LABORATORY AND CLINICAL EXPERIENCES WITH GLUTETHIMIDE

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For several years glutethimide (Doriden) has been utilized as an oral nonbarbiturate sedative and hypnotic.[1-4] One advantage of this drug is the slight depressant effect on respiration, even when large doses are administered.[5] Because of its sedative properties and sparing effect on respiration, glutethimide was evaluated for preoperative medication by a double-blind technique. At the same time, an intravenous preparation of the drug became available, so its usefulness as a short-acting intravenous hypnotic drug was investigated in the laboratory and clinic. Because of the close chemical relationship between glutethimide and glutarimide (Megimide), an investigation was undertaken to see if this analeptic possessed a specific antagonistic effect against glutethimide. A specific antagonist to the effects of an acceptable intravenous hypnotic would be of value in anesthesiology.

Preoperative Medication

In the double-blind study, adult, male patients received: (1) glutethimide 500 mg. at bedtime and glutethimide 1 Gm. with atropine 0.6 mg. 1.5 to 2 hours before operation; (2) the same doses of glutethimide and atropine, with promethazine 50 mg. before operation; or (3) placebo tablets. All doses of the hypnotic were given orally as 250 mg. tablets, and all drugs were administered in random fashion. Three anesthesia residents evaluated the patients prior to induction of anesthesia. The code to the drugs was held by a person not associated with the operating room; it was not broken until completion of the study.

Table 1 shows the results of this study. No appreciable differences regarding degree of wakefulness or sedation could be found between the glutethimide groups or the placebo groups, with or without the addition of promethazine. We have been unable to support previous suggestions that glutethimide is of value as a sedative in preoperative medication.[6, 7] We believe that, with the stress and fear associated with thoughts of anesthesia and surgery, the doses of glutethimide administered, although greater than those prescribed for "insomnia," were insufficient to produce consistently a recognizably drowsy and calm state in the patient.

Intravenous Administration

Glutethimide is not readily soluble in water, and therefore a suitable solution for intravenous injection was difficult to prepare. That employed in this study was a 5.0 per cent solution of glutethimide in 70 per cent polyethylene glycol-400. *In vitro*, the solvent did not produce hemolysis, but the solvent plus the drug produced definite gross hemoly-

TABLE 1

Preoperative Medication Study

	Glutethimide, 58 Patients		Placebo, 57 Patients	
	Number	Per Cent	Number	Per Cent
Wide awake	30	51	35	61
Apprehensive	11	19	13	22
Alert	33	57	33	58
Drowsy	8	13	9	15
Asleep	0	0	1	
Calm	47	81	40	70
	Glutethimide + Promethazine, 93 Patients		Placebo + Promethazine, 65 Patients	
	Number	Per Cent	Number	Per Cent
Wide awake	36	38	32	49
Apprehensive	22	23	17	26
Alert	20	21	22	33
Drowsy	12	12	4	6
Asleep	4	4	0	0
Calm	56	60	33	50

Results of double blind study in which glutethimide, glutethimide + promethazine, or a placebo were administered with atropine to patients for preoperative medication.

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sis. However, in animals or humans, this hemolysis did not appear to act in a deleterious fashion significant enough to warrant discontinuance of the study. On injection into both animals and humans, evidence of irritation was noted. With the first injection into the awake animal, withdrawal motions were seen frequently lasting about 30 seconds until hypnosis supervened. The question arose as to whether, in the relatively aqueous blood stream, there was a temporary crystallization of the drug which produced the pain before it redissolved.

Animal Investigation

Comparison Between Glutethimide and Thiamylal Sodium. Preliminary intravenous injection indicated that in the dog glutethimide 40 mg. per kilogram produced a moderately profound sedative and hypnotic action approximately equivalent to that resulting from thiamylal sodium (Surital) 20 mg. per kilogram. The duration of action of these two drugs and their effects on respiration and circulation were compared following the rapid, intravenous administration of the doses noted above. Six mongrel dogs weighing between 8 and 15 kg. were studied: each dog served as his own control, in that the nonbarbiturate was given one day and then the ultra short-acting barbiturate administered several days later to the same dog under similar conditions. Glutethimide was alternated with thiamylal in the first of the two

