CYCLOHEXAMINE (CI-400): A NEW INTRAVENOUS AGENT

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THE SEARCH for a true intravenous anesthetic has challenged the imagination of pharmacologists and anesthesiologists. With the passing years new agents are synthesized and studied in a search for compounds of merit. Many drugs have been investigated since Oré of France first used intravenous chloral hydrate in 1872. The past few years have seen the introduction of several compounds which have not yet withstood the test of time; these drugs include steroids such as Viadril, "thiazanedione" represented by Dolitrone, and more recently, a B-vitamin derivative designated S.C.T.Z.

A series of cyclohexylamine derivatives has been synthesized and studied in the laboratory. These compounds differ from previous intravenous agents in that they are capable of producing sensory blockade of sufficient intensity for the completion of surgical procedures without concomitant sleep and without significant depression of respiration and circulation.

The first member of this series to be investigated clinically in anesthesia was 1-arylcyclohexylamine (designated CI-395 or Sernyl). This compound (fig. 1) produced sensory blockade of sufficient degree that minor surgical procedures could be performed. The addition of nitrous oxide anesthesia made possible the conduct of many major operations; succinylcholine was used if muscle relaxation was desired. Unfortunately, psychic disturbances such as severe emergence delirium, hallucinatory phenomena, bizarre behaviour patterns, echolalia, and logorrhea were frequently noted following the use of CI-395 so that the use of this compound in anesthesia was discontinued.

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Another drug in the series designated CI-400 or cyclohexamine has been studied clinically because laboratory evidence implied a lesser incidence of disturbances following its administration. Cyclohexamine forms the basis of this report. Its formula is shown in comparison with CI-395 (fig. 1).

CLINICAL PHARMACOLOGIC STUDIES

Unmedicated patients serving as their own controls were studied. The patients were informed that tests would be performed involving their cooperation, and they were assured that they would be fully anesthetized prior to the onset of surgery.

Venous pressure readings were obtained according to the method of Moritz and Tabora.[1] Circulation times were studied by the intravenous ether (arm to lung) test. Cardiac activity was monitered and recorded with the Cambridge cardioscope and "simpliscribe." Blood pressure and pulse were obtained in the standard fashion using a mercury manometer

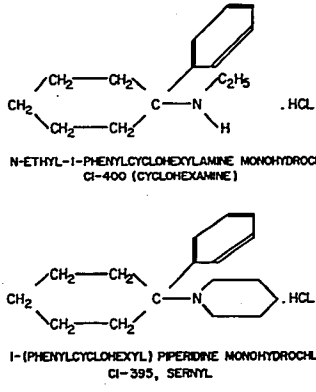

FIGURE 1.

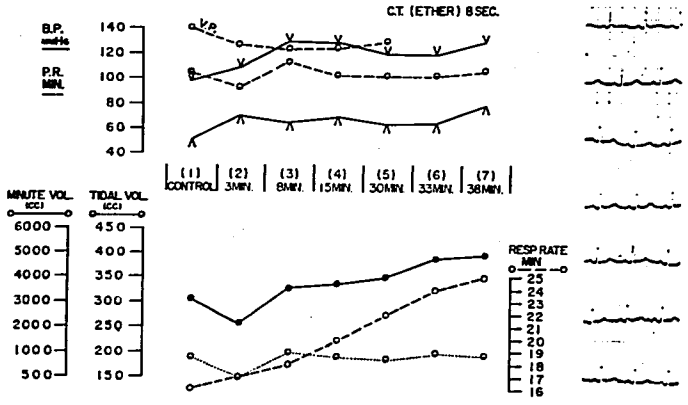

FIG. 2. Composite graph demonstrating the effect of cyclohexamine on respiration and circulation in an unmedicated patient. Electrocardiographic tracings are all lead two and correspond in descending order to the time units in the mid-portion of the graph. C.T. = arm to lung circulation time (ether). V.P. = Venous pressure inserted here with no reference scale, is merely intended to show trend. Note steadily increasing respiratory rate associated with the use of intravenous ether circulation time.

for the pressure readings. The pulse rates were cross-checked with electrocardiographic tracings taken during the study.

Respiratory studies were carried out during the test period with a Bennett meter. The patients were allowed to become accustomed to the face piece and meter before recording commenced.

