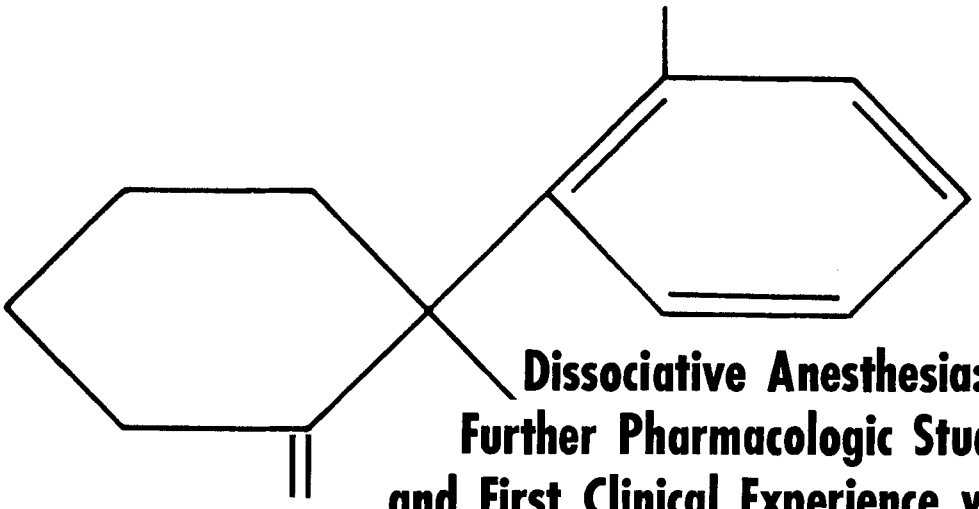

Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581

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THERE 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[1] its clinical usefulness as an anesthetic was investigated by Greifenstein and associates.[2]

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[3] 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.

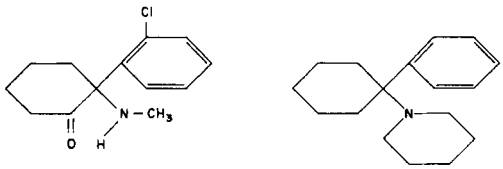

FIG. 1. Structural formulae of CI-581 and phencyclidine.

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.

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Studies in human volunteers[4] 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_2, pCO_2, 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_3, C_3, P_3, and O_1 to both ears as reference[5] 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,[6] 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.

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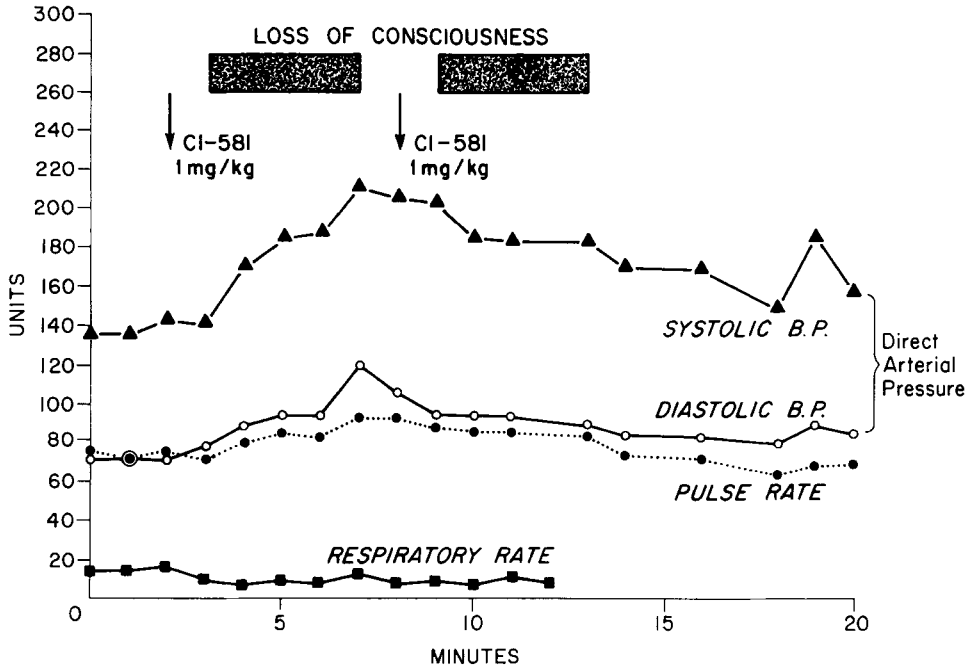

FIG. 2. Effects of CI-581 anesthesia on vital signs in an unpremedicated human volunteer.

