CLINICAL TRIALS OF 2-METHYL-3 THIAPENTAMETHYLENE - 1 : 5 - BIS (TRIMETHYLAMMONIUM IODIDE): A POTENT GANGLION-BLOCKING AGENT.*

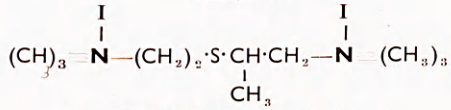
JOHN A. SIMPSON, M.B., M.R.C.P., F.R.F.P.S.
from The Gardiner Institute of Medicine, University of Glasgow.

The therapeutic value of ganglion-blocking drugs cannot yet be assessed, but it seems fair to state that those at present in use have proved disappointing to the clinician because of low potency or lack of specificity. The quaternary ammonium compounds differ in their effect on various animal species and in the type of autonomic ganglion most readily blocked. Clinical trials are necessary to establish the activity of any member of the series on the human subject as this is not predictable from animal experiments (Simpson, 1953). This paper reports the results of trials of 2-methyl-3 thiapentamethylene-1 : 5 bis (trimethylammonium iodide), known as Ro3-0484.

MATERIAL AND METHODS.

Material. Ro3-0484 is a compound resembling penta- and hexamethonium iodide in structure, two methonium groups being separated by a polymethylene chain of similar length but with a thio group replacing one methylene group. It is a stable drug : a solution of 50 mg. in 50 ml. water heated at 45°C for 500 hours remained perfectly clear, and after freeze drying the material was recovered unchanged. Its ability to block the cat's superior cervical ganglion exceeds that of hexamethonium but it is less toxic to mice (Table I). The chronic toxicity tests (Parkes, 1952) were indistinguishable from those of hexamethonium.

TABLE I.



2-methyl-3 thiapentamethylene-1 : 5-bis (trimethylammonium iodide)

Activity relative to hexamethonium = 1

Acute toxicity, I.V. in mice	0.66
Ganglion-blocking activity in cat nictitating membrane	ca. 2
Blood pressure	1
Duration of effect	1-2

*Based on a communication to the Scottish Society for Experimental Medicine at Aberdeen, 14th February, 1953.

Methods of clinical trials. Ro3-0484 was administered by parenteral injection. The intravenous and subcutaneous routes were only used in a few cases but as the results did not differ significantly from those obtained with intramuscular injection the latter route was used in the majority and all results have been considered together.

The effect on gastric secretion was assessed by the method of Kay and Smith (1950). The stomach was completely emptied every half hour for at least three hours by a No. 10 stomach tube, the patient being placed in various positions to ensure emptying of the stomach. All saliva was expectorated. The test was carried out at various times in the morning on fasting subjects, no food or gastric stimulant being taken until the end of the observation period. At least one control test was done in each instance on another day either before or after the trial. (It is realised that gastric acidity varies from day to day, but previous experience with hexamethonium showed a fairly consistent level of ' spontaneous ' acid secretion which was significantly lowered by hexamethonium—Scott *et al.*, 1950.) The time of injection was varied so that an impression of the duration of activity could be obtained.

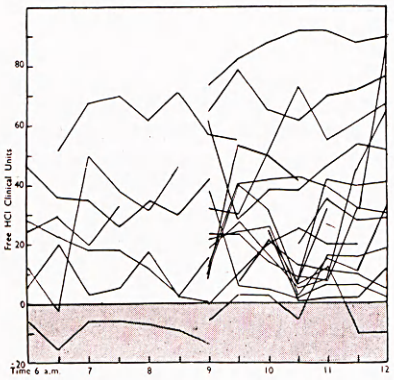


Fig. 1. Free HCl secreted spontaneously in control tests shows a wide range of acidity with no significant trend.

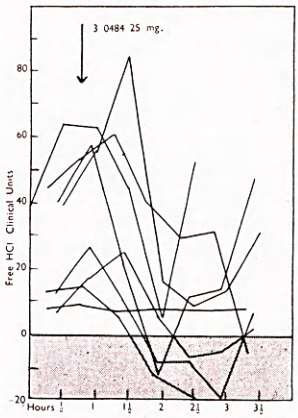


Fig. 2. Effect of 25 mg. Ro3-0484 injection on secretion of free HCl.