Composite graphs from two patients in this portion of the study are shown in figures 2 and 3. The control readings were obtained after the patients were as close to basal conditions as possible. Cyclohexamine was then administered intravenously, and readings obtained for the various procedures as indicated by the time units on the graphs. The dose of drug had been previously determined on the basis of its clinical application and also on the basis of experience with CI-395.

These studies indicated that there was a transient rise in blood pressure and in pulse rate following the intravenous administration of the drug. Electrocardiographic tracings revealed no disturbances in rhythm. Venous blood pressures showed transient increases over the control levels of the individual patients, although the readings remained within normal limits. The arm to lung circulation time was not altered by the test drug.

The respiratory studies indicated no depression of respiration following intravenous cyclohexamine. Restlessness occasionally occurred after the drug was given, and under these circumstances the tidal volume showed marked variation although the minute volume remained constant. These latter studies are not included in this report because the restlessness also interfered with the determination of venous pressures and circulation times. The use of intravenous ether to study the circulation time resulted in a disturbance of respiratory rate so that patients for circulation time studies could not be used to furnish respiratory data.

Neurological observations were made on the patients who received cyclohexamine intravenously. The onset of drug action was accompanied by a sensation of dizziness; restlessness occurred in some patients at this point and then disappeared as the patient became unresponsive to painful and auditory stimuli. The eyelid reflex and pupillary light response remained intact. Corneal anesthesia was present,

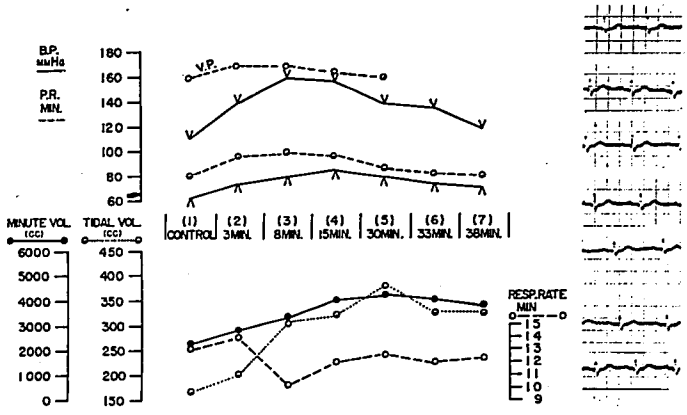

FIG. 3. Composite graph demonstrating the effect of cyclohexamine on respiration and circulation in an unmedicated patient. Electrocardiographic tracings are all lead two and correspond in descending order to the time units in the mid-portion of the graph. V.P. = Venous pressure inserted here with no reference scale, is merely intended to show trend. Note relatively stable respiratory rate in absence of ether circulation time.

and nystagmus in both horizontal and vertical planes was observed.

Skeletal muscle tone remained intact and in some instances increased tone in the extremities was observed. An extremity placed in an awkward position would be so maintained by the patient for long periods of time.

As the drug effect waned, patients once again responded to auditory and painful stimuli. They were often disoriented as to time and place; echolalia and logorrhea were noted frequently. Vivid dreams, often of a morbid nature, occurred under the influence of the drug; patients stated they were dead and therefore had to be reassured as to their whereabouts. At times it was not possible to reach through the patient's dream to afford reassurance, so vivid was their hallucination. The intravenous use of chlorpromazine or triflupromazine was effective in ameliorating the psychic disturbances following cyclohexamine in the unmedicated patient.

CLINICAL STUDIES

Adult Premedication. Cyclohexamine was substituted for narcotics and tranquilizers used for premedication; it was combined with a belladonna derivative. Accordingly, 128 adult patients received cyclohexamine 5–15 mg. with atropine 0.2–0.6 mg., intramuscularly one hour prior to surgery (table 1). Doses were determined primarily by the patients psychic and physical status with a secondary correlation to body weight (0.1 mg./lb.). Restlessness not infrequently preceded the calming action of cyclohexamine. Diphenhydramine was added to the premedicating schedule as a mild supplementary sedative. Increased salivation was noted in 26 per cent of this group of patients.

