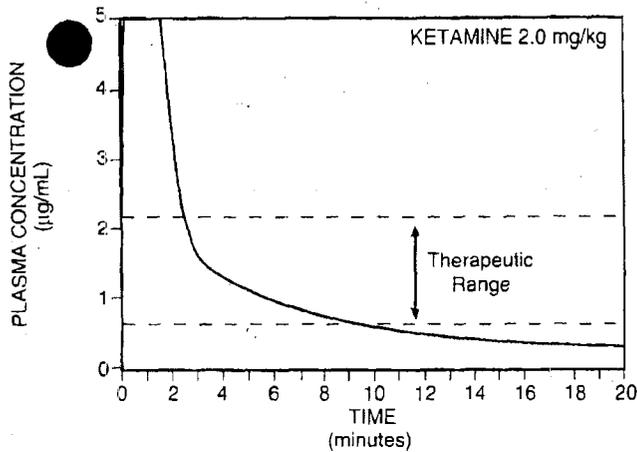


Figure 9-12. Stereoisomers of ketamine as it is formulated.



**Figure 9-13.** Simulated time course of plasma levels of ketamine following an induction dose of 2.0 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2 µg/mL, with awakening usually occurring at levels lower than 0.5 µg/mL.

body clearance (1.4 L/min) is approximately equal to liver blood flow, which means that changes in liver blood flow affect clearance. Thus, the administration of a drug such as halothane, which reduces hepatic blood flow, reduces ketamine clearance.<sup>128, 129</sup>

## Pharmacology

### Effects on the Central Nervous System

Ketamine produces dose-related unconsciousness and analgesia (Chs. 35 and 52). The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, unlike other states of anesthesia that resemble normal sleep. The ketamine-anesthetized patients have profound analgesia but keep their eyes open and maintain many reflexes. Corneal cough, and swallow reflexes may all be present but should not be assumed to be protective.<sup>130</sup> There is no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a  $pK_a$  near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and therefore has an onset of action within 30 seconds of administration. The maximal effect occurs in about 1 minute. After ketamine administration, pupils dilate moderately and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although there is great interindividual variability, plasma levels of 0.6 to 2.0 µg/mL are considered the minimum concentrations for general anesthesia,<sup>127, 128</sup> but children may require slightly higher plasma levels (0.8–4.0 µg/mL).<sup>131</sup> The duration of ketamine anesthesia after a single administration of a general anesthetic dose (2 mg/kg IV) is 10 to 15 minutes<sup>119</sup> (see Fig. 9-13), and full orientation to person, place, and time occurs within 15 to 30 minutes.<sup>132</sup>

The S enantiomer enables quicker recovery (by a couple of minutes) than the racemic mixture.<sup>133</sup> This is thought to be due to the lower dose necessary to produce an equi-anesthetic effect and to the 10 percent faster hepatic biotransformation.<sup>134</sup>

The duration of ketamine anesthesia is determined by the dose; higher doses produce more prolonged anesthesia,<sup>135</sup> and the concurrent use of other anesthetics also prolongs the time of emergence. Because there is a reasonably good correlation between blood level of ketamine and CNS effect, it appears that ketamine's relatively short duration of action is due to its redistribution from the brain and blood to the other tissues in the body. Thus, the termination of effect after a single bolus administration of ketamine is caused by drug redistribution from the well-perfused to the less well-perfused tissues. Concomitant administration of benzodiazepines, a common practice, may prolong ketamine's effect.<sup>136</sup> When used in combination with a benzodiazepine, the S enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture.<sup>137</sup> Analgesia occurs at considerably lower blood levels than loss of consciousness. The plasma level at which pain thresholds are elevated is 0.1 g/mL or higher.<sup>128</sup> This means that there is a considerable period of postoperative analgesia after ketamine general anesthesia and that subanesthetic doses can be used to produce analgesia.

The primary site of CNS action of ketamine appears to be the thalamocortical projection system.<sup>138</sup> The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus while simultaneously stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization*<sup>119</sup> of nonspecific pathways in mid-brain and thalamic areas.<sup>139, 140</sup> There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important to transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers.<sup>141</sup> Blockade of CNS sodium channels has been shown not to be the mechanism of action by which ketamine produces anesthesia.<sup>142</sup> There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects.<sup>118, 119, 143, 144</sup> The S-(+) enantiomer has been shown to have some opioid  $\mu$ -receptor activity, accounting for part of its analgesic effect.<sup>145</sup> N-Methyl-D-aspartate (NMDA) receptor interaction may mediate the general anesthetic effects as well as some analgesic actions of ketamine.<sup>146–148</sup> The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity.<sup>149</sup> Although some drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and intracranial pressure (ICP). Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta-wave activity,<sup>135</sup> as well as by petit mal seizure-like activity in the hippocampus,<sup>150</sup> ketamine increases CMRO<sub>2</sub>. Whereas theta-wave activity signals the analgesic activity of ketamine, alpha waves indicate its absence. There is an increase in CBF, which appears higher

the increase in  $CMRO_2$  would mandate. With the increase in CBF as well as the generalized increase in sympathetic nervous system response, there is an increase in ICP after ketamine.<sup>151, 152</sup> The increase in  $CMRO_2$  and CBF can be blocked by the use of thiopental<sup>153</sup> or diazepam.<sup>152, 154</sup> Cerebrovascular responsiveness to carbon dioxide appears to be preserved with ketamine; therefore, reducing  $PaCO_2$  attenuates the rise in ICP after ketamine<sup>152</sup> (Ch. 56).

Ketamine, like other phencyclidines, produces undesirable psychologic reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions*. The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience).<sup>155</sup> These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear.<sup>119</sup> They occur in the first hour of emergence and usually abate within 1 to several hours. It has been postulated that the psychic emergence reactions occur secondary to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception and/or misinterpretation of auditory and visual stimuli.<sup>118</sup> Their incidence ranges from as low as 3 to 5 percent<sup>118, 119</sup> to as high as 100 percent.<sup>155</sup> A clinically relevant range is probably 10 to 30 percent of adult patients who receive ketamine as a sole or major part of the anesthetic technique.

Factors that affect the incidence of emergence reactions are age,<sup>156</sup> dose,<sup>119</sup> gender,<sup>157</sup> psychologic susceptibility,<sup>158</sup> and concurrent drugs. Playing music during anesthesia does not attenuate the incidence of psychotomimetic reactions.<sup>159</sup> Pediatric patients do not report as high an incidence of unpleasant emergence reactions as do adult patients, nor do men as compared with women. Larger doses and rapid administration of large doses seem to predispose patients to a higher incidence of adverse effects.<sup>160, 161</sup> Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions,<sup>158</sup> and people who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine.<sup>160</sup> Numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine<sup>118, 119, 162</sup>; the benzodiazepines seem to be the most effective group of drugs to attenuate or to treat ketamine emergence reactions. Midazolam,<sup>118</sup> lorazepam,<sup>163</sup> and diazepam<sup>164</sup> are useful in reducing reactions to ketamine. The mechanism is not known, but it is probable that both the sedative and amnesic actions of the benzodiazepines make them superior to other sedative-hypnotics. Midazolam has also been shown to reduce the psychotomimetic effect of the S enantiomer.<sup>165</sup>

### Effects on the Respiratory System

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide.<sup>166</sup> There can be a transient (1–3-min) decrease in minute ventilation after the bolus administration of an anesthetizing dose of ketamine (2 mg/kg IV).<sup>135, 167, 168</sup> Unusu-

ally high doses can produce apnea,<sup>169</sup> but this is seldom seen. Arterial blood gases are generally preserved when ketamine is used alone for anesthesia or analgesia. However, with the use of adjuvant sedatives or anesthetic drugs, respiratory depression can occur. Ketamine has been shown to affect ventilatory control in children and should be considered a possible respiratory depressant when the drug is given to them in bolus doses.<sup>170, 171</sup>

Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved.<sup>172, 173</sup> Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm.<sup>174</sup> The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine.<sup>175</sup> Owing to its bronchodilating effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy.<sup>176</sup>

A potential respiratory problem, especially in children, is the increased salivation that follows ketamine administration. This can produce upper airway obstruction, which can be further complicated by laryngospasm. The increased secretions may also contribute to or may further complicate laryngospasm. In addition, although swallow, cough, sneeze, and gag reflexes are relatively intact after ketamine, there is evidence that silent aspiration can occur during ketamine anesthesia.<sup>130</sup>

### Effects on the Cardiovascular System

Ketamine also has unique cardiovascular effects; it stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output (see Table 9-4). Other anesthetic induction drugs either cause no change in hemodynamic variables or produce vasodilation with cardiac depression. The S enantiomer, despite hope that reducing the dose by half (equi-anesthetic potency) would attenuate side effects, is equivalent to the racemic mixture regarding hemodynamic response.<sup>165</sup> The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart is able to increase oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption.<sup>177</sup> The hemodynamic changes are not related to the dose of ketamine (e.g., there is no hemodynamic difference between administration of 0.5 and 1.5 mg/kg IV).<sup>178</sup> It is also interesting that a second dose of ketamine produces hemodynamic effects less than or even opposite to those of the first dose.<sup>179</sup> The hemodynamic changes after anesthesia induction with ketamine tend to be the same in healthy patients and in those with a variety of acquired or congenital heart diseases.<sup>168, 178, 180-182</sup> In patients with congenital heart disease, there are no significant changes in shunt directions or fraction<sup>183</sup> or systemic oxygenation after ketamine induction of anesthesia.<sup>184</sup> In patients who have elevated pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine

seems to cause a more pronounced increase in pulmonary than systemic vascular resistance.<sup>182, 183, 185, 186</sup>

The mechanism by which ketamine stimulates the circulatory system remains enigmatic. It appears not to be a peripheral mechanism such as baroreflex inhibition,<sup>187, 188</sup> but rather to be central.<sup>189-191</sup> There is some evidence that ketamine attenuates baroreceptor function via an effect on NMDA receptors in the nucleus tractus solitarius.<sup>192</sup> Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response.<sup>193</sup> Ketamine also causes the sympathoneuronal release of norepinephrine, which can be detected in venous blood.<sup>194</sup> Blockade of this effect is possible with barbiturates, benzodiazepines, and droperidol.<sup>191, 193-195</sup> Ketamine *in vitro* probably has negative inotropic effects. Myocardial depression has been demonstrated in isolated rabbit hearts,<sup>196</sup> intact dogs,<sup>197</sup> chronically instrumented dogs,<sup>198</sup> and isolated canine heart preparations.<sup>199</sup> However, in isolated guinea pig hearts, ketamine was the least depressant of all the major induction drugs.<sup>200</sup> The finding that ketamine may exert its myocardial effects by acting on myocardial ionic currents (which may exert different effects from species to species or among tissue types) may explain the tissue and animal model variances in direct myocardial action.<sup>201</sup>

The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. There are some peripheral nervous system actions of ketamine that play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect<sup>202, 203</sup> and inhibits extraneuronal norepinephrine uptake.<sup>204, 205</sup>

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block the ketamine-induced tachycardia and systemic hypertension. Successful methods include use of adrenergic antagonists (both  $\alpha$  and  $\beta$ ), as well as a variety of vasodilators<sup>206</sup> and clonidine.<sup>207</sup> However, probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It is also possible to lessen the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without a benzodiazepine.<sup>208</sup> Other general anesthetics, particularly the inhalation anesthetics,<sup>209</sup> blunt the hemodynamic effect of ketamine. Ketamine can produce hemodynamic depression in the setting of deep anesthesia, when sympathetic responses do not accompany its administration.

