An Anesthetic Agent: 2-Orthochlorophenyl, 2-Methylamino Cyclohexanone HCl (CI-581)

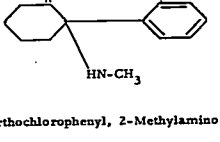
Robert W. Virtue, M.D.,* Joseph M. Alanis, M.D.,† Masahiro Mori, M.D.,‡
Robert T. Lafargue, M.D.,‡ John H. K. Vogel, M.D.,§
David R. Metcalf, M.D.¶

GREIFENSTEIN [1] and Johnstone [2] administered Sernyl (phencyclidine: 1-phenyl, 1-piperidyl cyclohexane) to man for anesthesia. Adequate analgesia and sedation were produced with spontaneous maintenance of respiration and blood pressure. The duration of action and emergence excitement were too great to recommend use of the drug. It will be shown here that CI-581, a congener of phencyclidine, is an effective anesthetic in man.

CI-581 is a white crystalline substance which melts at 259° [3]; it is the hydrochloride of 2-(o-chlorophenyl) 2-methylamino cyclohexanone (fig. 1). Water solubility at 25° is 22.5 per cent (w/v). The *p*H of 1 and 5 per cent solutions is 4.45 and 4.30, respectively.[4] Studies on mice, rats, pigeons, guinea pigs, dogs and monkeys [3] showed variation of the dose for surgical anesthesia from 7 mg./kg. in the monkey to 128 mg./kg. in the mouse. The signs of anesthesia were central nervous depression progressing through catalepsy to general anesthesia. Only one monkey convulsed at near-lethal levels, in distinct contrast to the frequent convulsions with phencyclidine. Light and corneal reflexes usually persisted when complete surgical anesthesia was present. Pharyngeal reflexes were also present. Organic toxicity could be demonstrated in the animals tested.

Methods

Animal Studies. Before administering CI-581 to man we observed the effect on the hypovolemic dog and the effect of epinephrine in anesthetized animals. A femoral artery of each of 10 dogs was cannulated under local anesthesia. A short length of polyethylene tubing containing heparinized saline connected the arterial cannula to a mercury manometer for observation of blood pressure. ECG leads were attached. Epinephrine was injected intravenously over a 50-second period starting with 0.01 mg./kg.[5] and increasing the dose until ventricular arrhythmias appeared, thus obtaining a challenge dose effect. CI-581, 9 mg./kg., was then given intravenously in a 1 per cent solution over a period of 15 seconds. The eyes of the animal were closed or fixed and there was no response to painful stimulus within approximately 15 seconds. Two minutes later the challenge dose of epinephrine was injected over a 50-second period. No further manipulation was done until the dog moved spontaneously and responded to painful stimuli. Blood was then withdrawn from the femoral artery until one thirtieth of the body weight had been removed or until the systolic pressure had dropped to 35 mm. of mercury. Five to ten minutes were required. A ten-minute period was allowed



2-Orthochlorophenyl, 2-Methylamino Cyclohexanone

CI-581

FIGURE 1.

* Professor, Division of Anesthesiology.
† Clinical Instructor, Division of Anesthesiology.
‡ Senior Fellow in Cardiology.
§ Assistant Professor of Medicine and Associate Director, Clinical Cardiovascular Laboratory.
¶ Director, Division of Electroencephalography, Department of Psychiatry.
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for stabilization. CI-581 and epinephrine were then injected using the same doses as previously.

Volunteer Subjects. Eight healthy persons ranging from 21 to 30 years of age volunteered (in accordance with FDA regulations) to be anesthetized with CI-581. They were given 0.4 mg. atropine intravenously. Control values were obtained for: (a) arterial blood constituents; glucose,[6] urea,[7] P_{CO_2}, *p*H, lactic acid dehydrogenase,[8] serum glutamic oxaloacetic transaminase,[9] serum glutamic pyruvic transaminase,[9] leucine amino peptidase,[10] isocitric dehydrogenase[11] and aldolase.[12]

Respiratory rate and volume were measured; the subjects then inhaled 5 per cent CO_2 in air (nonrebreathing system) for 3 minutes and the respiratory rate and volume were measured during the 3rd minute.

Control circulatory values obtained included systemic and venous blood pressure, pulse rate, and cardiac output. For the latter, a short length of polyethylene 160 tubing was introduced into the brachial artery by the Seldinger technique.[13] A polyethylene 60 tube was introduced into the antecubital vein either percutaneously or via a 16 gauge thin-walled needle, and advanced into the superior vena cava. Cardiac output was determined by means of indicator-dilution technique using Cardiogreen dye.* Blood pressures were recorded with a P_{23db} Statham transducer.

