THE EFFECT OF PHENGLUTARIMID (ATURBANE) ON SALIVARY SECRETION IN MAN

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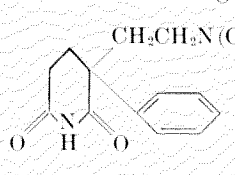
PHENGLUTARIMID was introduced in 1958 for the treatment of extrapyramidal disturbances. Since the agent has been shown experimentally to have strong peripheral parasympatholytic properties in animals, its effect on salivary secretion in man seemed worthy of investigation.

CHEMISTRY AND PHARMACOLOGY [1]

Phenglutarimid, 2-(2-diethylaminoethyl)-2-phenylglutarimide, is a white crystalline, highly soluble powder with a melting point of 175–177 C. It has the following structural formula:



In animals, phenglutarimid has shown a spasmolytic effect on isolated intestine and has inhibited the bronchoconstricting effect of acetylcholine. Small doses of the drug inhibit the salivation caused in rabbits by pilocarpine. In absolute doses, phenglutarimid was about half as effective as atropine in this respect and had no effect on blood pressure but inhibited the hypotension caused by acetylcholine in anaesthetized rabbits and cats. With relatively large intravenous doses, blood pressure was lowered in these same animals, whereas in anaesthetized dogs no appreciable change in blood pressure and heart rate was observed. Phenglutarimid has a relatively low toxicity by all routes of administration. In large doses, used for the control of Parkinsonism, the most troublesome side effects have been dryness of the mouth and blurred vision in 10–15 per cent of the patients. Restlessness, excitation, dizziness, fatigue and drowsiness, tachycardia and rare urinary retention were observed in a few instances.

Accepted for publication March 20, 1959. The authors are in the Department of Anaesthesia, University of Saskatchewan and University Hospital, Saskatoon, Saskatchewan, Canada.

METHOD

Six healthy medical student volunteers, five men and one woman, were studied. Each volunteer underwent five studies at intervals of not less than 24 hours. Ten minutes after the intravenous injection of phenglutarimid a salivary stimulant was injected. This consisted of 3 ml. of a mixture containing carbamylcholine chloride (Carbachol) 0.004 per cent (0.12 mg.) and epinephrine 0.002 per cent (0.06 mg.), injected intravenously at a rate of 1 ml. per minute. Epinephrine was included in the stimulating mixture in order to counteract the undesirable cardiovascular side effects associated with the intravenous administration of carbamylcholine chloride. Saliva was collected from the parotid duct over a period of 30 minutes following the injection of the mixture; collection was by means of a suction cup device described in a previous communication.[2] Care was taken to use the parotid on the same side in each experiment since there is a difference between the amount of saliva secreted from the two parotids.

In the first study the effect of phenglutarimid 5 mg., was investigated; in the second series of tests 2.5 mg. was given, and in the third 1 mg. In the fourth series, the carbamylcholine chloride-epinephrine stimulating solution only was administered to obtain control values of salivary secretions in the absence of prior parasympathetic blocking. In the fifth study, phenglutarimid 5 mg. alone was administered and its clinical side effects were noted.

No attempt was made to evaluate the duration of action of phenglutarimid. To do this, a continuous drip of carbamylcholine chloride and epinephrine must be set up to continue stimulation of salivary secretion beyond the period of action of the antisialogogue. This is impractical since after a period of the time the volunteers become too uncomfortable from the effects of the infusion.[2]