## Uses

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions, have placed ketamine outside the realm of routine clinical use. Nevertheless, ketamine has an important niche in the practice of anesthesiology: when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction and maintenance of general anesthesia.

## Induction and Maintenance of Anesthesia

Poor-risk patients (ASA class IV) with respiratory and cardiovascular system disorders (excluding ischemic heart disease), represent the majority of candidates for ketamine induction; this is particularly true for patients with bronchospastic airway disease or patients with hemodynamic compromise based either on hypovolemia or cardiomyopathy (not coronary artery disease). Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction in patients with reactive airway disease. Otherwise healthy trauma victims whose blood loss is extensive are also candidates for rapid-sequence anesthesia induction with ketamine.<sup>210</sup> Patients with septic shock may also benefit from ketamine.<sup>211</sup> However, ketamine's intrinsic myocardial depressant effect may manifest in this situation if trauma or sepsis has caused depletion of catecholamine stores prior to the patient's arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of blood volume. Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis.<sup>212</sup> The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent induction and maintenance drug in this setting. Ketamine is also often used in patients with congenital heart disease, especially those in whom the propensity for right-to-left shunting exists. Use of ketamine has also been reported in a patient susceptible to malignant hyperthermia who had a large anterior mediastinal mass,<sup>213</sup> when spontaneous ventilation was required and inhalation anesthetics were contraindicated.<sup>213-215</sup>

Ketamine combined with diazepam or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease (Ch. 49). The combination of a benzodiazepine<sup>208</sup> or of a benzodiazepine plus sufentanil<sup>216</sup> with ketamine attenuates or eliminates the unwanted tachycardia and hypertension as well as postoperative psychologic derangements. With this technique, there are minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. No comparison of this technique with a continuous benzodiazepine-opioid technique has been made.

Low-dose ketamine as an analgesic has been used following thoracic surgery,<sup>217</sup> in which its lack of respiratory depressant properties and its equivalent pain relief as compared with meperidine make it a third choice when one wishes to avoid narcotics because of their respiratory depressant effects and when there is reason also to avoid nonsteroidal agents such as ketorolac. Additional analgesic use can be considered in asthmatic patients.<sup>218</sup>

## Sedation

Ketamine is particularly suited for sedation of the pediatric patient undergoing procedures away from the operat-

ing room. Pediatric patients have fewer adverse emergence reactions<sup>156</sup> than adults, and this feature makes the use of ketamine in pediatrics more versatile. Ketamine is used for sedation and/or general anesthesia for the following pediatric procedures: cardiac catheterization, radiation therapy, radiologic studies, dressing changes,<sup>219</sup> and dental work.<sup>136</sup> Caution is advised in use of ketamine for cardiac catheterization in pediatric patients with elevated pulmonary vascular resistance, because this can be increased by ketamine.<sup>220</sup>

Ketamine is often used repeatedly in the same patient. Unfortunately, the literature does not provide information on how many times ketamine anesthesia can safely be administered to one individual, whether frequency of administration is related to tolerance following multiple administrations, and whether or not there are detrimental effects of frequent/long-term use.

Usually, a subanesthetic dose ( $\leq 1.0$  mg/kg IV) is used for dressing changes; this dose gives adequate operating conditions but a rapid return to normal function, including the resumption of eating, which is important in maintaining proper nutrition in burn patients.<sup>118,119</sup> Often, ketamine is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation.

In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia. In this setting, ketamine can be used prior to the application of painful blocks,<sup>221</sup> but more commonly it is used for sedation or supplemental anesthesia during long or uncomfortable procedures. When used for supplementation of regional anesthesia, ketamine (0.5 mg/kg IV) combined with diazepam (0.15 mg/kg IV) is better accepted by patients and is not associated with greater side effects as compared with unsedated patients.<sup>222</sup> Ketamine in low doses can also be combined with nitrous oxide and propofol for the supplementation of conduction or local anesthesia. These techniques of ketamine administration are used in outpatient and inpatient settings, and although patients are comfortable and cooperative, dreams and other unpleasant emergence reactions can occur.<sup>118</sup> In outpatients, premedication with midazolam, concurrent propofol infusion, and intermittent ketamine (for analgesia) in doses less than 3 mg/kg are recommended.<sup>223</sup>

### Doses and Routes of Administration

Ketamine can be administered intravenously, intramuscularly, orally, nasally, and rectally.<sup>224</sup> Most clinical use involves the intravenous and intramuscular routes, by which the drug rapidly achieves therapeutic levels. The dose depends on the desired therapeutic effect and on the route of administration. Table 9-7 contains general recommended doses for the intravenous and intramuscular administration of ketamine for various therapeutic goals.<sup>118</sup> Because of their side effects, most anesthetic drugs require that dosage be reduced in elderly and seriously ill patients; such a recommendation probably is prudent with ketamine, although data supporting this are not available. Patients who have been

**Table 9-7. Uses and Doses of Ketamine**

Induction of general anesthesia <sup>a</sup>		
0.5–2 mg/kg IV		
4–6 mg/kg IM		
Maintenance of general anesthesia		
0.5–1 mg/kg IV	prn	with N <sub>2</sub> O 50% in O <sub>2</sub>
15–45 $\mu$ g/kg/min IV		with N <sub>2</sub> O 50–70% in O <sub>2</sub>
30–90 $\mu$ g/kg/min IV		without N <sub>2</sub> O
Sedation and analgesia		
0.2–0.8 mg/kg IV		over 2–3 min
2–4 mg/kg IM		

<sup>a</sup>Lower doses are used if adjuvant drugs such as midazolam or thiopental are also given.

critically ill for a prolonged period may have exhausted their catecholamine stores and may exhibit the circulatory depressant effects of ketamine.<sup>225</sup> Ketamine can be given epidurally and intrathecally for operative and postoperative pain control. The dose used in cancer pain is 1.0 mg (with benzethorium chloride as preservative and 0.05 mg morphine) twice daily, with additional morphine as required.<sup>226</sup> The peak action after intravenous administration occurs in 30 to 60 seconds. Onset occurs in about 5 minutes, with peak effect in about 20 minutes after intramuscular administration. An oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes. The continuous infusion of intravenous ketamine with or without concomitant drugs is a satisfactory method to keep blood levels in the therapeutic range. The use of concomitant drugs such as benzodiazepines permits a lower dose requirement for ketamine while enhancing recovery by reducing emergence reactions. The interaction of ketamine with propofol is strictly additive and not synergistic; thus, the dose of each would be reduced by about half when used together for induction.<sup>227</sup>

For sedation, ketamine may be given intramuscularly if the patient wishes to avoid awareness of intravenous catheter placement. It has also been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87 percent of children within 45 minutes in another study.<sup>228,229</sup> In at least one case, deep sleep was produced by a supposedly sedative oral dose.<sup>230</sup>

### Side Effects and Contraindications

The common psychologic emergence reactions are discussed earlier. Contraindications to ketamine relate to specific pharmacologic actions and patient diseases. Patients with increased ICP and with intracranial mass lesions should not receive ketamine because it can increase ICP and has been reported to cause apnea on this basis.<sup>231</sup> The S-(+) enantiomer also increases CBF and is probably similarly contraindicated.<sup>232</sup> Ketamine is also contraindicated in patients with an open eye injury or other ophthalmologic disorder, in whom a ketamine-induced increase in intraocular pressure would be detrimental (Ch. 63). Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it is contraindicated as the sole anesthetic in patients with ischemic heart disease.<sup>181</sup> Likewise, it is unwise to give

ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure. Psychiatric disease such as schizophrenia or a history of adverse reaction to ketamine or one of its congeners also constitutes a contraindication.<sup>119</sup> One should also consider carefully using ketamine when there is a possibility of postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma) and a ketamine-induced psychomimetic effect would cloud the differential diagnosis.

Other side effects include potentiation of nondepolarizing neuromuscular blockade by an undefined mechanism.<sup>233, 234</sup> Finally, because ketamine's preservative, chlorobutanol, has been demonstrated to be neurotoxic, subarachnoid administration is contraindicated.<sup>235</sup> It is probably unwise to administer the drug epidurally for this reason.

## ETOMIDATE

### History

Etomidate (Amidate, Hypnomidate) was synthesized<sup>236</sup> in 1964 and was introduced into clinical practice<sup>237</sup> in 1972. Its properties include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery following either a single dose or a continuous infusion. In animals, etomidate also provides a wider margin of safety (median effective dose/median lethal dose [ED<sub>50</sub>/LD<sub>50</sub>]) than thiopental (26.4 versus 4.6).<sup>238</sup> These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically ill patients. Anesthesiologists' enthusiasm for etomidate, however, was tempered by reports that the drug can cause temporary inhibition of steroid synthesis after both single doses and infusions.<sup>239-241</sup> This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a relatively high incidence of nausea and vomiting) led to several editorials<sup>242-244</sup> questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly following those editorials, but it has been expanding over the past several years owing to a rediscovery of etomidate's beneficial physiologic profile combined with a lack of any new reports describing clinically significant adrenocortical suppression.