Electroencephalograms were recorded in 7 subjects with a 10 channel Grass model 6 electroencephalograph using one channel to record ocular movements, 2 for heart rate and respiration, and 7 channels for EEG. Testing of deep tendon reflexes, corneal reflexes and pupil response was accomplished periodically during and after administration of CI-581 and during recovery. The ability to calculate "serial sevens" (subtraction of 7s, starting at 100) was evaluated; a standard scorable memory task was assigned, learning was assured before anesthesia, and recall was tested during recovery. Mental status and sensorium were evaluated periodically during recovery. These neurological, psychological and sensorial factors were also tested during deliberately prolonged induction in one case. In four additional cases (without cardiopulmonary and blood studies) EEG recording was combined with neurological examination and systematic evaluation of mental status; auditory evoked responses were tested in one individual.† In one case the EEG was recorded on magnetic tape for future computer analysis in order to demonstrate by means of autocorrelation analysis the subtle but specific EEG alterations induced by CI-581.[14, 15]

After completion of the control measurements the subjects were given CI-581 intravenously, 2.2 mg./kg., in 15 seconds. Measurements of respiratory rate, blood pressures and cardiac output were made at 5, 10, 20 and 30 minutes. Continuous EEG and ECG monitoring were performed. At 20 minutes the subjects again breathed 5 per cent CO_2 in air for 3 minutes and respiratory rate and volume were determined during the third minute. Arterial blood samples were drawn for P_{O_2} and P_{CO_2} at the end of the third minute. At 30 minutes, blood samples were taken for glucose, urea, enzymes, P_{O_2} and P_{CO_2}. Blood samples were withdrawn 2 days later for glucose, urea and enzyme values. The first injection of CI-581 rendered the subjects quiet and analgesic for 8 to 10 minutes, at which time motion of head or hands was a sign that further administration was necessary. Additional doses were 1.1 mg./kg. Each of these lasted about the same length of time as the first one.

Surgical Patients. CI-581 was administered (in accordance with FDA regulations) to 150 patients for surgical operations which demanded no muscular relaxation. The cases were chosen for various reasons: some (eye, ENT) so the surgeon could have unhampered access to the head; some because the patient was prone and wanted to be asleep (rectal culdoscopy); some because of difficult induction by usual methods (cystoscopy in pediatric patients with chubby arms); some because of need for rapid analgesia without depression of circulation (cesarian section for hemorrhage or prolapsed cord); and some in situations where a relatively long-acting intravenous induction agent could be used prior to

* Supplied by Hynson, Westcott and Dunning.

† Evoked responses were done by Dr. Geary McCandless, Director, Audiology Research Laboratory, University of Colorado Medical Center.

methoxyflurane. The drug was given intravenously 121 times, and intramuscularly 29 times. Fifty-eight of the patients were under 15, and 63 were between 16 and 29 years of age. Earlier reports have indicated that there appeared to be fewer adverse effects in the younger group.[16] Rate and minute volume of respiration and response to 5 per cent CO_2 in air were measured in 34 subjects before and during anesthesia in the same manner as in the healthy volunteer subjects. Arterial blood samples were withdrawn from 20 patients to determine effect on blood gases. The intravenous induction dose of CI-581 for surgical patients was 2.2 mg./kg.; subsequent doses were 1.1 mg./kg. Intramuscular doses were either 8.8 or 11.0 mg./kg., and were not repeated. Urine was collected from three patients at 4, 8, 24, 48 and 72 hours after intravenous injection and analyzed for unchanged CI-581 and for two unknown metabolites,[17] using carbon tetrachloride extraction and gas chromatography with a Tinopal GS dye derivative.‡

Results

Animals. Administration of CI-581 to healthy dogs (table 1) was followed by a 24 per cent increase of blood pressure. The blood pressure of the hypovolemic animal rose only 4 per cent. Epinephrine produced hypertension in both groups but showed no sign of sensitization of the heart by CI-581. The blood pressure reached a higher maximum after epinephrine in normovolemia than after hypovolemia (204 versus 165) but the baseline in the first situation was higher than in the second (137 versus 53). Actual elevation therefore was greater under hypovolemic conditions. Duration of sleep as shown by withdrawal on pinching the toe webs or by spontaneous motion of the head was essentially the same for each set of conditions.

‡ Mr. Tsun Chang of the Parke, Davis Laboratories kindly carried out these analyses.