The use of cyclohexamine as preanesthetic

TABLE 1

CYCLOHEXAMINE FOR ADULT PREMEDICATION—128 PATIENTS

PREOPERATIVE SEDATION

Psychic State	Awake	Drowsy	Asleep	Per Cent Series
Calm	58 (32)	17 (8)	10 (1)	67
Apprehensive	37 (9)	3	—	31
Disoriented	1	2	—	2

Figures in parentheses represent the number of patients who received diphenhydramine in addition to cyclohexamine.

medication was associated with increased pulse rates and transient rises in blood pressure. In an attempt to study these changes, the patients were divided into four age groups. The changes in pulse rate and in blood pressure occurred most frequently in the youngest age group (tables 2 and 3).

Pediatric Premedication. Cyclohexamine was used for premedication in children and combined with methantheline bromide as the drying agent (table 4). A similar series of pediatric patients received pentobarbital or pentobarbital-meperidine with methantheline bromide. Increased salivation was noted in 30 per cent of the cyclohexamine series as compared to 5 per cent in the barbiturate series. Preoperative sedation was better in the cyclohexamine series (68 per cent) as compared to the standard premedicant series (50 per cent).

Surgical Anesthesia. The sensory blocking action of cyclohexamine was studied during surgery. The patients were premedicated with atropine, atropine-meperidine, or atropine-meperidine-tranquilizer. Cyclohexamine was administered slowly through the tubing of an intravenous infusion after the vital signs had been observed. The initial dose of drug was 9–10 mg. with subsequent 1.5–3.0 mg. increments until the patients no longer responded to painful or auditory stimuli. Minor surgical procedures could then be performed. Occasionally, an hypnotic dose of a short acting barbiturate was injected because of restlessness.

Tracheal intubation could be accomplished in these patients without the use of muscle relaxing drugs. Bucking occurred, however, so that patients whose trachea had been intubated required either nitrous oxide or a short acting barbiturate to quiet them. Laryngospasm occurring during tracheal intubation without the use of a muscle relaxant could be terminated easily by the removal of the laryngoscope or endotracheal tube.

Major surgery required supplementation of cyclohexamine with nitrous oxide and a barbiturate. Muscle relaxation could be obtained only when drugs such as succinylcholine were used. Under these circumstances cyclohexamine (15 mg.) appeared as effective as meperidine (100–150 mg.) for supplementation of anesthesia. The cardiovascular and respiratory depression commonly seen following meperidine was not observed.

Cyclohexamine was used to produce surgical anesthesia either alone or in conjunction with a nitrous oxide-barbiturate sequence in 282 unselected patients ranging in age from 2 months to 83 years. The operations ranged from superficial minor surgery such as excision

TABLE 2

CYCLOHEXAMINE FOR ADULT PREMEDICATION—128 PATIENTS
EFFECT UPON PULSE RATE

Number of Patients	Ages	Increase in Beats per Minute			Per Cent Series
		10–20	22–30	32–40	
49	16–40	17	6	5	22
21	41–55	7	1	0	6
27	56–70	7	4	0	8.5
31	71+	9	2	0	8.5

TABLE 3

CYCLOHEXAMINE FOR ADULT PREMEDICATION—128 PATIENTS
EFFECT UPON BLOOD PRESSURE(†)

Number of Patients	Ages	30 mm. Hg	40 mm. Hg	50 mm. Hg	60 mm. Hg	Over 60 mm. Hg	Per Cent Series
49	16–40	7	2	3	1	2	12
21	41–55	2	1	4	—	1	4
27	56–70	2	—	3	—	2	5
31	71+	2	2	1	—	1	5

TABLE 4

CYCLOHEXAMINE FOR PEDIATRIC PREMEDICATION
PREOPERATIVE SEDATION

Psychic State	Awake	Drowsy	Asleep	Per Cent Series
Calm	32	4	7	68
Apprehensive	19	1	—	32
Disoriented	—	—	—	—

Drug	Dose	Time Preoperative	Route
CI-400	0.1 mg./lb.	½–1 hour	Intramuscular
Banthine	0.2 mg./lb.	½–1 hour	Intramuscular

TABLE 5

COMPARATIVE INCIDENCE (PER CENT) OF SIDE EFFECTS OF ANILERINE (40 MG. INTRAMUSCULAR), MEPERIDINE (100 MG. INTRAMUSCULAR), AND CYCLOHEXAMINE (15 MG. INTRAVENOUS)