### Physicochemical Characteristics

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate).<sup>238</sup> Its chemical structure is illustrated in Figure 9-14. Etomidate exists as two isomers, but only the (+) isomer is active as a hypnotic.<sup>245</sup> Its molecular weight is 342.36 kd.<sup>245</sup> Etomidate is water insoluble and is unstable in a neutral solution. It therefore has been formulated with several solvents.<sup>246</sup> Currently, it is supplied as a 2-mg/mL propylene glycol (35% by volume) solution with a pH of 6.9 and an osmolality of 4,640 mOsm/L. Unlike sodium thiopental, when etomidate is mixed with other commonly used anesthetic agents such as neuromuscular blockers, vasoactive drugs, or lidocaine, it does not cause precipitation.<sup>247</sup>

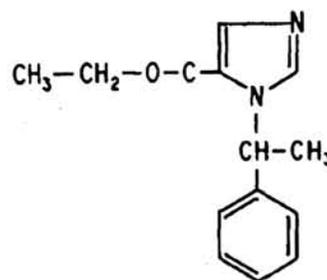


Figure 9-14. The structure of etomidate, an imidazole derivative.

### Metabolism, Induction, and Maintenance of Anesthesia

Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) or by *N*-dealkylation.<sup>245</sup> The main metabolite is inactive.<sup>247</sup> Only 2 percent of the drug is excreted unchanged, the rest being excreted as metabolites by the kidney (85%) and bile (13%).<sup>247</sup>

Etomidate has been used for both induction and maintenance of anesthesia (Table 9-8). The induction dose of etomidate varies from 0.2 to 0.6 mg/kg,<sup>237, 246, 248, 249</sup> and it is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate.<sup>237</sup> Onset of anesthesia following a routine induction dose of 0.3 mg/kg etomidate is rapid (one arm-brain circulation) and is equivalent to that obtained with an induction dose of thiopental or methohexital.<sup>237, 246, 250</sup> The duration of anesthesia following a single induction dose is linearly related to the dose—each 0.1 mg/kg administered provides about 100 seconds of sleep.<sup>251</sup> Repeat doses of etomidate, either by bolus or infusion, prolong the duration of hypnosis. Recovery following etomidate is still usually rapid.<sup>237, 248, 252-256</sup> The addition of small doses of fentanyl with etomidate for short surgical procedures reduces the required dose of etomidate and allows earlier awakening. In children, induction by rectal administration of etomidate has been obtained with 6.5 mg/kg. Hypnosis occurs in 4 minutes. At this dose, hemodynamics are unaltered, and recovery is still rapid.<sup>257</sup>

Various infusion schemes have been devised to utilize etomidate as a maintenance agent for the hypnotic component of anesthesia. Most regimens aim to achieve a plasma level of 300 to 500 ng/mL, which is the concentration necessary for hypnosis.<sup>258-261</sup> Both two- and three-stage infusions have been successfully used. These consist of an initial rapid infusion of 100 µg/kg/min for 10 minutes followed by 10 µg/kg/min thereafter,<sup>261</sup> or of 100 µg/kg/min for 3 minutes, 20 µg/kg/min for 27 minutes, and 10 µg/kg/min there-

Table 9-8. Uses and Doses of Etomidate

Induction of general anesthesia	0.2-0.6 mg/kg IV
Maintenance of general anesthesia	10 µg/kg/min IV with N <sub>2</sub> O and an opiate
Sedation and analgesia	5-5 µg/kg/min IV only for short periods of sedation because of inhibition of corticosteroid synthesis

**s.21(1)(a)**  
**s.21(1)(b)**



**Daniel Galarneau**

2004-10-07 01:31 PM

To: Theresa Schopf/HC-SC/GC/CA@HWC  
cc: Suzanne Trottier/HC-SC/GC/CA@HWC  
Subject: Re: Ketamine

Daniel  
Theresa Schopf



**Theresa Schopf**

10/07/2004 11:37 AM

To: Daniel Galarneau/HC-SC/GC/CA@HWC  
cc: Suzanne Trottier/HC-SC/GC/CA@HWC  
Subject: Ketamine

Hi Daniel,

I spoke to Mark K quickly about this and he is looking into it. Ketamine may be a distant derivative of phencyclidine. You may want to hold on to the documents for the time being. (not send to VDD and TPD yet)

Theresa

----- Forwarded by Theresa Schopf/HC-SC/GC/CA on 2004-10-07 11:34 AM -----



**Theresa Schopf**

2004-10-05 03:34 PM

To: status@hc-sc.gc.ca  
cc: Shereen Khan/HC-SC/GC/CA@HWC, Cynthia Sunstrum/HC-SC/GC/CA, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine

Hi Mark,

A vet from Toronto told me today that ketamine is a derivative of phencyclidine and therefore should be included under Schedule I Item 14 of the CDSA.

I found one website [www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm)

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(*o*-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

Please let me know if this is reasonable as it would impact our scheduling of ketamine.

Thanks  
Theresa

**Franca Beraldin**  
2004-10-25 04:37 PM

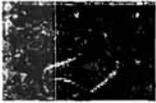
To: Mark Kozlowski/HC-SC/GC/CA@HWC  
cc: Richard Laing/HC-SC/GC/CA@HWC  
Subject: Réf. : Re: Réf. : Ketamine, a derivative of Phencyclidine 

Further to our discussion, Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. In CDSA, the definition of "analog means a substance that, in relation to a controlled substance, has a substantially similar chemical structure;". The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine.

This is our comprehension

Thank you for your attention!

Franca J Beraldin  
450-646-1353 poste 211  
Mark Kozlowski



**Mark Kozlowski**  
2004-10-20 13:54

Pour : Franca Beraldin/HC-SC/GC/CA@HWC  
cc : Richard Laing/HC-SC/GC/CA@HWC  
Objet : Re: Réf. : Ketamine, a derivative of Phencyclidine 

Franca,

I've just faxed you 2 articles, which to me seem to state otherwise. Perhaps, I am misunderstanding them. Could you please confirm. Thanks.

Mark Kozlowski  
Evaluation and Authorization Officer /  
Agent d'évaluation et autorisations  
Office of Controlled Substances /  
Bureau des substances contrôlées  
Health Canada / Santé Canada  
Telephone / Téléphone: (613) 957-1063  
Facsimile / Télécopieur: (613) 952-2196

**s.21(1)(a)**

Franca Beraldin

**Franca Beraldin**  
20/10/04 01:03 PM

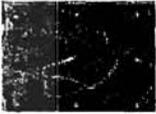
To: Mark Kozlowski/HC-SC/GC/CA@HWC  
cc: Richard Laing/HC-SC/GC/CA@HWC  
Subject: Réf. : Ketamine, a derivative of Phencyclidine 

Yes, Ketamine has a similar structure of Phencyclidine but it is not a derivative of Phencyclidine.

You could send me the articles. If you need more informations, please don't hesitate to contact us.

Franca J Beraldin

450-646-1353 poste 211  
Mark Kozlowski



**Mark Kozlowski**  
2004-10-19 13:54

Pour : Richard Laing/HC-SC/GC/CA@HWC, Franca Beraldin/HC-SC/GC/CA@HWC  
cc :  
Objet : Ketamine, a derivative of Phencyclidine

Good Afternoon,

I'm looking for some confirmation on Ketamine being a derivative of Phencyclidine. I have found journal articles stating this and I can fax them to you if required. Since, we are in the process of scheduling Ketamine, this will effect where it is placed in the CDSA. If you have any questions, please let me know. Thank you.

Mark Kozlowski  
Evaluation and Authorization Officer /  
Agent d'évaluation et autorisations  
Office of Controlled Substances /  
Bureau des substances contrôlées  
Health Canada / Santé Canada  
Telephone / Téléphone: (613) 957-1063  
Facsimile / Télécopieur: (613) 952-2196

**s.21(1)(a)**

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 19/10/04 01:51 PM -----



**Cynthia Sunstrum**  
14/10/04 05:47 PM

To: Mark Kozlowski/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA@HWC, Jaspinder Koma/HC-SC/GC/CA@HWC, Shereen Khan/HC-SC/GC/CA@HWC, Theresa Schopf/HC-SC/GC/CA@HWC, Carole Bouchard  
Subject: Re: Ketamine

Mark:

Thank you for your research. Your finding suggests that ketamine has always been captured under Schedule I Item 14 of the CDSA and therefore would not need to be "scheduled" per se. In view of the foregoing, please verify your findings with other chemists (in DAS?) and process this in the same way you would any formal ruling on status (i.e. through Carole's office).

In the interim, we will do some further research into why ketamine was included in Schedule F of the FDA if indeed it was already a substance controlled under the CDSA or former NCA (Daniel - please coordinate with Shereen).

Cynthia

Status

**Status**  
Sent by: Mark Kozlowski  
2004-10-14 03:12 PM  
To: Theresa Schopf/HC-SC/GC/CA@HWC  
cc: Cynthia Sunstrum/HC-SC/GC/CA@HWC, Shereen Khan/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Daniel Galarneau/HC-SC/GC/CA@HWC  
Subject: Re: Ketamine 

Theresa,

I've done the research and I have 2 articles, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine. This being said, what should be done for requests received for Ketamine until it is scheduled. Thanks.

MK

Theresa Schopf



**Theresa Schopf**  
05/10/04 03:34 PM  
To: status@hc-sc.gc.ca  
cc: Shereen Khan/HC-SC/GC/CA@HWC, Cynthia Sunstrum/HC-SC/GC/CA, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine

Hi Mark,

A vet from Toronto told me today that ketamine is a derivative of phencyclidine and therefore should be included under Schedule I Item 14 of the CDSA.

I found one website [www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm)

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (+)-2-(o-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

Please let me know if this is reasonable as it would impact our scheduling of ketamine.

Thanks  
Theresa



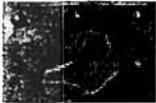
**Shereen Khan**  
2004-11-02 11:02 AM

To: Mark Kozlowski/HC-SC/GC/CA@HWC  
CC:  
Subject: Re: Ketamine

Thanks Mark.

sk

Mark Kozlowski



**Mark Kozlowski**  
2004-11-02 11:00 AM

To: Shereen Khan/HC-SC/GC/CA@HWC  
CC:  
Subject: Re: Ketamine

Shereen,

I'm still waiting for a response, from one more chemist, Richard Laing, on this issue. I haven't received anything, but I have received the following from Franca Beradlin:

"Further to our discussion, Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. In CDSA, the definition of "analog means a substance that, in relation to a controlled substance, has a substantially similar chemical structure;". The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine.