TABLE 1. Blood Pressures, 10 Dogs (Effects of CI-581 Epinephrine, and of Hemorrhage)

Conditions		mm. Hg	
Controls, awake		111 ± 3.3*	A
Asleep with CI-581, 9 mg./kg.		137 ± 5.6	B
After epinephrine, 0.01 mg./kg. in 50 seconds		204 ± 9.5	C
Awake (avg. duration of sleep 9.1 ± 0.6 min.)	H	117 ± 7.6	D
After bleeding, 1/30 of body weight		51 ± 10.0	E
Asleep with CI-581, 9 mg./kg.		53 ± 9.8	F
After epinephrine, as above		165 ± 10.4	G
Duration of sleep 11.1 min. ± 0.8	J		

* Standard Error of the mean.
Not significant: E–F, H–J.
$P < 0.001$: A–B, A–C, A–E, A–F, A–G, B–C, F–G, C–D, D–E.
$P < 0.01$: C–G.

Volunteers. Table 2 indicates that CI-581 had little effect on minute volume of respiration (7.81 versus 8.02 liters/minute) and little effect on response to 5 per cent CO_2 (14.19 versus 13.86 liters/minute). Resting Pa_{O_2} was

TABLE 2. Ventilatory Data and Blood Gases of 8 Volunteers Receiving CI-581

	Awake, Breathing air	Awake, Breathing 5% CO_2	Asleep with CI-581 Breathing air	Asleep with CI-581 Breathing 5% CO_2
Minute volume, liters	7.81 ± .66* A	14.19 ± 1.56 B	8.02 ± .84 C	13.86 ± 1.11 D
Respiratory rate	12.7 ± 1.26	15.0 ± 1.87	15.9 ± 1.24	15.90 ± 1.44
V_mResponse: $\frac{CO_2}{Air}$:		$\frac{14.19}{7.81} = 1.82$		$\frac{13.86}{8.02} = 1.73$
Pa_{O_2}	72.9 ± 1.14	77.7 ± 6.02	68.00 ± 3.06	76.5 ± 5.22
Pa_{CO_2}	31.1 ± 0.91 E	35.2 ± 2.08	35.0 ± 1.23	37.0 ± 1.25 F
*p*H	7.46 ± 0.019 G	7.43 ± 0.015	7.42 ± 0.012	7.40 ± 0.017 H

$P < 0.001$: A–B, C–D, E–F.
$P < 0.01$: G–H.
* = S.E. mean.

TABLE 3. Circulatory Measurements—7 Volunteers Receiving CI-581

	Controls Awake	Asleep 5 Min.	Asleep 10 Min.	Asleep 20 Min.	Asleep 30 Min.
Mean arterial pressure mm. Hg	98 ± 1.1 A	120.7 ± 3.6 B	120.0 ± 3.0 B	111.7 ± 4.2 B	111.3 ± 3.4 B
Heart rate per min.	75.4 ± 2.3 C	100.6 ± 5.8 D	105.1 ± 5.4 D	93.4 ± 4.6 D	87.9 ± 4.7 E
Cardiac output (liters/min.)	8.70 ± .71 F	12.30 ± 0.93 G	10.56 ± 0.71	9.40 ± 0.45	9.31 ± 0.30
Cardiac index (liters/min.)	4.50 ± 0.32 H	6.40 ± 0.39 I	5.58 ± 0.36 K	4.77 ± 0.26 J	4.83 ± 0.30 J
Stroke volume (ml.)	119.1 ± 8.4	117.0 ± 10.4	105.9 ± 9.9	100.0 ± 8.7	107.4 ± 9.4
Stroke index (ml.)	61.3 ± 3.5	62.3 ± 5.1	55.0 ± 6.3	52.1 ± 4.7	56.1 ± 4.9
Peripheral arterial resistance (dynes-sec.-cm.$^{-5}$ -m.^{2})	1,647 ±132	1,463 ±134	1,662 ±447	1,900 ±143	1,728 ±167
Venous pressure (mm. Hg)	5.9 ± 0.84 L	7.8 ± 1.11	7.43 ± 2.15	8.43 ± 1.31	9.57 ± 3.05 M

P <0.001 A-B, C-D, F-G, H-I, I-J. Average minutes before verbal response (3 doses), 50.
P <0.05 C-E, H-K, L-M. Average minutes to establish walking equilibrium, 307.

normal for this altitude (73 mm. of mercury [20]) and fell to 68 mm. of mercury when the subjects were asleep.