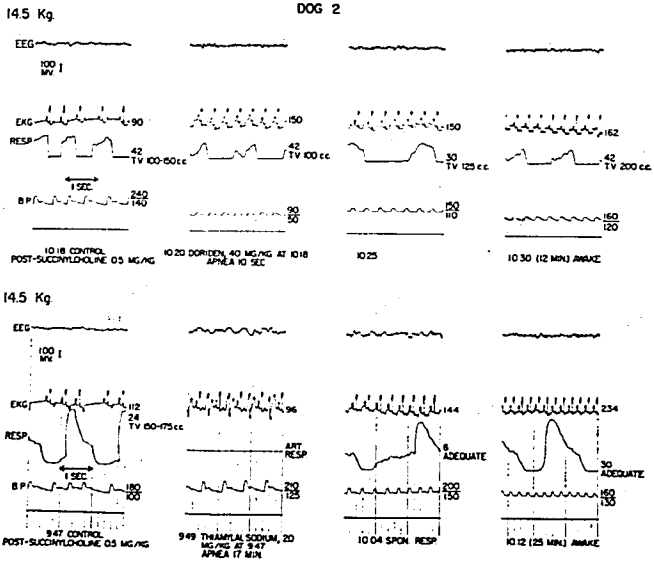

FIG. 1. Excerpts of recordings from Grass EEG machine to show comparison between intravenous administrations of equivalent doses of glutethimide and thiamylal. EEG—fronto-parietal electrodes embedded in skull. ECG—lead 2—standard limb needle electrodes. *Respiration*—animal receiving oxygen—respiratory patterns recorded with pneumotachygraph in series with endotracheal nonrebreathing technique—tidal volumes measured with Bennett ventilation meter. When apnea was more prolonged than one minute, artificial respiration with the Palmer pump, employing normal tidal volumes, was utilized to prevent hypoxia and hypercarbia. *Arterial blood pressure*—recorded from femoral artery by means of indwelling polyethylene catheter through Statham strain gauge and demodulator.

TABLE 2

COMPARISON BETWEEN GLUTETHIMIDE AND THIAMYLAL SODIUM

Glutethimide (40 mg. per kg.)					Thiamylal Sodium (20 mg. per kg.)				
Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time	Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time
1	0	—	−30	9′	1	27′	—	−11	?(33+′)
2	10″	−33	−62	12′	2	17′	−80	+16	25′
3	10″	−45	−26	13′	3	2′	−75	N.C.	?(30+′)
4	10″	−16	−10	8′	4	2′	−66	+38	?(11+′)
5	0	−88	−35	20′	5	0	−55	+66	?(25+′)
6	10″	−33	−18	11′	6	40″	−91	+31	38′
Average	6.6″	−43	−30	12′	Average	8′	−73	+23	32′

The length of apnea is shown in seconds or minutes. The percentage reduction in minute volume respiration from the control is noted following restitution of spontaneous respiration. The percentage reduction or increase in systolic blood pressure from the control is noted.

experiments. Preliminary preparation of the animals, which involved endotracheal intubation with a cuffed tube, venous and arterial cutdowns for injections and pressure recordings, and insertion of electroencephalographic electrodes into the skull, was carried out after intravenous injection of succinylcholine 0.5 mg. per kilogram. Controlled respiration was maintained with a Palmer pump until the animal had recovered normal respiratory exchange, and then the hypnotic drug was administered to the "unsedated" animal. This technique avoided the complication of prior sedation. Figure 1 shows the typical results obtained during two experiments in the same animal. Table 2 compares the results obtained in 6 animals. The following observations were made: (1) Following rapid, intravenous injection induction of hypnosis was rapid (20 to 30 seconds) and similar with both drugs. (2) Apnea and the subsequent respiratory depression were more profound with thiamylal than with glutethimide. (3) Cardiovascular depression, as reflected by hypotension was more marked with glutethimide than with thiamylal. (4) The waking time after single rapid intravenous injections was shorter with glutethimide than with thiamylal.