This is our comprehension

Thank you for your attention!

Franca J Beraldin  
450-646-1353 poste 211"

Hope this helps. If you have any more questions, please let me know.

MK

Shereen Khan



**Shereen Khan**  
02/11/04 09:44 AM

To: Mark Kozlowski/HC-SC/GC/CA@HWC  
CC:  
Subject: Re: Ketamine



Hi Mark, I'd like to know, what is the current the status of the "status decision" regarding the ketamine issue?

If you could get back to me before noon today that would be great because there is a meeting this afternoon with HPFB and Cynthia would like to bring this issue up with them.

Thanks

Shereen Khan

Regulatory Officer  
Policy and Regulatory Affairs Division  
Office of Controlled Substances  
Drug Strategy and Controlled Substances Programme  
HECS Branch, Health Canada  
Phone: (613) 946-0121  
Fax: (613) 946-4224

----- Forwarded by Shereen Khan/HC-SC/GC/CA on 2004-11-02 09:40 AM -----

**Status**  
Sent by: Mark Kozlowski  
2004-10-14 03:12 PM  
To: Theresa Schopf/HC-SC/GC/CA@HWC  
cc: Cynthia Sunstrum/HC-SC/GC/CA@HWC, Shereen Khan/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Daniel Galarnreau/HC-SC/GC/CA@HWC  
Subject: Re: Ketamine 

Theresa,

I've done the research and I have 2 articles, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine. This being said, what should be done for requests received for Ketamine until it is scheduled. Thanks.

MK

Theresa Schopf

 **Theresa Schopf**  
05/10/04 03:34 PM

To: status@hc-sc.gc.ca  
cc: Shereen Khan/HC-SC/GC/CA@HWC, Cynthia Sunstrum/HC-SC/GC/CA, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine

Hi Mark,

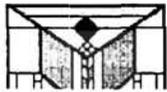
A vet from Toronto told me today that ketamine is a derivative of phencyclidine and therefore should be included under Schedule I Item 14 of the CDSA.

I found one website [www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm)

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-( $\sigma$ -Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

Please let me know if this is reasonable as it would impact our scheduling of ketamine.

Thanks  
Theresa



**Daniel Galarneau**

2004-11-08 11:07 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC  
CC:  
Subject: Re: Ketamine: Schedule Status

What is December 13, 1995? (at least that is how you respond in Jeopardy!).

Cynthia Sunstrum



**Cynthia Sunstrum**

11/05/2004 02:58 PM

To: Daniel Galarneau/HC-SC/GC/CA  
CC:  
Subject: Ketamine: Schedule Status

Daniel:

Has Shereen made any progress in tracking down information on when ketamine was added to Schedule F?

Cynthia

----- Forwarded by Cynthia Sunstrum/HC-SC/GC/CA on 2004-11-05 02:56 PM -----



**Cynthia Sunstrum**

2004-11-05 02:56 PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Ian Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

#### **Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(o-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia



**Cynthia Sunstrum**

2004-11-09 10:41 AM

To: Eric Ormsby/HC-SC/GC/CA@HWC  
cc: Mark Kozlowski/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Theresa Schopf, Daniel Galarneau/HC-SC/GC/CA, Shereen\_Khan  
Subject: Re: Ketamine: Schedule Status

Excellent Eric...thanks for quick response.

Eric Ormsby

**Eric Ormsby**

2004-11-09 10:20 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC  
cc:  
Subject: Ketamine: Schedule Status

Amirthini does our nomenclature and structure stuff for schedule F ... hope this helps  
----- Forwarded by Eric Ormsby/HC-SC/GC/CA on 11/09/2004 10:19 AM -----

**Amirthini Rajkumar**

11/09/2004 10:14 AM

To: Eric Ormsby/HC-SC/GC/CA@HWC  
cc:  
Subject: Ketamine: Schedule Status

Hello Eric,

Regarding the request you sent I did some research on Ketamine and Phencyclidine.

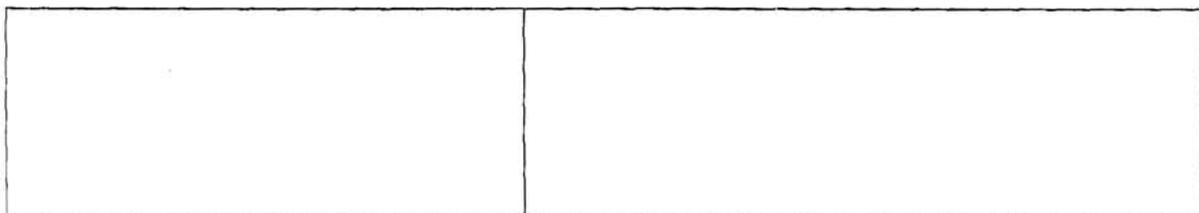
Ketamine ( (as ketamine hydrochloride) ) is a non-barbiturate anesthetic approved for use in humans and animals. It is currently listed in Schedule F to the Food and Drug Regulations as *Ketamine and its salts*

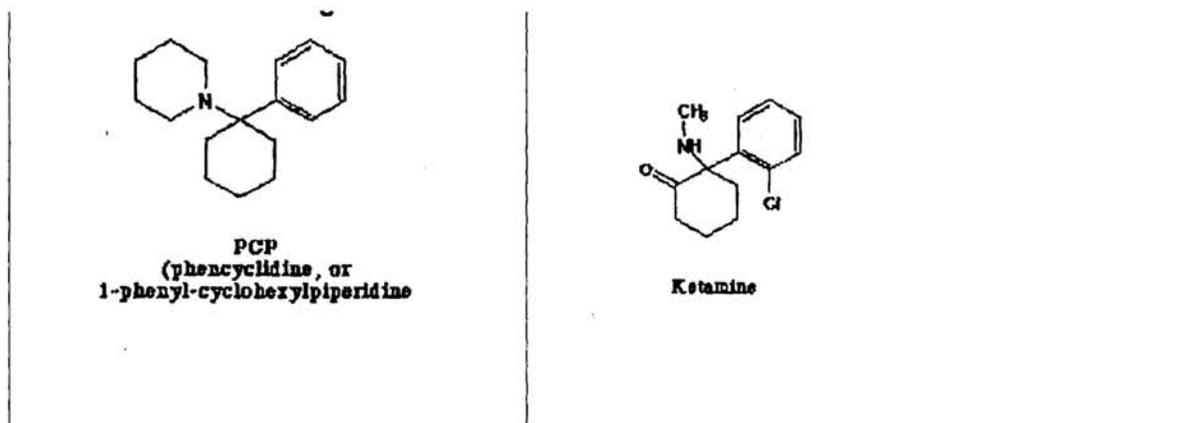
Chemical name of Ketamine hydrochloride: (±)-2-(o-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

Phencyclidine is listed as a controlled substance in CDSA. Chemical name of Phencyclidine is 1-phenyl-cyclohexylpiperidine (PCP)

Phencyclidine was formerly used as a surgical anesthetic in both humans and veterinary practice, but it is not currently manufactured, and has been placed under Schedule II of the Controlled Substance Act (CSA) in the US. Ketamine is listed in Schedule III of the CSA.  
e.g: [http://en.wikipedia.org/wiki/Controlled\\_Substances\\_Act](http://en.wikipedia.org/wiki/Controlled_Substances_Act)

Structures of both drugs are given below:





Derivatives are defined as: A compound that can be imagined to arise from a parent compound by replacement of one atom with another atom or group of atoms (<http://www.chemistry-dictionary.com>). e.g: Esters are derivatives of their corresponding acids Hence Ketamine is not considered as a derivative of Phencyclidine.

Ketamine is pharmacologically similar to Phencyclidine. Based on the structures given above, both ketamine and Phencyclidine are structurally related. The following article indicates Ketamine as an analog of Phencyclidine. Several other PCP analogs are also listed in this article.  
[http://www.rhodium.ws/chemistry/pcp/pcp\\_index.html](http://www.rhodium.ws/chemistry/pcp/pcp_index.html)

However, as per the definition stated in US Control Substance Act, Ketamine is not considered as an analogue of Phencyclidine. Currently, there are only three PCP analogs listed in Schedule I of CSA (Thiophene analog of Phencyclidine, Ethylamine analog of Phencyclidine and Pyrrolidine analog of Phencyclidine). Ketamine is listed in Schedule III of CSA

According to US, Control Substance Act, the term "controlled substance analogue" means a substance -

- (i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
- (ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or
- (iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.

Such [REDACTED] -

- (i) a controlled substance;
- (ii) [REDACTED];

- (iii) *with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 355 of this title to the extent conduct with respect to such substance is pursuant to such exemption; or*
- (iv) *any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance.*

**Conclusion:** Based on the above information, Ketamine is not considered as a derivative or an analog of Phencyclidine.

Regards,  
Amirthini



**Cynthia Sunstrum**

2004-11-18 10:50 AM

To: Ian Alexander/HC-SC/GC/CA@HWC  
cc: Arnost Vilim/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Daniel Galarneau/HC-SC/GC/CA@HWC, Denis Girard/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Hieu Vu/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC, Shereen\_Khan, Theresa Schopf/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

Thanks Ian, Very helpful. We will be in touch with our final determination and should this have any impact on our proposed regulatory submission.

Cynthia

Ian Alexander

**s.21(1)(a)**  
**s.21(1)(b)**

**Ian Alexander**

2004-11-18 08:29 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC  
cc: Ben Lobo/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Daniel Galarneau/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Hieu Vu/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC, Shereen\_Khan, Theresa Schopf/HC-SC/GC/CA@HWC, Denis Girard/HC-SC/GC/CA@HWC, Arnost Vilim/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

Hi Cynthia,

Ian

Phencyclidine, [1-(1-phenylcyclohexyl)piperidine]] and Ketamine, [2-(2-chlorophenyl)-2-(methylamino) cyclohexanone] are chemically quite different in structure.

In my opinion, ketamine is not a derivative of phencyclidine. Phencyclidine is a tertiary amine while ketamine is a secondary amine with a ketone functional group derived from cyclohexanone. It is not substantially similar in chemical structure to be considered as an analogue of phencyclidine as defined in the CDSA. The name Ketamine is probably derived from the fact that it can be considered as a keto-amine (or ketamine in short) based on the chemical functional groups it contains.