Table 3 gives the circulatory data from 7 volunteers. Blood pressure, cardiac output and heart rate rose soon after injection of CI-581 with little change in peripheral resistance. All values approached control levels at the end of 30 minutes of anesthesia.

EEG and associated sensorial changes during induction were similar in all cases. With doses of 2.2 mg./kg. intravenously in 20 seconds there was a regular shift from dominant alpha frequencies to fast theta (5–7/sec.) within 20–25 seconds of injection, as demonstrated by the EEG and autocorrelation display (figs. 2, 3, and 4); there was no significant change in voltage during this period. Al-

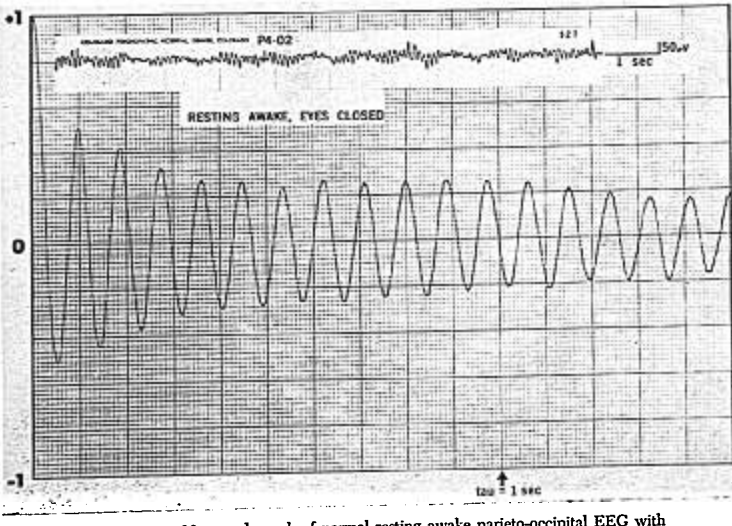

FIG. 2. Top, 10-second epoch of normal resting awake parieto-occipital EEG with autocorrelogram below.

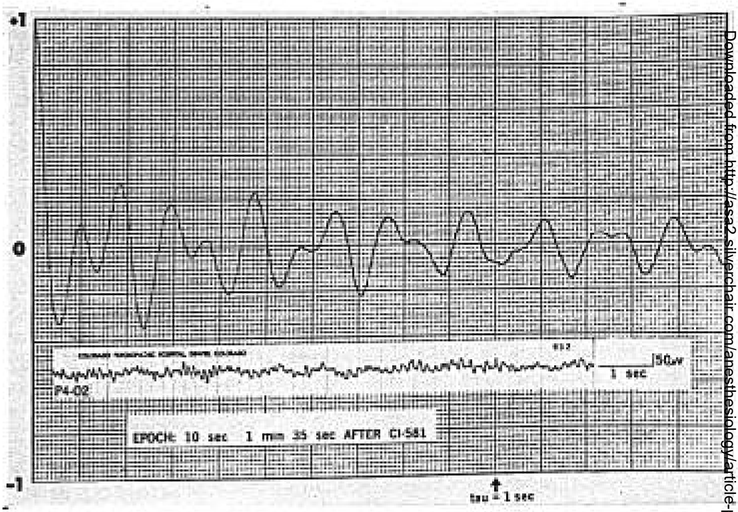

FIG. 3. EEG sample and autocorrelogram showing initial CI-581 effect. Small amounts of 10-second alpha rhythms persist in the midst of irregular theta activity. This typical example shows a slightly delayed CI-581 effect due to deliberate attempt to achieve slow induction.

this time there was mild delirium (slurred spech, mild confusion and difficulty with serial sevens) but no change in deep tendon reflexes. This condition lasted from 30 to 60 seconds after which rapid onset of unconsciousness supervened.

During the 30 to 60 seconds of transition from initial EEG and sensorial alteration to unconsciousness, the EEG developed less-rhythmic, slow theta activity in the 3–5 per second range (fig. 5). The onset of unconsciousness, always associated with this variable EEG picture, could not be assigned to a specific EEG pattern. Delirium became more marked during this period; subjects slightly confused maintained intact sensorium although deepening drowsiness was evident. It was difficult to detect the onset of unconsciousness because the eyes often remained open, the transition was rapid, EEG changes were not marked, and common signs such as respiratory obstruction and loss of muscle tone were absent. Following development of slow theta activity, further administration of CI-581 did not result in more greater EEG slowing, although transitory burst-suppression activity was induced in one case (fig. 6). With recovery, EEGs showed a return of slow "awake" alpha rhythms before alertness or eye-opening developed. Specific EEG abnormalities suggestive of pathological CNS activation were never observed; drug-induced EEG activity such as fast rhythms induced by barbiturates did not occur.