Comparisons Between Hypnotic Drugs and Analeptic Administration. To determine if bemigride possessed a specific analeptic action towards glutethimide, and to compare its

TABLE 3

COMPARISON BETWEEN GLUTETHIMIDE AND GLUTETHIMIDE-BEMIGRIDE

Glutethimide (40 mg. per kg.)					Glutethimide (40 mg. per kg.) + Bemigride (200 mg.)				
Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time	Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time
1	0	—	−30	9′	1	0	—	+12	8′
2	10″	−57	−20	8′	2	40″	−60	+ 3	10′
3	10″	−33	−62	12′	3	20″	−50	+ 3	15′
4	10″	−45	−26	13′	4	0	+25	−22	13′
5	10″	−16	−10	8′	5	0	−66	−23	12′
6	0	−77	−35	20′	6	0	−88	+51	30′
7	10″	−33	−18	11′	7	60″	−79	−14	20′
Average	7″	−43	−28	11′	Average	17″	−53	+ 1	15′

Interpretation is similar to that noted in table 2.

TABLE 4

COMPARISON BETWEEN THIAMYLAL SODIUM AND THIAMYLAL SODIUM-BEMIGRIDE

Thiamylal Sodium (20 mg. per kg.)					Thiamylal Sodium (20 mg. per kg.) + Bemigride (200 mg.)				
Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time	Dog	Length Apnea	Minute Vol. %	B.P. %	Waking Time
1	20″	−44	N.C.	34′	1	0	−66	N.C.	10′
2	21′	−37	−24	?(24+′)	2	17′	−33	−27	?(35+′)
3	0	−60	+20	30′	3	17′	−75	N.C.	34′
4	0	−12	+25	30′	4	1′	−37	+33	17′
Average	6′	−38	+ 5	31′	Average	9′	−53	+ 1	20′

Interpretation is similar to that noted in table 2.

action against thiamylal, experiments were performed in dogs utilizing a protocol similar to that outlined above (fig. 1). In preliminary experiments we found that bemigride 200 mg. was an average subconvulsive dose in the sedated animal; therefore, this amount was administered in each experiment. The doses of glutethimide and thiamylal were similar to those used previously. Again, each dog served as his own control, and was subjected to two experiments several days apart.

Table 3 shows the results in 7 dogs to which glutethimide was administered alone or simultaneously with bemigride. The effect of

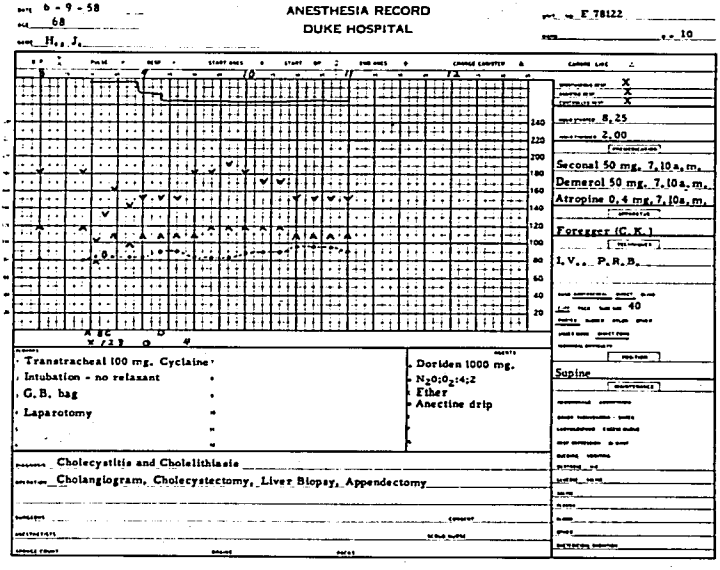

FIG. 2. Anesthetic record of a 68 year old woman showing reduction of blood pressure associated with intravenous glutethimide utilized for induction of anesthesia.

administering thiamylal intravenously with and without bemigride to 4 dogs is seen in table 4.

On the basis of these acute experiments, we concluded: (1) Bemigride did not show a specific analeptic action towards glutethimide: its only effect was to prevent or lessen the hypotension associated with glutethimide administration. (2) Bemigride did not show a specific or nonspecific analeptic action towards thiamylal.