Although not strictly right from a chemical structure point of view Ketamine is often referred to in a pharmacological context as a "derivative" of phencyclidine. From a chemical structure point of view, I agree that ketamine is not a derivative of phencyclidine but rather an analogue since in my view there is substantial similarity in structure with phencyclidine.

Cynthia Sunstrum



**Cynthia Sunstrum**

2004-11-05 02:56  
PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Ian Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

**Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(o-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

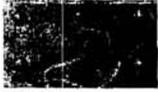
We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia



**Mark Kozlowski**  
2004-11-22 01:14 PM

To: Richard Laing/HC-SC/GC/CA@HWC  
cc:  
Subject: Ketamine: Schedule Status

Richard,

I will be forwarding you some email I received regarding Ketamine, as background for the status decision that is coming through. Thanks.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 22/11/04 01:11 PM -----



**Cynthia Sunstrum**  
05/11/04 02:56 PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Ian Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galarnau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

**Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(*o*-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

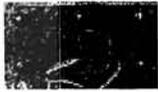
We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia



**Mark Kozlowski**  
2004-12-03 09:23 AM

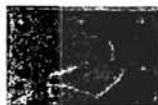
To: Richard Laing/HC-SC/GC/CA@HWC  
cc:  
Subject: URGENT - Status decision of Ketamine

Richard,

This one is becoming more urgent, as they want to move on the scheduling. Thanks.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 03/12/04 09:20 AM -----



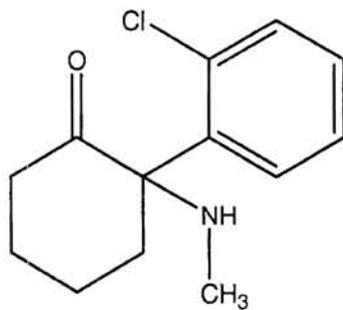
**Mark Kozlowski**  
22/11/04 01:28 PM

To: Richard Laing/HC-SC/GC/CA  
cc:  
Subject: Status decision of Ketamine

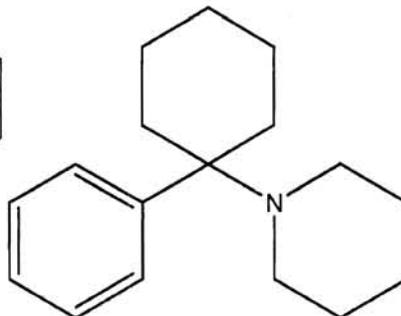
Good Afternoon Richard,

We received the attached status request on the following substance. This substance should be considered controlled under the CDSA because, the substance is an analogue of Phencyclidine, which is Item 14 in Schedule I of the CDSA. I have the documents that states this if you require them. I have also forwarded you different emails on the topic. The substance is:

Ketamine  
2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone



Ketamine



Phencyclidine

Do you agree that this substance is controlled under the CDSA? Thank you.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 22/11/04 01:18 PM -----



**Cynthia Sunstrum**  
18/11/04 11:07 AM

To: Richard Laing/HC-SC/GC/CA@HWC  
cc: Theresa Schopf/HC-SC/GC/CA, Jaspinder Komal/HC-SC/GC/CA@HWC, Daniel Galarneau/HC-SC/GC/CA@HWC, Margaret Fuller/HC-SC/GC/CA, Shereen Khan/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC, Louis Proulx/HC-SC/GC/CA@HWC  
Subject: Re: Ketamine: Schedule Status

Richard:

It was great to see you again at the Meth Summit.

Further to our very brief discussion concerning ketamine, attached is the latest input we have received from the Veterinary Drugs Directorate. I don't know if Mark has been sending you the other comments we received in response to my e-mail of November 5, 2004 (if not - Mark please forward to Richard and any other DAS personnel who have had input thus far).

Your comments and others indicate that the determination is leaning toward classification of ketamine as an analogue of phencyclidine but not a derivative. If an analogue, as per the definition in the CDSA, it would still be captured in Schedule I. As such, it remains unclear how it ended up in Schedule F of the FDA when scheduled in December 1995.

When you spoke, you indicated agreement that ketamine should be explicitly listed in the CDSA Schedules in any event. The issue will be in which schedule to list it. Our proposal before the analogue business unfolded was CDSA Schedule III and schedule to Part G of the FDR (the draft RIAS is attached FYI - will need to be revised to reflect latest developments). This would implement same offences, controls, penalties as per other club drugs including ecstasy, GHB and crystal meth. In view of comments made about re-scheduling of meth, do you have any comments about our proposed scheduling for ketamine?

As communicated to Mark, I would like to have a status decision ASAP but before the end of this month so that we can proceed with the scheduling (or re-scheduling?) of ketamine under the CDSA. Urgency further reinforced by Meth Summit data (including yours!).

Thanks

Cynthia



RIAS-draft-E-2.wpd

**s.21(1)(a)**  
**s.21(1)(b)**

----- Forwarded by Cynthia Sunstrum/HC-SC/GC/CA on 2004-11-18 09:49 AM -----

**Ian Alexander**

2004-11-18 08:29 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC

cc: Ben Lobo/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC,  
Daniel Galarneau/HC-SC/GC/CA@HWC, Eric  
Ormsby/HC-SC/GC/CA@HWC, Hieu Vu/HC-SC/GC/CA@HWC,  
Jaspinder Komal/HC-SC/GC/CA@HWC, Mark  
Kozlowski/HC-SC/GC/CA@HWC, Shereen\_Khan, Theresa  
Schopf/HC-SC/GC/CA@HWC, Denis Girard/HC-SC/GC/CA@HWC,  
Arnost Vilim/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

Hi Cynthia,

Ian

Phencyclidine, [1-(1-phenylcyclohexyl)piperidine] and Ketamine, [2-(2-chlorophenyl)-2-(methylamino)cyclohexanone] are chemically quite different in structure.

In my opinion, ketamine is not a derivative of phencyclidine. Phencyclidine is a tertiary amine while ketamine is a secondary amine with a ketone functional group derived from cyclohexanone. It is not substantially similar in chemical structure to be considered as an analogue of phencyclidine as defined in the CDSA. The name Ketamine is probably derived from the fact that it can be considered as a keto-amine (or ketamine in short) based on the chemical functional groups it contains.

Although not strictly right from a chemical structure point of view Ketamine is often referred to in a pharmacological context as a "derivative" of phencyclidine. From a chemical structure point of view, I agree that ketamine is not a derivative of phencyclidine but rather an analogue since in my view there is substantial similarity in structure with phencyclidine.

Cynthia Sunstrum



Cynthia Sunstrum  
2004-11-05 02:56 PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Ian Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galameau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

**Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-( $\alpha$ -Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia

**REGULATORY IMPACT ANALYSIS STATEMENT**  
**RÉSUMÉ DE L'ÉTUDE D'IMPACT DE LA RÉGLEMENTATION**

(This statement is not part of the Regulation.)

(Ce résumé ne fait pas partie du règlement.)

**Department or Agency**

**Ministère ou organisme**

Health

Santé

**Title of Proposal**

**Titre du projet**

Addition of the substance Ketamine to  
Schedule III of the *Controlled Drugs and  
Substances Act*, and Part I of the Schedule to  
Part G of the *Food and Drug Regulations*

**Statutory Authority**

*Controlled Drugs and Substances Act*, c. 19,  
subsection 55(1)

**Fondement législatif**

*Loi réglementant certaines drogues et autres  
substances*, ch. 19, paragraphe 55(1)

**Submitted for Consideration for:**

Pre-publication (75-day comment period)

**Soumis en vue de:**

Publication préalable (période de  
commentaires de 75 jours)

---

Minister of Health / Ministre de la Santé

**Draft - 2004-08-23**

## **REGULATORY IMPACT ANALYSIS STATEMENT**

(This statement is not part of the regulation)

### **Description**

The purpose of this regulatory initiative is to add the substance ketamine hydrochloride (ketamine) to Schedule III of the *Controlled Drugs and Substances Act* (CDSA), and to Part I of the schedule to Part G of the *Food and Drug Regulations* (FDR), which will provide a higher level of control over the substance than currently exists.

Ketamine is a non-barbiturate anaesthetic used in humans and animals. It is currently listed in Schedule F, Part I of the FDR, which means that it requires a prescription for human and veterinary use. In Canada ketamine is commonly used as an anaesthetic for animals.

Concern expressed by health professionals and law enforcement has resulted in requests to Health Canada for action to be taken to prevent the theft and illicit use of this substance.

Ketamine has become popular as a "party drug" at raves due to its dissociative effects; it creates the illusion of an "out of body experience". Ketamine is also used as a "date rape" drug. Ketamine seizures by police have been increasing in recent years. The main source of illicit ketamine is through the diversion of legitimate pharmaceutical products. For these reasons additional controls over ketamine in Canada are warranted.

To address this issue we propose to control ketamine within the framework of the CDSA and its related regulations. The CDSA provides a legislative framework for the control of substances that can alter mental processes and may produce harm to the health of an individual or to society when diverted or misused. Except as authorized under its regulations, activities such as possession for trafficking, trafficking, importation, exportation, possession for exportation, and production of controlled substances are prohibited under the CDSA.

The substances controlled under the CDSA are grouped into eight schedules (Schedules I to VIII). Schedules I to V list the controlled substances, Schedule VI lists precursor chemicals, and Schedules VII and VIII refer exclusively to cannabis and cannabis resin.

Each schedule is associated with particular offences, prohibitions, and punishments described in Part I of the Act. Schedules I, II and III are subject to the same offences with varying punishments. These offences include: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The offences for Schedule IV are similar to those of Schedules I, II, and III except that there is no offence for simple possession. The offences for Schedules V and VI include: importation, exportation and possession for the purpose of exportation.

Draft - 2004-08-23

- 2 -

Part G of the FDR derives its legislative authority from the CDSA, and governs the activities of producers, distributors, importers, exporters, health care professionals, and hospitals related to controlled drugs (e.g., stimulants, sedatives, and androgenic anabolic steroids). Part G is divided into Parts I, II and III. Drugs listed in Part I have a higher abuse liability and increased level of control within the regulations compared to drugs listed in Parts II and III.