CI-581 was injected slowly in small doses in one case in an attempt to obtain more detailed EEG and behavioral observations during induction. In this case EEG and associated sensorial changes were as reported for rapid "standard" induction. Careful questioning revealed no evidences or delusions of hallucinations.

Behavioral, sensorial and neurologic changes tended to parallel EEG changes. Rapid injection of the drug resulted in rapid onset of unconsciousness (60 seconds), but small repeated doses prolonged the induction period; interrogation of subjects indicated that they

felt separated from their extremities, "numb all over" and had strong urges to feel their own hands, face, etc., to be sure of being intact. Delirium and confusion were always under some control; subjects realized they were confused. Full EEG recovery occurred within 15 minutes of arousal, but behavioral recovery required 4 to 5 hours, accompanied by intermittent but lessening confusion, parasthesias and vertigo.

Auditory evoked responses (fig. 7) were obtained in one subject using a summing computer.§ Within 20 seconds after CI-581 the all-over response was reduced and there was specific depression of wave forms after 200 msec. No evoked response was seen after the onset of unconsciousness.

§ Nuclear Data, Enhancetron.

Recovery time of this group averaged 307 minutes, varying from 224 to 372 minutes. Recovery time was taken as the period before return to walking equilibrium.

All values obtained for blood glucose, urea, and for enzymes involved in protein and carbohydrate metabolism were within the normal limits observed in our laboratory, both at the end of the anesthetic period and 2 days later.

Surgical Patients. Duration of analgesic effect of the induction dose of CI-581 (2.2 mg./kg.) averaged 6.7 minutes. This was significantly lengthened by premedication with meperidine (8.7 minutes), secobarbital (9.5 min.) or morphine (10.0 min.). Because a few of the early patients who received no premedication salivated moderately, either atropine or scopolamine 0.4 mg./70 kg., was

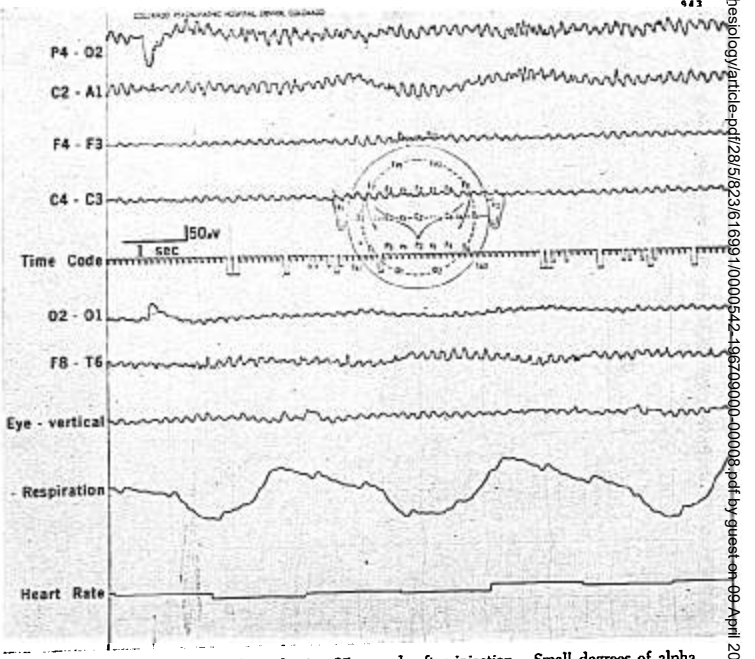

FIG. 4. Typical rhythmic theta slowing 25 seconds after injection. Small degrees of alpha activity persist.