Clinical Investigation

Fifty-eight patients between 13 and 74 years of age received glutethimide intravenously in doses ranging between 350 and 3,500 mg. There were 27 females and 31 males in the study. Preoperative medication consisted usually of meperidine and atropine. The drug was injected by means of a 3-way stopcock into a vein on the forearm which had been cannulated previously with an 18-gauge needle. A test dose of 100 mg. was administered first, and then further increments of 100–200 mg. injected as required. Usually unconsciousness and a hypnotic state was achieved rapidly with 500 mg., but the dose required varied between 200 mg. in a 33 year old female and 1,500 mg. in a 23 year old male. Prior to the onset of unconsciousness, pain of varying degrees was noted by 16 (27 per cent) of the patients. This pain was limited to the arm in which the injection was made in all but two patients who had distress radiating to the thorax. In 7 patients (12 per cent) excitement was noted during the induction phase: in three of these patients garrulousness was marked. A reduction in blood pressure greater than 30 mm. of mercury was seen in 6 patients (fig. 2). In all patients

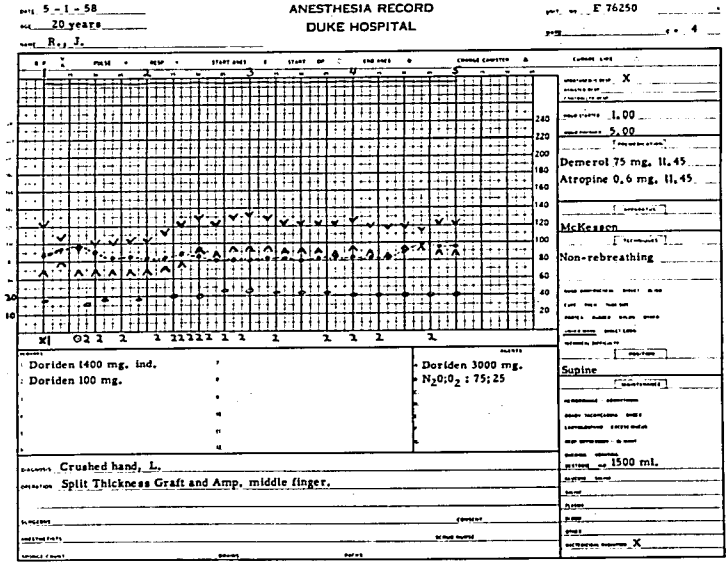

Fig. 3. Anesthetic record of a 20 year old man given glutethimide 3,000 mg., with nitrous oxide and oxygen, over a period of 4 hours. Note the frequency of additional doses of glutethimide during maintenance of anesthesia.

the hypotension was short-lived, and recovery to "safe" levels occurred spontaneously.

For the most part, glutethimide was used as an agent to induce anesthesia. It was found to be compatible with ethyl ether, cyclopropane, halothane and muscle relaxants. In several patients gluthethimide in combination with nitrous oxide and oxygen was utilized for the maintenance of anesthesia. Figure 3 duplicates the anesthetic record of a patient given 3,000 mg. of glutethimide over a period of four hours. In these patients the recovery of full consciousness occurred in one to three hours postoperatively.

We were unable to determine the length of action of a single dose of glutethimide. However, an estimate of the short-acting effect of the drug could be obtained by noting the frequency with which the drug had to be injected to maintain anesthesia (fig. 3).

The following comparison of glutethimide and thiamylal as agents for induction of anesthesia can be made:

(1) The onset of unconsciousness and hypnosis was as rapid with glutethimide as with barbiturate, although the dose required was more variable with glutethimide.

(2) Glutethimide produced less respiratory depression than equivalent doses of thiamylal. There was little change in respiratory rate with either drug, but reduction in tidal volume was markedly less with glutethimide.

(3) Pharyngeal and laryngeal reflexes were more depressed with glutethimide than with thiamylal. Following the production of unconsciousness with glutethimide, oropharyngeal airways could be inserted without reaction, and in several patients (fig. 2) orotracheal intubation was performed with relative ease.

(4) The introduction of ethyl ether into the anesthetic system was accomplished with greater facility following induction of anesthesia with glutethimide than with thiamylal. After glutethimide, breath-holding, coughing and laryngeal stridor were absent. This finding probably was related to the diminished reflexes noted above.