Canada is a signatory to United Nations drug control conventions, and as such has an obligation to meet international requirements. Although ketamine is not currently listed in any of the United Nations drug control conventions, a number of countries have chosen to impose strict controls over it, including the United States, Australia, Belgium, Italy, France, Greece, Luxembourg, and China.

### **Alternatives**

To determine in which schedule to the CDSA a substance should be listed, Health Canada considers several factors, including: international requirements, the dependence potential and likelihood of abuse of the substance, the extent of its abuse in Canada, the danger it represents to the safety of the public, and the usefulness of the substance as a therapeutic agent.

#### ***Options for CDSA Schedule***

Listing of ketamine under Schedule III of the CDSA was the only option considered as it would be consistent with Canada's treatment of two other drugs subject to abuse and used in drug facilitated sexual assault: gamma-hydroxybutyrate (GHB), and flunitrazepam. Schedule III of the CDSA was also considered appropriate because it allows for a simple possession charge to be laid. In the case of ketamine, a possession charge could serve as a deterrent to non-medical use, and act as an added tool for law enforcement. Controlled substances listed in Schedule III of the CDSA that have some therapeutic use are commonly regulated either under Part G of the FDR or the *Benzodiazepines and Other Targeted Substances Regulations (Targeted Substances Regulations)* with the former having more stringent controls over distribution.

#### ***Options for Regulatory Control***

Substances listed in Schedule III of the CDSA are generally regulated under one of three sets of regulations under the CDSA:

- Part I to Part G of the FDR
- Part J of the FDR
- *Targeted Substances Regulations*

Each of these regulatory instruments carries a different level of control, which impacts licensed dealers, pharmacists, practitioners, and hospitals.

Substances listed in Part I to Part G of the FDR have an increased risk of abuse liability compared to substances listed in Parts II and III to Part G of the FDR. Currently the majority of

Draft - 2004-08-23

- 3 -

substances in Part I are found in Schedule III of the CDSA. As previously mentioned, GHB is a substance abused in a manner similar to ketamine, and is regulated under Part I. It was originally developed as an anaesthetic, and like ketamine, had gained popularity as a date rape and party drug.

Part J of the FDR regulates controlled substances that have no recognized medical use; substances listed in the Schedule to Part J of the FDR are defined as "restricted drugs", and include such substances as LSD and mescaline. Ketamine is a marketed drug with recognized medical use, therefore Part J is not a viable option for control.

The majority of substances under the *Targeted Substances Regulations* are classified as benzodiazepines, and have legitimate therapeutic uses. They do, however, possess a risk of being abused. Presently all substances within the *Targeted Substances Regulations* can be found in Schedule IV to the CDSA except for one, flunitrazepam, which was placed in Schedule III of the CDSA as a result of the danger associated with its use as a date rape drug. As previously mentioned, Schedule III of the CDSA allows for a possession charge to be laid.

Since ketamine is currently used by veterinarians as an anaesthetic for animals, Part J of the FDR was not considered to be a viable option for regulatory control. However, because ketamine poses an increased risk of abuse, a characteristic shared by many of the substances listed in the Part I of the Schedule to Part G of the FDR, regulation of ketamine under this part would be consistent with the existing regulatory framework, and would provide adequate protection for the Canadian public.

### **Benefits and Costs**

Benefits and costs involved with the control of ketamine will derive increased security requirements such as special storage, and record keeping practices. This will affect practitioners, pharmacists, hospitals, pharmaceutical industry, law enforcement, and the Canadian public as follows:

#### Practitioners, Pharmacists, and Hospitals

In the case of products containing ketamine, the three mentioned groups will be affected in a similar manner. They will face increased record keeping requirements, and will be required to retain information regarding products containing ketamine such as prescriptions received in pharmacies, or information regarding the use of ketamine by practitioners. They will also be required to take additional steps to protect products containing ketamine in their possession from loss or theft, and to report to the Minister of Health within 10 days of the discovery of a loss or theft.

The cost to these groups should be minimal as most of them will have the required security setting in place, as well as experience in handling the various record keeping requirements for other controlled substances with which they deal. The increased security will aid in protecting

**Draft - 2004-08-23**

- 4 -

these groups from future potential loss and theft. Regulation of ketamine within the framework of the CDSA will not create an obstacle for its legitimate use.

#### Pharmaceutical Industry

Currently parties that fabricate, package or label, perform tests, distribute, import or wholesale products containing Schedule F drugs require an establishment licence to carry out these functions as prescribed by section C.01A.003 of the FDR. In order to continue performing the mentioned functions, these parties will be required to obtain a dealer's licence for controlled substances if they do not already hold one. Those currently holding a dealer's license for other controlled substances will need to amend their licence to include ketamine.

Once a dealer's licence is obtained for products containing ketamine, it will be necessary for the licensed dealer to abide by the regulations in Part I of Part G of the FDR, which are under the scope of the CDSA. This will require them to ensure that product is stored according to security requirements detailed in a publication entitled "Directive on Physical Security Requirements for Controlled Substances".

In addition, the prescription status label currently found on products containing ketamine must be replaced with a controlled drug label, resulting in a cost to the industry. In Canada, all prescription drugs must have a 'Pr' on the outside label of the product, and all controlled drugs must have a 'C' on outside labels as dictated by section C.01.004 of the FDR. This cost will be minimized by proposing a deferred implementation of the labelling requirements until one year from the date on which the amendments come into force. This transition period will allow the industry to organize an appropriate method for implementing the new labelling requirement. Overall costs should be minimal for those already possessing a dealer's licence.

#### Law Enforcement

Law enforcement agencies will benefit from this initiative by being able to charge persons who illegally possess ketamine, a charge that could not be exercised with ketamine as a prescription drug. Punishments for participating in illicit activities are more severe under the CDSA compared to the FDA, and this should act as a deterrent to non-medical use. Costs will be minimal for the required enforcement activities.

#### Canadian Public

This regulatory amendment will benefit Canadians as the control of ketamine will aid in reducing diversion, health risks, and crime associated with its illicit use. Those possessing it illegally will be subject to sanctions under the CDSA.

#### **Consultations**

A Notice of Intent (NOI) to interested stakeholders was published in *Canada Gazette*, Part I (CGI) on February 7, 2004. The following stakeholders were notified directly of the publication:

**Draft - 2004-08-23**

- 5 -

- The pharmaceutical industry including licensed dealers,
- Pharmaceutical associations,
- Deans of Pharmacy, Medicine, Dentistry and Veterinary Medicine,
- Provincial and Territorial Ministries of Health,
- Registrars of Pharmacy, Medicine, Dentistry and Veterinary Medicine

Comments received from stakeholders were supportive of the decision to place ketamine within the framework of the CDSA.

### **Compliance and Enforcement**

This regulatory initiative will not alter existing compliance and enforcement mechanisms under the CDSA and its regulations. These mechanisms can now be applied in situations involving ketamine. Compliance activities are carried out by local and federal law enforcement agencies as well as federal inspectors. This amendment will provide law enforcement with the tools necessary to combat illegal possession, trafficking, importation, exportation, and production of ketamine. Failure to comply with the proposed regulatory amendment could lead to administrative sanctions such as revocation of a licence or permit, and criminal sanctions such as fines or imprisonment.

### **Contact**

Shereen Khan  
Office of Controlled Substances  
Drug Strategy and Controlled Substances Programme  
Healthy Environments and Consumer Safety Branch  
Address Locator: 3503D  
Ottawa, Ontario K1A 1B9

Telephone Number: (613) 946-0121  
FAX: (613) 946-4224  
Electronic Mail: [OCS\\_Policy\\_and\\_Regulatory\\_Affairs@hc-sc.gc.ca](mailto:OCS_Policy_and_Regulatory_Affairs@hc-sc.gc.ca)



**Richard Laing**

2004-12-03 01:52 PM

To: Mark Kozlowski/HC-SC/GC/CA@HWC  
cc:  
Subject: Re: Status decision of Ketamine 

Good Morning Mark,

I have reviewed the documentation and opinions regarding the chemistry and modes of action of Ketamine in relation to Phencyclidine, Item 14 Schedule I of the CDSA.

I concur that Ketamine is an analogue of Phencyclidine (PCP) whereby chemically it shares a high degree of similarity to PCP and to other PCP analogues, such as PCE, and has a similar mode of action and effect. As such, Ketamine should be considered a controlled substance under the CDSA.

Sincerely yours,

Richard Laing  
A/Manager Drug Analysis Service Laboratory - Burnaby  
3155 Willingdon Green,  
Burnaby, BC  
V5G 4P2

phone 604-666-3582  
cell 604-240-0235  
Mark Kozlowski



**Mark Kozlowski**

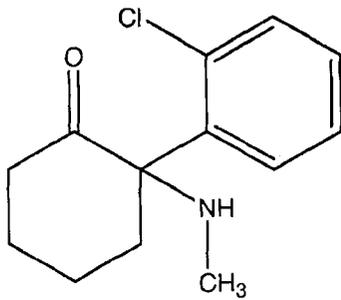
2004-11-22 10:28 AM

To: Richard Laing/HC-SC/GC/CA@HWC  
cc:  
Subject: Status decision of Ketamine

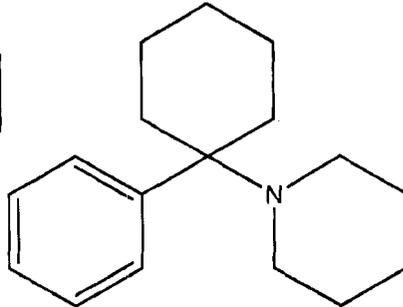
Good Afternoon Richard,

We received the attached status request on the following substance. This substance should be considered controlled under the CDSA because, the substance is an analogue of Phencyclidine, which is Item 14 in Schedule I of the CDSA. I have the documents that states this if you require them. I have also forwarded you different emails on the topic. The substance is:

Ketamine  
2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone



Ketamine



Phencyclidine

Do you agree that this substance is controlled under the CDSA? Thank you.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 22/11/04 01:18 PM -----



Cynthia Sunstrum

18/11/04 11:07 AM

To: Richard Laing/HC-SC/GC/CA@HWC

cc: Theresa Schopf/HC-SC/GC/CA, Jaspinder

Komal/HC-SC/GC/CA@HWC, Daniel

Galarneau/HC-SC/GC/CA@HWC, Margaret Fuller/HC-SC/GC/CA,

Shereen Khan/HC-SC/GC/CA@HWC, Mark

Kozlowski/HC-SC/GC/CA@HWC, Louis Proulx/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

Richard:

It was great to see you again at the Meth Summit.