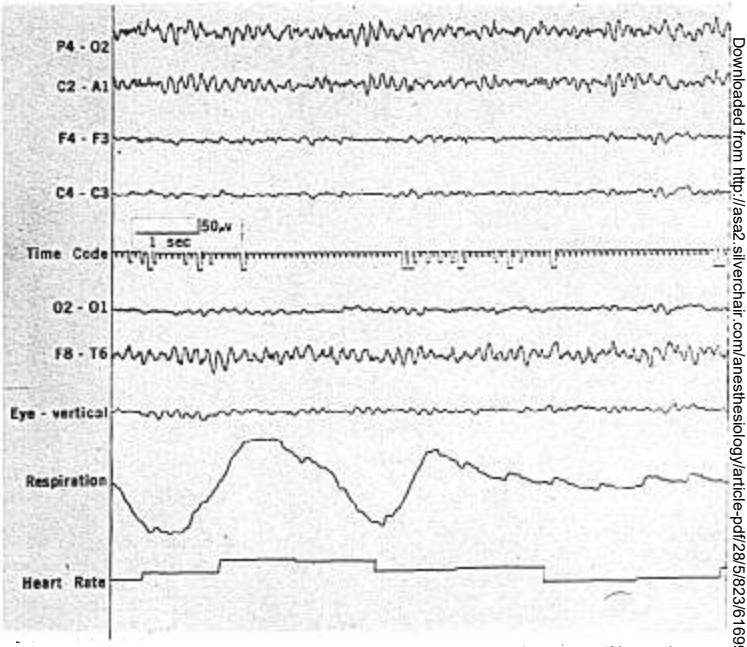

FIG. 5. Moderately regular medium voltage theta activity 60 seconds after CI-581 injection.

given intramuscularly when the patient was called to the operating room in most of the cases.

Analgesia and amnesia obtained with CI-581 were remarkable. Incision could be made 30 seconds after intravenous injection. No patient had any memory of the incision although ability to recall events immediately prior to incision was excellent. Many subjects had lucid dreams, some pleasant. Five patients had disagreeable dreams. All subjects awakened quietly. If stimulated early in the recovery period, diplopia or nausea appeared in about one-third of the cases. Recovery took place 5 to 6 hours after intramuscular injection.

Abdominal relaxation was essentially absent. Successful performance of herniorrhapy required administration of muscle relaxants. Laryngeal and pharyngeal reflexes were maintained in most cases. Bronchoscopy could not be accomplished with the use of CI-581 alone.

Two patients became temporarily apneic on rapid injection of CI-581. Most subjects had a moderate diminution of respiratory minute volume immediately after injection, but measurement of minute volume 3 minutes post-administration showed no change from control. Table 4 summarizes the data from 34 subjects whose minute volumes were measured awake and asleep, with and without breathing 5 percent CO_2 in air. The results were similar to those obtained from the healthy volunteers. Response to CO_2 was unaffected by CI-581.

Table 5 presents a summary of blood pressure, pulse and respiratory changes ob-

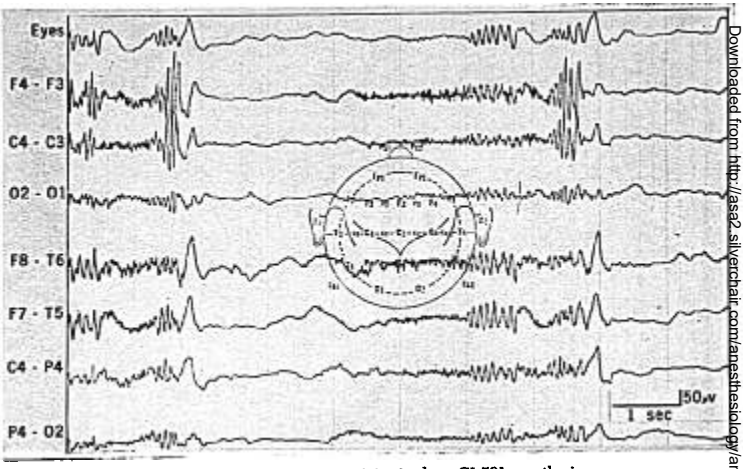

FIG. 6. Burst-suppression activity in deep CI-581 anesthesia.

served in the 150 patients. Heart rate and blood pressure invariably rose soon after administration and gradually tapered off. Respiration was little affected. As indicated, recovery times were greater than expected after use of other anesthetics.

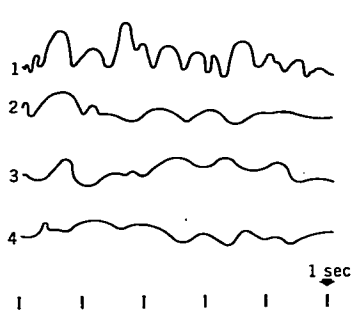

FIG. 7. Auditory evoked responses, vertex to ear electrodes. *1.* Preanesthetic response. *2.* Early induction (10 seconds after CI-581) showing beginning disappearance of late components. *3.* 20 seconds after CI-581 (subject still conscious) showing further depression in magnitude of response. *4.* Testing during unconsciousness showing no visible evoked response.