(5) Evaluation of the relative cardiovascular depression with the two drugs was difficult. Hypotension occurs in a certain percentage of patients with the ultra short-acting barbiturates, just as with glutethimide. The glutethimide series was too small to make accurate comparisons.

(6) The local irritation associated with glutethimide injection was marked, while that seen with the barbiturates is practically nonexistent. Postoperatively, localized areas of thrombosis or thrombophlebitis were noted in 60 per cent of the patients who received glutethimide: this complication is rare with the barbiturates. When seen, the irritation extended for approximately one inch along the vein and was not as extensive or troublesome as that seen with hydroxydione.[5]

Summary

This animal and clinical investigation has shown that glutethimide, although ineffective when administered orally as a preoperative sedative, does provide satisfactory hypnosis for induction of anesthesia when injected intravenously. Its advantages include rapid onset of action and less depression of respiration than seen with thiamylal, along with desirable depression of pharyngeal and laryngeal reflexes. Among its disadvantages are the insolubility of the drug in aqueous solution, the hemolysis noted when mixed with blood, the local vascular irritative phenomena seen with and following injections, and a transitory, though obvious, cardiovascular depression occasionally seen. Bemigride, although closely related chemically to glutethimide, did not show a specific antagonistic action towards the hypnotic.

Any drug which is to compete successfully with the thiobarbiturates as they are at present used in anesthesia must have specific and obvious advantages, with no drawbacks over the present compounds. The present preparation of glutethimide does not fulfil these requisites.

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ADRENAL INSUFFICIENCY In normal subjects the intramuscular injection of 25 units of ACTH will cause at least a 50 per cent reduction of urinary sodium excretion. In patients with adrenal cortical insufficiency no appreciable decrease in urinary sodium occurs over a 4-hour period. (*Batchelor, T. M., and Mosher, R. E.: Urinary Sodium Retention After ACTH Stimulation: Rapid Single Screening Test for Adrenal Cortical Insufficiency, Amer. J. M. Sc. 239: 172 (Feb.) 1960.*)

GANGLION BLOCKING DRUGS All ganglion blocking agents probably initiate the same hemodynamic pattern in man. The fall in systemic blood pressure is caused by a reduction in systemic vascular resistance and by a reduction in cardiac output. Cardiac output may increase, however, particularly in patients in heart failure or in those with mitral stenosis. Blood flows to the various organs are usually decreased, but an increase may occur to the extremities. Vascular resistance is reduced in the cerebral and coronary vessels, is variable in the renal vessels, and uncertain in the splanchnic and extremity vessels. Pulmonary artery pressure usually falls. There is a local vascular adjustment of the cerebral vessels so that they are dilated when pressure is reduced. The behavior of the renal and splanchnic vessels is the opposite of the cerebrals. (*Aviado, D. M.: Hemodynamic Effects of Ganglion Blocking Drugs, Circulation Res. 8: 304 (March) 1960.*)

PHEOCHROMOCYTOMA Just before beginning anesthesia for surgical correction of pheochromocytoma, 5 mg. of Regitine should be given intravenously. There are theoretic reasons for avoiding ether, ethylene-ether, cyclopropane, or spinal anesthesia. Curare and atropine are also best avoided. Because dibenamine produces a slowly developing but prolonged lowering of the blood pressure, it should not be used to lower blood pressure elevations during surgery. Hypertensive episodes are best controlled by utilizing 5 mg. increments of Regitine intravenously as frequently as necessary. Single doses of Regitine larger than 5 mg. may be hazardous. Profound hypotension may occur following excision of the tumor; 8 mg. of norepinephrine in 1,000 cc. of 5 per cent dextrose in water may be used as a regulated intravenous drip to control this. With bilateral tumors, excision may result in adrenal cortical insufficiency; accordingly, hydrocortisone, in 100 mg. doses, should be available for intravenous administration during the operation. Since cardiac arrest may occur during the anesthesia, the patient's left chest should be prepared and draped together with the operative site so that cardiac massage, if necessary, can be performed under sterile conditions. (*Hume, D. M.: Pheochromocytoma in Adult and in Child, Amer. J. Surg. 99: 458 (April) 1960.*)