Further to our very brief discussion concerning ketamine, attached is the latest input we have received from the Veterinary Drugs Directorate. I don't know if Mark has been sending you the other comments we received in response to my e-mail of November 5, 2004 (if not - Mark please forward to Richard and any other DAS personnel who have had input thus far).

Your comments and others indicate that the determination is leaning toward classification of ketamine as an analogue of phencyclidine but not a derivative. If an analogue, as per the definition in the CDSA, it would still be captured in Schedule I. As such, it remains unclear how it ended up in Schedule F of the FDA when scheduled in December 1995.

When you spoke, you indicated agreement that ketamine should be explicitly listed in the CDSA Schedules in any event. The issue will be in which schedule to list it. Our proposal before the analogue business unfolded was CDSA Schedule III and schedule to Part G of the FDR (the draft RIAS is attached FYI - will need to be revised to reflect latest developments). This would implement same offences, controls, penalties as per other club drugs including ecstasy, GHB and crystal meth. In view of comments made about re-scheduling of meth, do you have any comments about our proposed scheduling for ketamine?

As communicated to Mark, I would like to have a status decision ASAP but before the end of this month so that we can proceed with the scheduling (or re-scheduling?) of ketamine under the CDSA. Urgency further reinforced by Meth Summit data (including yours!).

Thanks

Cynthia



RIAS-draft-E-2.wpd

----- Forwarded by Cynthia Sunstrum/HC-SC/GC/CA on 2004-11-18 09:49 AM -----

Ian Alexander

2004-11-18 08:29 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC

cc: Ben Lobo/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC,  
Daniel Galarneau/HC-SC/GC/CA@HWC, Eric  
Ormsby/HC-SC/GC/CA@HWC, Hieu Vu/HC-SC/GC/CA@HWC,  
Jaspinder Komal/HC-SC/GC/CA@HWC, Mark  
Kozlowski/HC-SC/GC/CA@HWC, Shereen\_Khan, Theresa  
Schopf/HC-SC/GC/CA@HWC, Denis Girard/HC-SC/GC/CA@HWC,  
Amost Vilim/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

s.21(1)(a)  
s.21(1)(b)

Hi Cynthia,

Ian

Phencyclidine, [1-(1-phenylcyclohexyl)piperidine] and Ketamine, [2-(2-chlorophenyl)-2-(methylamino)cyclohexanone] are chemically quite different in structure.

In my opinion, ketamine is not a derivative of phencyclidine. Phencyclidine is a tertiary amine while ketamine is a secondary amine with a ketone functional group derived from cyclohexanone. It is not substantially similar in chemical structure to be considered as an analogue of phencyclidine as defined in the CDSA. The name Ketamine is probably derived from the fact that it can be considered as a keto-amine (or ketamine in short) based on the chemical functional groups it contains.

Although not strictly right from a chemical structure point of view Ketamine is often referred to in a pharmacological context as a "derivative" of phencyclidine. From a chemical structure point of view, I agree that ketamine is not a derivative of phencyclidine but rather an analogue since in my view there is substantial similarity in structure with phencyclidine.

Cynthia Sunstrum



Cynthia Sunstrum

2004-11-05 02:56 PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC,  
Brigitte Zirger/HC-SC/GC/CA@HWC, Ian  
Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf,  
Jaspinder Komal/HC-SC/GC/CA@HWC, Mark



Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

**Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(*o*-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia



Health Canada Santé Canada



**STATUS DECISION OF CONTROLLED AND NON-CONTROLLED SUBSTANCE(S)**

Substance: Ketamine

Based on the current information available to the Office of Controlled Substances, it appears that the above substance is:

Controlled   
Not Controlled

under the schedules of the *Controlled Drugs and Substances Act* (CDSA) for the following reason(s):

- this substance is an analogue of Phencyclidine, which is Item 14 in Schedule I of the CDSA.

Supporting document(s) attached:

Prepared by:   
MARK KOZLOWSKI

Date: 22/11/04

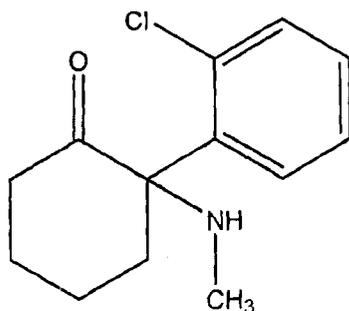
Verified by: See email  
RICHARD LAING

Date: 03/12/04

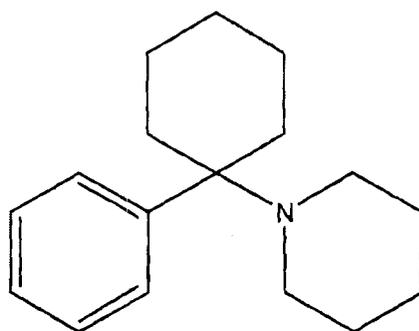
Approved by:   
DIRECTOR, OFFICE OF CONTROLLED SUBSTANCES

Date: 9/12/04

after discussion  
- PARD  
Cynthia  
regarding  
regulatory issue  
to be implemented  
when notes  
have been  
sent to PARD  
for review



Ketamine



Phencyclidine



OCS Policy and  
Regulatory Affairs

2005-05-02 01:26 PM

To: OCS Policy and Regulatory Affairs/HC-SC/GC/CA@HWC  
cc: (bcc: Beth Pieteron/HC-SC/GC/CA)  
Subject: Notice: Status of ketamine under CDSA -- Avis: Statut de la kétamine  
en vertu de la LRCDAS

### Notice: Status of ketamine under CDSA

On February 7, 2004, Health Canada published a Notice to Interested Parties in *Canada Gazette*, Part I, with respect to a proposal to control ketamine under the *Controlled Drugs and Substances Act* (CDSA) and its Regulations.

Ketamine is a non-barbiturate anaesthetic approved for use in both humans and animals. It has been listed in Schedule F of the *Food and Drug Regulations* (FDR) since at least 1995. Ketamine has become popular as a "party or club" drug due to its dissociative effects; it creates the illusion of an "out of body experience". Ketamine is also used as a "date rape" drug.

Further research and analysis of the options for scheduling under the CDSA concluded that ketamine is an analogue of phencyclidine (PCP), and is, therefore, captured as item 14 in Schedule I of the CDSA and item 14 in the *Narcotic Control Regulations* (NCR) which states:

"Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues"

Section 58 of the CDSA gives priority to substances listed under its Act and Regulations, stating:

"In the case of any inconsistency or conflict between this Act or the regulations made under it, and the *Food and Drugs Act* or the regulations made under that Act, this Act and the regulations made under it prevail to the extent of the inconsistency or conflict."

With this determination, all offences and penalties associated with Schedule I to the CDSA are now applicable to ketamine including: possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production.

Any persons involved in the distribution of any product containing ketamine must now comply with the requirements of the NCR. All persons conducting research using ketamine must now apply for an exemption under CDSA.

Health Canada will take action to remove ketamine from Schedule F of the FDR and explicitly list it in Schedule I to the CDSA and the Schedule to the NCR within the next months to avoid further confusion with respect to the regulatory status of this substance. Notification of this amendment will be published in *Canada Gazette*, Part II.

Notices are being sent to the following groups:

- Provincial and territorial licensing authorities for medicine, dentistry, veterinary medicine, and pharmacy
- Associations for practitioners, pharmacists and hospitals

- Manufactures and distributors involved in the distribution of ketamine
- Deans of Pharmacy, Medicine, Dentistry, and Veterinary Medicine at all Universities across Canada
- Law enforcement agencies, and
- Federal prosecutors.

A notice will also be posted on Office of Controlled Substances website with contact information ([http://www.hc-sc.gc.ca/hecs-sesc/hecs/dscs\\_whatsnew.htm](http://www.hc-sc.gc.ca/hecs-sesc/hecs/dscs_whatsnew.htm)).

All parties will be expected to come into full compliance with these new requirements by August 31, 2005.

### **Avis: Statut de la kétamine en vertu de la LRCDas**

Le 7 février 2004, Santé Canada a publié un Avis aux intéressés dans la *Gazette du Canada*, Partie I, dans lequel il proposait d'ajouter la kétamine aux substances figurant dans les annexes de la *Loi réglementant certaines drogues et autres substances* (LRCDas) et de ses règlements d'application.

La kétamine est un anesthésique non barbiturique dont l'utilisation est approuvée tant chez l'humain que chez les animaux; elle figure à l'annexe F du *Règlement sur les aliments et drogues* (RAD) depuis au moins 1995. La kétamine est devenue populaire dans les partys et les boîtes de nuit en raison de ses effets dissociatifs, c'est-à-dire qu'elle donne l'illusion de vivre une « expérience extra-corporelle ». La kétamine est également utilisée comme « drogue du viol ».

À la lumière de recherches et de l'analyse des options associées à l'ajout de la kétamine aux substances figurant dans les annexes de la LRCDas on en est arrivé à la conclusion que la kétamine était un analogue de la phencyclidine (PCP) et que, par conséquent, elle était visée par l'article 14 de l'annexe I de la LRCDas et par l'article 14 de l'annexe du *Règlement sur les stupéfiants* (RS), qui se lisent comme suit :

*Phencyclidine ((phényl-1 cyclohexyl)-1 pipéridine), ses sels, dérivés et analogues, ainsi que les sels de ses dérivés et analogues.*

L'article 58 de la LRCDas donne préséance aux substances répertoriées dans sa *Loi* et son règlement d'application, lequel stipule :

« Les dispositions de la présente loi ou de ses règlements l'emportent respectivement sur les dispositions incompatibles de la *Loi sur les aliments et drogues* ou de ses règlements.  
»

Suite à cette décision, toutes les infractions et amendes associées à l'annexe I de la LRCDas, s'appliquent dorénavant à la kétamine; il est donc interdit de posséder de la kétamine, d'en faire le trafic, d'en posséder en vue d'en faire le trafic, d'en produire, d'en importer, d'en exporter ou d'en posséder en vue d'en faire l'exportation.