Only 23 per cent of the injected CI-581 was accounted for in urine by the methods used; one per cent was excreted unchanged within 24 hours. The demethylated derivative was found in the urine to the extent of only 0.5 per cent, all within 24 hours; 21.6 per cent was measured in urine as a demethylated and oxidized compound (1-chlorophenyl, 5, 6-dihydrocyclohexanone-2) in the first, second and third 24-hour samples.

Discussion

Central Nervous System. An outstanding property of CI-581 which distinguishes it from other anesthetics is the rapidity of onset of excellent analgesia. There is presently no more rapid method for induction of analgesia than the intravenous administration of CI-581.

Reasoning from observation of drug-induced delirium, minimal EEG change, lack of EEG slow bursts, and depression of later portions of the auditory evoked response, CI-581 seems to have a primary effect on the cortex.

Respiration. CI-581 usually produced a mild early depression which is rapidly followed not only by normal volume, but by

TABLE 4. Ventilatory Data and Blood Gases of 34 Surgical Patients Receiving CI-581

	Pts.	Awake, Breathing Air Vol.	Awake, Breathing 5% CO_2 Vol.	Asleep Breathing Air Vol.	Asleep Breathing 5% CO_2 Vol.
Min. vol./liter	34	5.18 ± 0.28 A	10.05 ± 0.50 B	5.69 ± 0.32 C	10.91 ± 0.60 D
Rate		19.4 ± 1.23	21.8 ± 1.65	19.1 ± 1.27	22.6 ± 1.53
V_m Response $\frac{CO_2}{Air}$:		$\frac{10.05}{5.18} = 1.94$		$\frac{10.91}{5.69} = 1.92$	
Pa_{O_2}	20	70.9 ± 1.79 E	82.2 ± 1.67 F	67.4 ± 2.50 G	78.0 ± 1.88 H
Pa_{CO_2}	20	33.0 ± 0.82 J	37.4 ± 0.88 K	35.9 ± 1.14 L	40.5 ± 1.07 M
*p*H	20	7.416 ± 0.60 N	7.368 ± 0.87 P	7.386 ± 0.65 Q	7.345 ± 0.70 R

$P < 0.001$: A–B, C–D, E–F, G–H, F–G, J–K, J–M, N–P, N–Q, N–R, Q–R.
$P < 0.01$: L–M.
$P < 0.05$: J–L, K–M, P–R.

normal response to carbon dioxide challenge.

Circulation. A safety factor offered by CI-581 in the animal experiments was the lack of sensitization of the myocardium to epinephrine. The increase in heart rate of human subjects, with the concomitant increase of cardiac output and systemic blood pressure, suggest that there may have been an acute intravascular release of epinephrine resulting in combined alpha and beta adrenergic receptor stimulation. This concept would correlate well with th animal studies in which it was shown tha. following hemorrhage, which would stimulate release of epinephrine, CI-581 had little effect on blood pressure. With or without hypovolmia, however, administration of epinephrine had similar effects.

In contrast to most anesthetic agents presently in use, administration of CI-581 resulted in an increase in cardiac output and blood pressure with little change in peripheral resistance. The increase of cardiac output was mediated almost entirely by an increased heart rate, as there was no change in stroke volume.

Behavior. Cerebral effects of CI-581 differ considerably from those of other anesthetics. If one judges from the seeming paucity of effect on the reticular activating system, it may be that the essential effect is cortical. Regardless of the site of action one result of the agent is difficulty in orientation during recovery. Response to stimulation may be obtained very rapidly following the analgesic period, but 2 to 3 hours elapse before the patient can focus his eyes and concentrate his thoughts. Vividness of dreams exceeds that experienced with the use of presently used agents.

Metabolism. CI-581 showed little systemic effect as measured by enzymatic activity and blood constituents. Much remains to be learned about the metabolism of CI-581, for only 23 per cent of the material was accounted for. Presently we know that oxida-

TABLE 5. Average Values Obtained from 150 Surgical Patients Receiving CI-581 (Average Number of Doses = 5.2)

	Control Awake	Highest Value During Anesthesia	Time after Induction Highest Value Occurred	Lowest Value
Blood pressure (mm. Hg.)	116/74	150/96	12.0 min.	123/81
Pulse	96.7	120	12 min.	95
Respiratory rate	21.5	27.3	16.6 min.	20.7

Average Recovery Times of 150 Surgical Patients After Receiving CI-581

	Orientation	Ambulation
Intravenous administration	131 min.	176 min.
Intramuscular administration	179 min.	218 min.

tion and demethylation are two routes of metabolism of the drug.