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 unpremedicated prison 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

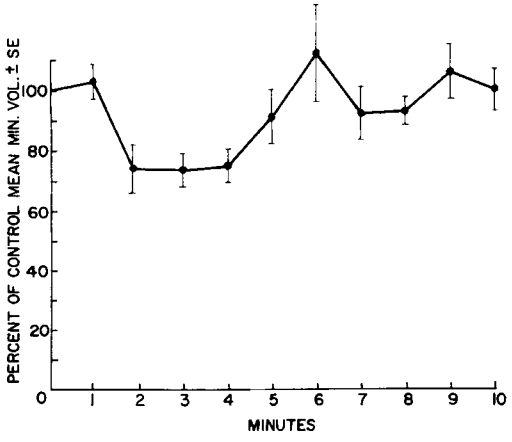

FIG. 3. Alteration of per cent mean respiratory minute volume following intravenous CI-581 (0.45 mg. per lb.) in 6 unpremedicated human volunteers.

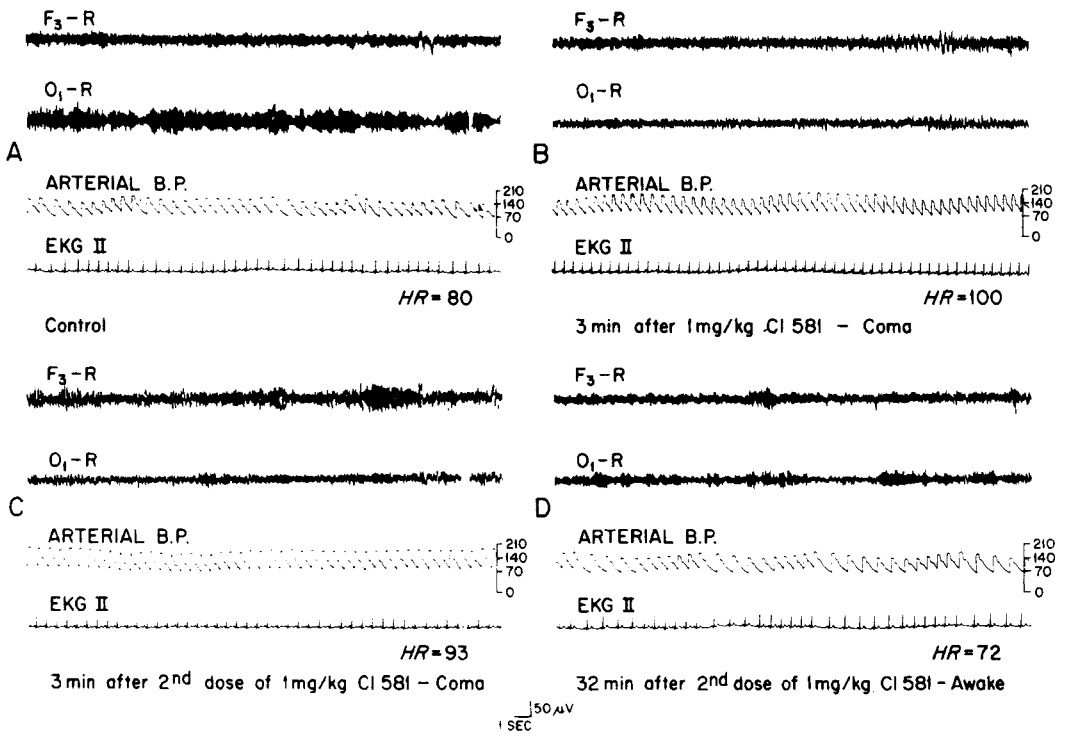

FIG. 4. Alterations of EEG and ECG recordings and arterial blood pressure in an unpremedicated human volunteer given CI-581 in 2 intravenous doses, 6 minutes apart.