Toutes les personnes impliquées dans la distribution de n'importe quel produit contenant de la kétamine doivent maintenant se conformer au RS. Toutes les personnes dont les travaux de recherche font intervenir de la kétamine doivent dorénavant faire application pour obtenir une exemption en vertu de la LRCIDAS. Le Bureau des Substances Contrôlées examinera les demandes au cas par cas.

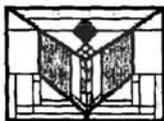
Santé Canada prendra les mesures nécessaires pour retirer la kétamine de l'annexe F du RAD et l'inscrire formellement à l'annexe I de la LRCIDAS et dans l'annexe du RS au cours des prochains mois afin de dissiper toute confusion à l'égard du statut réglementaire de la kétamine. Cette modification sera annoncée dans la *Gazette du Canada*, Partie II.

Des avis ont été envoyés aux organismes suivants:

- Organisme de réglementation professionnelle provinciaux et territoriaux de médecine, de médecine dentaire, de médecine vétérinaire et de pharmacie
- Associations de praticiens, de pharmaciens et des hôpitaux,
- Fabricants et distributeurs de kétamine
- Doyens de faculté de pharmacie, médecine, médecine dentaire, et médecine vétérinaire de toutes les universités canadiennes
- Organismes d'application de la loi
- Procureurs fédéraux

L'avis sera affiché sur le site internet du BSC (  
[http://www.hc-sc.gc.ca/hecs-sesc/sesc/sasc\\_quoideneuf.htm](http://www.hc-sc.gc.ca/hecs-sesc/sesc/sasc_quoideneuf.htm)).

Toutes les parties devront se conformer aux nouvelles exigences d'ici le 31 août 2005.



**Daniel Galarneau**  
Sent by: Suzanne  
Trottier

2005-06-10 10:28 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC, Carole  
Bouchard/HC-SC/GC/CA@HWC, Beth  
Pierson/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA@HWC  
Subject: Status of Ketamine regulatory submission

The ketamine regulatory submission was hand-delivered to ADMO yesterday, June 9th, 2005.

Suzanne Trottier

Regulatory Clerk  
Policy and Regulatory Affairs Division  
Office of Controlled Substances  
MacDonald Bldg, 123 Slater St., Room A304  
Address Locator: 3503D  
Ottawa, ON K1A 0K9  
Tel: (613) 946-0124



**Mark Kozlowski**  
2004-12-03 09:23 AM

To: Richard Laing/HC-SC/GC/CA@HWC  
cc:  
Subject: URGENT - Status decision of Ketamine

Richard,

This one is becoming more urgent, as they want to move on the scheduling. Thanks.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 03/12/04 09:20 AM -----



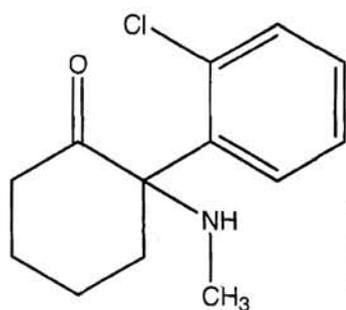
**Mark Kozlowski**  
22/11/04 01:28 PM

To: Richard Laing/HC-SC/GC/CA  
cc:  
Subject: Status decision of Ketamine

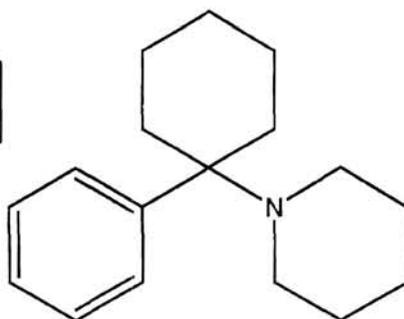
Good Afternoon Richard,

We received the attached status request on the following substance. This substance should be considered controlled under the CDSA because, the substance is an analogue of Phencyclidine, which is Item 14 in Schedule I of the CDSA. I have the documents that states this if you require them. I have also forwarded you different emails on the topic. The substance is:

Ketamine  
2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone



Ketamine



Phencyclidine

Do you agree that this substance is controlled under the CDSA? Thank you.

MK

----- Forwarded by Mark Kozlowski/HC-SC/GC/CA on 22/11/04 01:18 PM -----



**Cynthia Sunstrum**  
18/11/04 11:07 AM

To: Richard Laing/HC-SC/GC/CA@HWC  
cc: Theresa Schopf/HC-SC/GC/CA, Jaspinder Komal/HC-SC/GC/CA@HWC, Daniel Galarneau/HC-SC/GC/CA@HWC, Margaret Fuller/HC-SC/GC/CA, Shereen Khan/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC, Louis Proulx/HC-SC/GC/CA@HWC  
Subject: Re: Ketamine: Schedule Status

Richard:

It was great to see you again at the Meth Summit.

Further to our very brief discussion concerning ketamine, attached is the latest input we have received from the Veterinary Drugs Directorate. I don't know if Mark has been sending you the other comments we received in response to my e-mail of November 5, 2004 (if not - Mark please forward to Richard and any other DAS personnel who have had input thus far).

Your comments and others indicate that the determination is leaning toward classification of ketamine as an analogue of phencyclidine but not a derivative. If an analogue, as per the definition in the CDSA, it would still be captured in Schedule I. As such, it remains unclear how it ended up in Schedule F of the FDA when scheduled in December 1995.

When you spoke, you indicated agreement that ketamine should be explicitly listed in the CDSA Schedules in any event. The issue will be in which schedule to list it. Our proposal before the analogue business unfolded was CDSA Schedule III and schedule to Part G of the FDR (the draft RIAS is attached FYI - will need to be revised to reflect latest developments). This would implement same offences, controls, penalties as per other club drugs including ecstasy, GHB and crystal meth. In view of comments made about re-scheduling of meth, do you have any comments about our proposed scheduling for ketamine?

As communicated to Mark, I would like to have a status decision ASAP but before the end of this month so that we can proceed with the scheduling (or re-scheduling?) of ketamine under the CDSA. Urgency further reinforced by Meth Summit data (including yours!).

Thanks

Cynthia



RIAS-draft-E-2.wpd

s.21(1)(a)  
s.21(1)(b)

----- Forwarded by Cynthia Sunstrum/HC-SC/GC/CA on 2004-11-18 09:49 AM -----

Ian Alexander

2004-11-18 08:29 AM

To: Cynthia Sunstrum/HC-SC/GC/CA@HWC

cc: Ben Lobo/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Daniel Galameau/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Hieu Vu/HC-SC/GC/CA@HWC, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC, Shereen\_Khan, Theresa Schopf/HC-SC/GC/CA@HWC, Denis Girard/HC-SC/GC/CA@HWC, Arnost Vilim/HC-SC/GC/CA@HWC

Subject: Re: Ketamine: Schedule Status

*Duplicate  
Doc 17*

Hi Cynthia,

Ian

Phencyclidine, [1-(1-phenylcyclohexyl)piperidine]] and Ketamine, [2-(2-chlorophenyl)-2-(methylamino)cyclohexanone] are chemically quite different in structure.

In my opinion, ketamine is not a derivative of phencyclidine. Phencyclidine is a tertiary amine while ketamine is a secondary amine with a ketone functional group derived from cyclohexanone. It is not substantially similar in chemical structure to be considered as an analogue of phencyclidine as defined in the CDSA. The name Ketamine is probably derived from the fact that it can be considered as a keto-amine (or ketamine in short) based on the chemical functional groups it contains.

Although not strictly right from a chemical structure point of view Ketamine is often referred to in a pharmacological context as a "derivative" of phencyclidine. From a chemical structure point of view, I agree that ketamine is not a derivative of phencyclidine but rather an analogue since in my view there is substantial similarity in structure with phencyclidine.

Cynthia Sunstrum



Cynthia Sunstrum

2004-11-05 02:56 PM

To: Hieu Vu/HC-SC/GC/CA@HWC, Eric Ormsby/HC-SC/GC/CA@HWC, Brigitte Zirger/HC-SC/GC/CA@HWC, Ian Alexander/HC-SC/GC/CA@HWC, Ben Lobo/HC-SC/GC/CA@HWC  
cc: Daniel Galarneau/HC-SC/GC/CA, Shereen\_Khan, Theresa Schopf, Jaspinder Komal/HC-SC/GC/CA@HWC, Mark Kozlowski/HC-SC/GC/CA@HWC  
Subject: Ketamine: Schedule Status

As discussed at the HPFB/HECS bilateral meeting earlier this week, an issue has arisen with regards to our proposed regulatory action to schedule ketamine under the CDSA and the Schedule to Part G of the FDR. As you recall, ketamine is currently on Schedule F.

**Issue:** Is ketamine is a derivative of phencyclidine? As such, it would be captured under Schedule I Item 14 of the CDSA.

**Background:**

Item 14. of the CDSA : Phencyclidine (1--(1--phenylcyclohexyl)piperidine), its salts, derivatives and analogues and salts of derivatives and analogues

"analogue" is defined in the CDSA as a substance that, in relation to a controlled substance, has a substantially similar chemical structure; derivative is not defined in the CDSA.

A veterinarian from Toronto contacted OCS to advise that ketamine is a derivative of phencyclidine.

Our research thus far has yielded conflicting views. Information includes the following:

[www.rxlist.com/cgi/generic3/ketamine.htm](http://www.rxlist.com/cgi/generic3/ketamine.htm) states that ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated ( $\pm$ )-2-(o-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

- two articles have been found, one from a book and one from a scientific journal, stating that Ketamine is a derivative of Phencyclidine.

Doc 13  
OK

- comment from a chemist: "Ketamine and Phencyclidine are anesthetic agents. From the pharmacological family, yes, Ketamine is a derivative of Phencyclidine. From the chemical Family, no, Ketamine is not a derivative of Phencyclidine but it is more an analog. The manufacturing of Ketamine and the manufacturing of Phencyclidine involved processes totally different. This is why Ketamine is not the derivative of the Phencyclidine

**Advice requested:**

We would appreciate obtaining your input on the following:

- whether ketamine is, or should be considered, a derivative or analog of phencyclidine?
- historically, whether this issue may have been considered when ketamine was added to Schedule F (when was it added).

It would be greatly appreciated if you get back to us before the end of November so that the issue can be resolved and we can progress with the regulatory submission. DSCS will make the final determination based on all information collected.

Thanks in advance for your ongoing cooperation.

Cynthia

OK