TABLE 1

AMOUNTS OF SALIVA IN MILLILITERS COLLECTED FROM EACH OF SIX VOLUNTEERS

Subject	Phenglutarimid →	After 10 Minutes Carbachol-Epinephrine 3 ml. →	Amounts of Saliva Collected (ml.) Minutes After Stimulant 5	10	15	20	25	30
1	5 mg.		—	—	—	—	—	—
	2.5 mg.		—	—	—	—	—	—
	1 mg.		0.1	—	—	—	—	—
	—	Control	4.8	0.2	—	—	0.4	—
2	5 mg.		—	—	—	—	—	—
	2.5 mg.		—	0.6	0.2	—	—	—
	1 mg.		0.5	0.05	0.05	—	—	—
	—	Control	3.1	0.9	0.2	0.1	0.2	0.1
3	5 mg.		—	—	—	—	—	—
	2.5 mg.		—	—	—	—	—	—
	1 mg.		1.3	1.1	0.3	0.1	0.1	—
	—	Control	5.4	1.1	0.1	—	0.1	—
4	5 mg.		—	—	—	—	—	—
	2.5 mg.		0.1	0.1	0.1	—	—	—
	1 mg.		1.9	0.4	0.4	0.2	0.2	0.3
	—	Control	3.2	0.7	0.3	0.5	0.4	0.7
5	5 mg.		—	—	—	—	—	—
	2.5 mg.		—	—	0.1	—	—	—
	1 mg.		0.5	0.2	0.05	—	—	—
	—	Control	4.2	0.2	0.4	0.6	0.2	0.2
6	5 mg.		—	—	—	—	—	—
	2.5 mg.		—	—	—	0.1	—	—
	1 mg.		1.6	0.4	0.1	0.1	—	—
	—	Control	5.8	1.2	0.7	0.1	0.5	0.5

RESULTS

Amounts of saliva collected in each volunteer are listed in table 1. In the control series following stimulation, there is an initial peak of salivary secretion. This then diminishes rapidly but tends to increase again slightly towards the end of the collection period. The second rise is presumably due to resumption of secretory function after a period of exhaustion following excessive activity.

Averages of the ten-minute collections were calculated and are plotted in figure 1. Although collections of saliva were measured every 5 minutes and the peak effect of the salivary stimulant was reached within five minutes of injection, the total ten-minute collections are used in this graph so that it can be compared more readily with the results of similar previous studies of other antisialogogues in which the amounts of secretions were measured only every 10 minutes.[2, 3] Figure 1 shows that 5 mg. of phenglutarimid entirely and consistently abolish all salivary secretion, 2.5 mg. is on the average 97 per cent effective, and 1 mg. is 71.5 per cent effective.

Only minor cardiovascular changes were seen following the intravenous injection of phenglutarimid 5 mg. alone. There was a consistent increase of the pulse rate within one minute; this never exceeded 10 per cent of control readings and did not last more than two or three minutes in any of the six subjects. Blood pressure changes were in the order of a 5 per cent increase or decrease compared with the control systolic pressure; the pressure returned to control levels after two or three

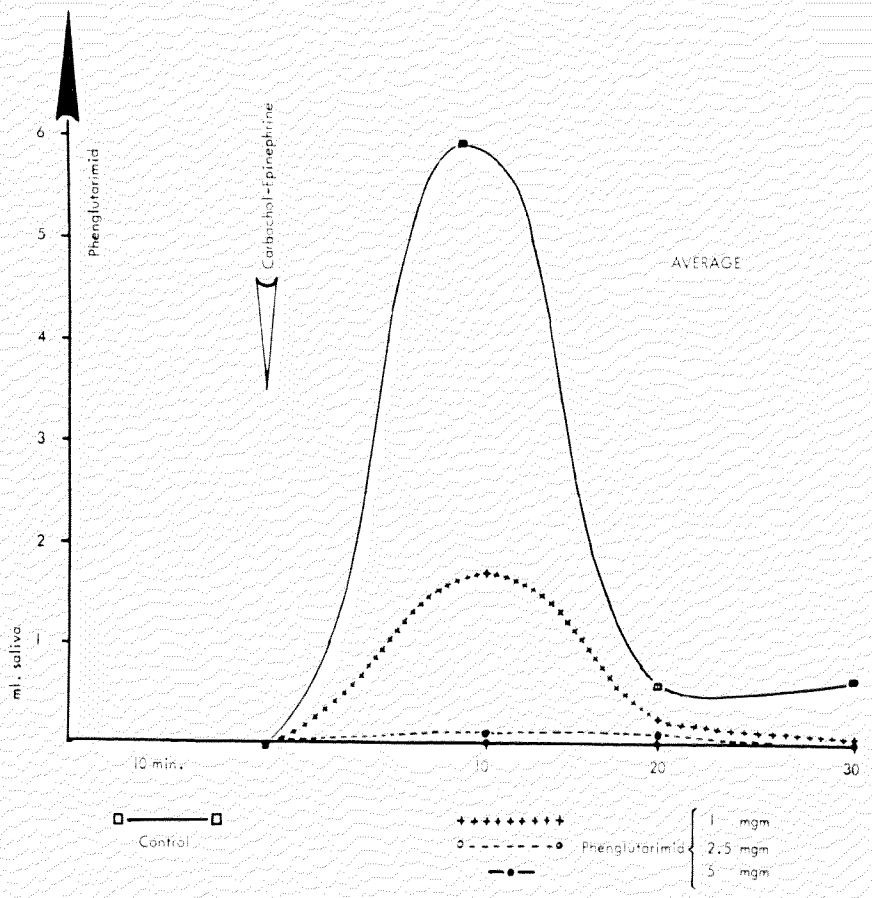


FIG. 1. Average parotid secretion of six subjects.