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,

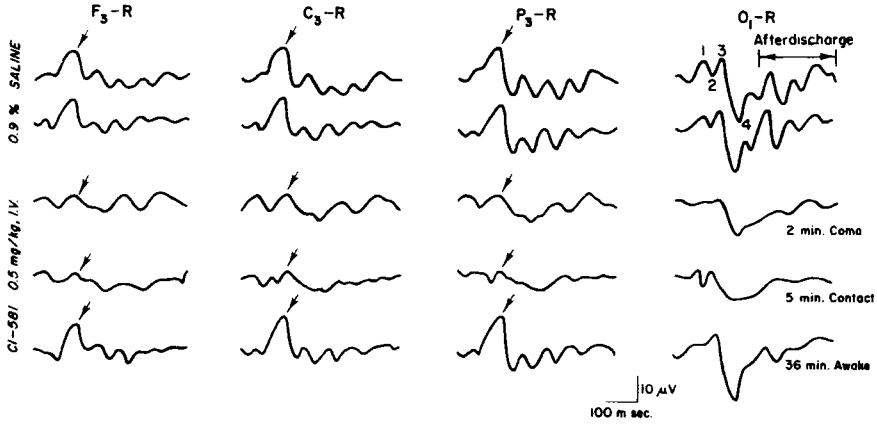

FIG. 5. Effects of CI-581 on visually evoked responses in an unpremedicated human volunteer, recorded from various brain areas.

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
Total	133

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, fundoscopy, 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 submandibular 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 ¼ to ½ 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

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

(4:2) 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.

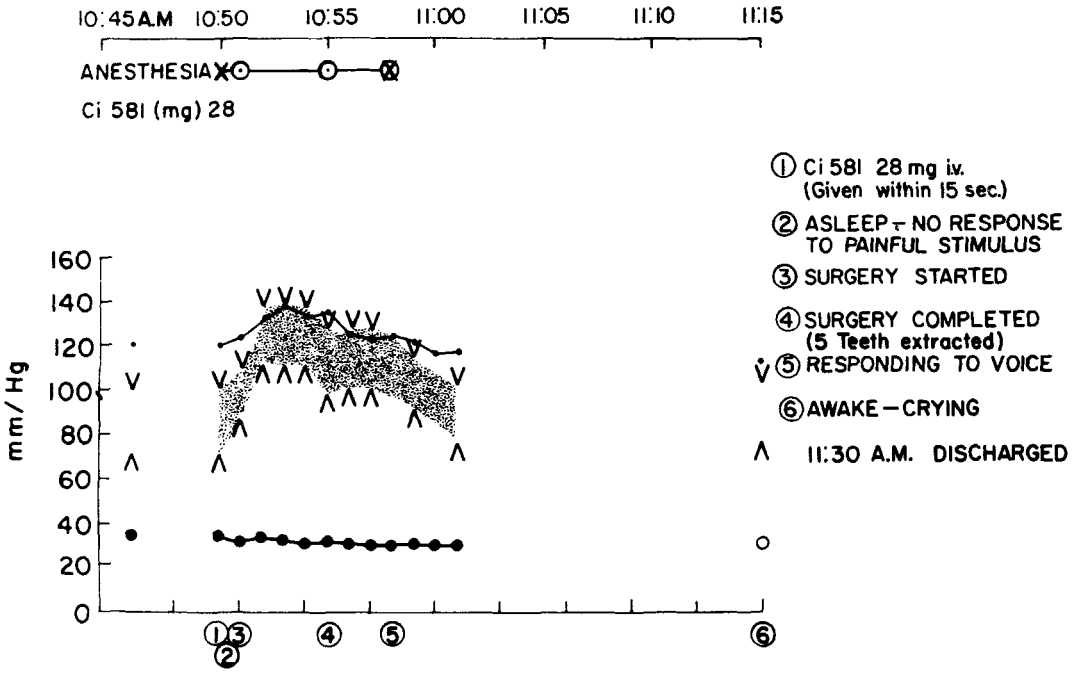

FIG. 6. Two-year-old white boy, 28 pounds. Preanesthetic medication: scopolamine hydrobromide, 0.2 mg. at 9:50 a.m. Surgical procedure: teeth extraction. Anesthesia: CI-581 intravenously. The intravenous injection was given within 15 seconds.