	Anileridine*	Meperidine*	Cyclohexamine Dilatation and Curettage	Cyclohexamine Other Surgery
Emergence delirium—mild	Not reported	Not reported	36	14
—severe	Not reported	Not reported	1	2
Excessive verbalization	60	30	21	5
Nausea	43	25	1	0
Vomiting	13	5	21	16
Headache	Not reported	Not reported	7	0
Dizziness	60	65	23	16
Auditory hallucinations	Not reported	Not reported	1	0
Visual difficulties	28	15	8	7
Speech difficulties	Not reported	Not reported	1	2
Disorientation	Not reported	Not reported	3	0
Catatonia	Not reported	Not reported	2	0
Shivering	10	8	1	0
Numbness	5	13	6	1
No complaints	Not reported	Not reported	24	48

* Keats, Telford and Kurosy: ANESTHESIOLOGY 18: 690, 1957.

of keloids and other peripheral tumors to orthopedic and abdominal procedures. In addition, 50 cesarean sections were accomplished satisfactorily in unmedicated patients (atropine only) with cyclohexamine and nitrous oxide.

Postoperative Period. The postoperative side effects associated with cyclohexamine in surgery were mainly psychic disturbances. The reactions noted have been compared with data obtained from a study by Keats, Telford and Kurosu [2] on two analgesic compounds administered in therapeutic doses (table 5). It is interesting to note the similarity of side effects occurring with the different groups. The patients who received cyclohexamine were divided into two general groups; dilatation and curettage, and surgical. There was some form of complaint in 76 per cent of the former group as compared to 52 per cent in the general surgical group, thus emphasizing the significance of the psychic element.

DISCUSSION

Recently several new intravenous anesthetic agents have been introduced and evaluated but the usefulness of these drugs has been limited because of the relative lack of sensory blocking action and because of concomitant depression of respiration and circulation. Cyclohexamine has been studied to determine its place if any in anesthesia. It should not be considered as the ultimate agent, but rather as the probable forerunner of an interesting series of drugs. These compounds produce sensory anesthesia sufficient for the performance of minor operations without depression of respiration or blood pressure.

Cyclohexamine has been used in place of meperidine in the nitrous oxide-barbiturate series without production of hypotension. Cyclohexamine does not depress vital signs, and therefore does not complicate anesthetic management with this technique.

One major problem with the use of unsupplemented cyclohexamine during surgery is the rather narrow therapeutic dose range. We have found the drug effective in the narrow range of 10–20 mg. with an average of 12–15 mg. Moreover, the therapeutic dose must be given at one time rather than intermittently as with the intravenous drip method. Another difficulty encountered was that increasing the dose did not produce a more intense sensory block, but rather exaggerated the undesirable postoperative side reactions.

The central nervous system site of action of

cyclohexamine is unknown. The drug apparently exerts its influence in subcortical areas. Clinical observations suggest a sympathomimetic activity associated with the administration of cyclohexamine. A rise in blood pressure and pulse rate was common. Not infrequently, patients receiving cyclohexamine became cool and moist to the touch; in 3 such patients cyanosis of the nailbeds appeared with no physiologic explanation other than drug action. The vascular effect of cyclohexamine was potent enough to prevent the hypotension one might anticipate when 15 mg. doses of chlorpromazine were added for supplementary effect.

The postoperative side effects of cyclohexamine have been previously compared to meperidine and anileridine. Emergence delirium and excessive, boisterous talk has disturbed and annoyed other patients in the recovery room. Patients to whom cyclohexamine has been given do not recall their recovery room stay.

Summary

Cyclohexamine is a new intravenous agent capable of producing analgesia suitable for the performance of minor surgery.

Pharmacologic studies in man have revealed no direct depression of respiration or circulation, and no disturbance of cardiac rhythm.

The drug has been used as premedication in 191 pediatric and adult patients scheduled for operation; sedation was good but there was a marked increase in salivation. Cyclohexamine was used alone or in combination with a nitrous oxide-barbiturate sequence to produce surgical anesthesia in 282 patients. Muscle relaxation was not obtained. Postanesthetic emergence delirium was commonly observed.

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REFERENCES

1. Friedberg, C. K.: Diseases of the Heart. Philadelphia, W. B. Saunders Co., 1950, p. 148.
2. Keats, A. S., Telford, J., and Kurosu, Y.: Studies of analgesic drugs: Anileridine dihydrochloride, Anesthesiology 18: 690, 1957.