The unusual combination of properties of CI-581 would render it a valuable part of the armamentarium of the anesthesiologist. It produces excellent analgesia rapidly without depression of circulation, and has little effect on respiration. These qualities would be of value in emergency situations where hemorrhage in severe and rapid action without depression is needed; placenta praevia and abruptio placentae would be included here. Advantages would also be found in operations about the head where the surgeon desires unhampered access to the operative field. Two other factors would tend to prevent its universal use. One is the prolonged recovery period of 2 to 3 hours. The other is vividness of dreams which may occasionally border on hallucinations. The advantages of CI-581 are physiological, while the possible disadvantages are psychological. A major disaster requiring rapid analgesia for large numbers of persons would find CI-81 superior to any drugs presently available.

Summary

CI-581 (2-orthochlorophenyl 2-methylamino cyclohexanone HCl), a congener of phencyclidine, was administered to healthy normo- and hypovolemic dogs with and without intravenous epinephrine. The drug raised blood pressure in the normovolemic animals but not in the hypovolemic dogs. Epinephrine elevated blood pressure in both groups. No sensitization of the myocardium to epinephrine occurred.

CI-581 was administered intravenously to healthy volunteers. Blood pressure, heart rate and cardiac output were elevated rapidly with little change in peripheral resistance. Rate and volume of respiration as well as response to 5 per cent carbon dioxide in air were essentially unchanged. EEG patterns during anesthesia evidenced minimal rhythmic slowing, but additional CI-581 did not produce severe slowing (burst-suppression activity was seen once). Volunteers reported that during recovery they felt they were separated from their extremities and knew they were somewhat confused. Confusion was always under some control. Blood glucose, NPN, and enzymatic studies to measure alterations of carbohydrate and protein metabolism showed little change, at the termination of anesthesia and 2 days later.

One hundred fifty patients, 80 per cent of whom were under 30 years old, received CI-581 for surgical anesthesia. Analgesia and amnesia were outstanding. Relaxation was absent; pharyngeal and laryngeal reflexes were present. As in the volunteers, respiration was little affected and response to CO_2 was unchanged. Blood pressure rose. Waking periods were relatively long, averaging about 3 hours. There was no excitement during waking, if the patients were undisturbed. Five of the 150 patients had disagreeable dreams which were so vivid that they said they would henceforth prefer other types of anesthesia.

Major physiological advantages are offered by CI-581, which may in some cases be accompanied by psychological disadvantages.

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Anesthesia

SPINAL HYPERTENSION An elderly male patient, scheduled to have a lower limb amputation, was given a spinal anesthetic accompanied by 50 mg. ephedrine intramuscularly as a prophylactic vasopressor. As the anesthetic level reached T-10, the blood pressure rose from 160 to 340 mm. of mercury systolic, and the patient complained of headache. Treatment with thiopental and meperidine were to no avail, but an infusion of trimetaphan (Arfonad) lowered the systolic pressure to 140 mm. of mercury and relieved the symptoms. It was then learned that the patient had been receiving 100 mg. of nialamide *t.i.d.* the day before surgery, so that the action of ephedrine was unopposed due to monoamine oxidase inhibition. Phentolamine is recommended for treatment of hypertension of this etiology, but trimetaphan is also effective. Monoamine oxidase inhibitors may also interfere with hydrolysis of other drugs such as narcotics and alcohol and thus potentiate their action too, especially producing respiratory depression. (*Clinical Anesthesia Conference: Hypertension Following Use of Monoamine Oxidase Inhibitor, New York J. Med. 67: 570 (Feb.) 1967.*)

AXILLARY BLOCK AND DIALYSIS Heretofore the insertion of arteriovenous shunts using local infiltration has been made difficult by the occurrence of vascular spasm. The changing caliber of the vessels has resulted in leakage and diminished flow at the shunt, necessitating frequent revisions. To obviate these difficulties and to permit more adequate cannulas to be employed, blocking of the brachial plexus was initiated. This technique, using the axillary approach, was undertaken on 30 cases. The resultant vasodilation and analgesia facilitated operation appreciably. Infrared photography and thermographic examination substantiating the clinical findings were done. Axillary block of the brachial plexus is regarded the method of choice for this procedure, providing excellent working conditions for the surgeons with a minimum of risk and discomfort for the patient. (*Urban, J. B., and others: Axillary Block and Dialysis, J.A.M.A. 199: 889 (March) 1967.*)