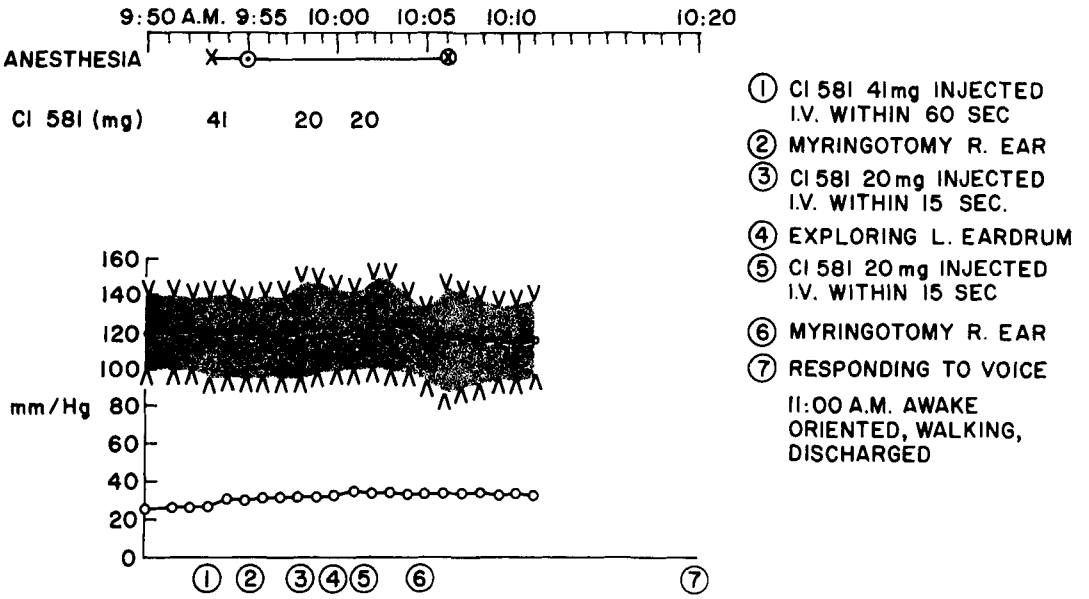

FIG. 7. Five-year-old white boy, 41 pounds, bilateral chronic otitis media, cleft palate. Preanesthetic medication: pentobarbital, 25 mg., scopolamine, 0.2 mg. at 8:55 a.m. Surgical procedure: bilateral myringotomy, insertion of myringeal tubes. Anesthesia: CI-581 intravenously. The CI-581 was injected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

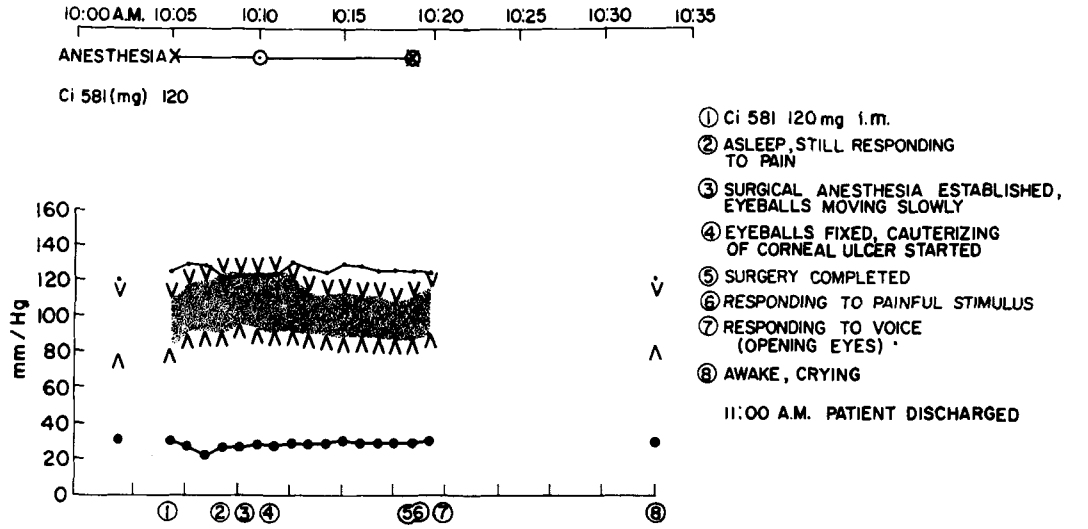

FIG. 8. Fifteen-month-old white girl, 30 pounds. Preanesthetic medication: pentobarbital, 30 mg., scopolamine, 0.2 mg. intravenously at 9:30 a.m. Surgical procedure: cauterization of corneal ulcer. Anesthesia: CI-581 intramuscularly.

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

for 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 postanesthetic 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 anesthestic 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.[7] 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

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[8] 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

the 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[9] 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 delerium 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 altered 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, particularly, methods for preventing its vasopressor and psychotomimetic effects.

ACKNOWLEDGMENT

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Generic and Trade Names of Drugs

Thiamylal—Surital
Chlorpromazine—Thorazine

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DISCUSSION

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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

with 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.