minutes. Neither of these changes were considered significant and may have been as much due to the trauma of venopuncture as to the actual injection of the drug. No changes in respiratory rate, depth or pattern were observed. Most subjects complained of a dry mouth within 5 to 6 minutes after injection and one stated that his palms felt dry. There were no other subjective signs such as dizziness, drowsiness, or blurred vision.

DISCUSSION

Phenglutarimid is a potent depressor of salivary secretion in man. Doses of 2.5 mg. intravenously being 97 per cent effective upon parotid secretion are thus equivalent in drying action to *d,l*-hyoscyamine (atropine) 0.6 mg. or *l*-hyoscine (scopolamine) 0.2 mg. under identical experimental conditions [3] (figure 2). In interpreting these results it should be remembered that parotid secretions only were collected. It is likely, but by no means proven, that total salivary production from all sources parallels that from the parotid gland. In absolute doses *d,l*-hyoscyamine is four times as effective as phenglutarimid in man as an antisialogogue, which differs from the relative values obtained in animal studies. The agent has a minimum of undesirable side-effects, even if administered in doses of 5 mg. intravenously, but also lacks the sedative properties of *l*-hyoscine, which are so useful in preoperative medication.

No attempt has been made to evaluate phenglutarimid clinically, but it would appear that the drug is worthy of being so tested. Only after exhaustive clinical evaluation will it be possible to say whether phenglutarimid

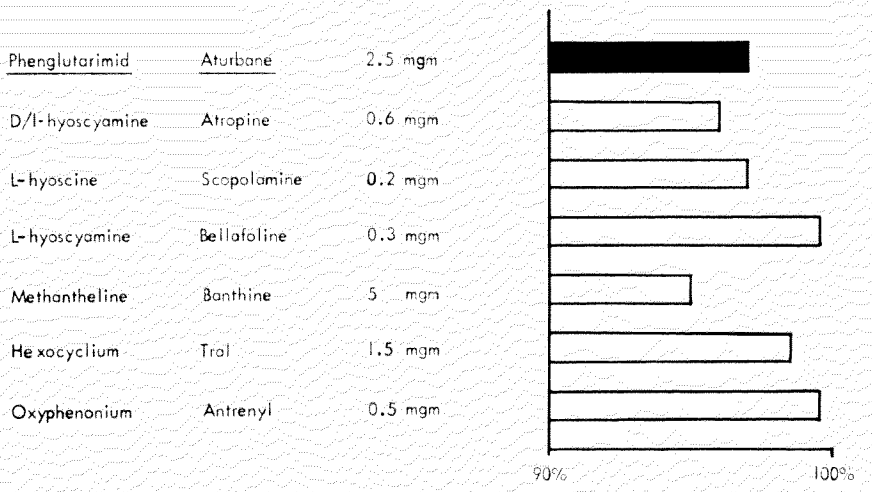


FIG. 2. Comparative antisialogogue activity of seven drugs.

has sufficient advantages over the less expensive belladonna alkaloids to warrant its routine use.

SUMMARY

Phenglutarimid, a synthetic parasympatholytic drug has been tested in six healthy volunteers in whom the effect of the drug on salivary secretion has been determined. Saliva was collected from the parotid duct following stimulation of secretion by the intravenous injection of a mixture of carbamylcholine chloride and epinephrine, following prior administration of various doses of phenglutarimid. It was found that phenglutarimid 2.5 mg. intravenously is 97 per cent effective as an antisialogogue, and is thus equal to *d,l*-hyoscyamine 0.6 mg. or *l*-hyoscine 0.2 mg. under the same experimental conditions. Cardiovascular and other side effects following the intravenous administration of 5 mg. of the drug are minimal. Phenglutarimid is an effective blocking agent of parotid salivary secretions.

Ciba Company Ltd., Montreal, supplied the phenglutarimid (Aturbane) used in this study.

REFERENCES

1. Ciba Company Ltd., Montreal, P.Q.: Aturbane—Orientation Data.
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