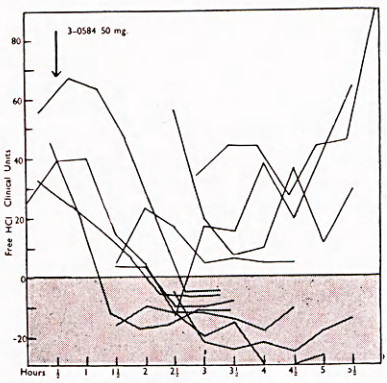


Fig. 3. Effect of 50 mg. Ro3-0484 injection on secretion of free HCl.

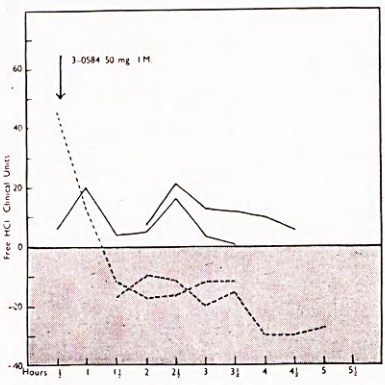


Fig. 4. Achlorhydria produced by 50 mg. Ro3-0484 in two cases with low acidity in control test.

——— control.
-------- after Ro3-0484.

The effect on HCl secretion of simultaneous injection of Ro3-0484 and 20 units of soluble insulin or 0.5 mg. histamine acid phosphate intramuscularly was compared with that of either stimulant alone. The free HCl content of each specimen was estimated by titration against $\frac{N}{10}$NaOH using Topfer's reagent as indicator. The volume of gastric juice secreted in each thirty minute period was measured but the average of all cases has been charted in order to even out inconsistencies due to inadequate aspiration or timing. If the stomach was not emptied before the drug was injected, the volume of the first specimen was omitted from the averages as its secretion time was unknown.

Gastric motility was recorded by the balloon and kymograph technique described by Kay (1947).

The blood pressure and pulse rate were recorded with the subject lying flat, sitting, and standing, every ten minutes until the greatest depression of blood pressure had been recorded and successive readings showed a rise. Thereafter the observations were made half-hourly until the pre-injection blood pressure had been recovered for three hours.

Grip-strength was estimated by a recording spring-dynamometer. Visual accommodation disturbances were assessed by noting complaints of difficulty in reading a newspaper given to each subject throughout the trial.

Test subjects. The effect on gastric secretion and motility was observed in normal volunteers and in patients with dyspepsia of different types (not all peptic ulcer) so that a fair scatter of HCl secretion types could be observed (30 subjects).

These patients were used for the observation of the effect of Ro3-0484 on the blood pressure of normotensive subjects and the effect was observed in ten cases of hypertension of different types and with all grades of fundal changes. The amount of Ro3-0484 available only permitted observation of the response to a single injection. No long-term studies were made.

Results. Ro3-0484 was rapidly absorbed from all parenteral routes of injection. Depression of blood pressure and paralysis of visual accommodation could be observed in ten minutes or less. The results of the trial are summarized in Table 2. The figures showing duration of activity

TABLE 2.
Summary of effects.

		Ro3-0484 Dose	
		25 mg.	50 mg.
Depression of HCl concentration	incidence	85%	90%
	duration	2-4 hrs.	3-6 hrs.
achlorhydria	incidence	60%	75%
Depression of rate of secretion of gastric juice ..	average	30%	72%
	duration	2-4 hrs.	3-5 hrs.
Inhibition of gastric motility	average	1½ hrs.	3 hrs.
Accommodation paresis	incidence	50%	75%
	duration	1-3 hrs.	1-8+ hrs.
Postural hypotension	duration	4-6 hrs.	8-12 hrs.

are derived from inspection of trends in Figs. 2 and 3 and are not intended to be exclusive owing to the limited extent of the trial. The control levels of HCl concentration in all patients tested with Ro3-0484 are shown graphed against time of day in Fig. 1. It will be seen that the spontaneous secretion varied from achlorhydria to hyperchlorhydria and that no particular spontaneous trend in HCl secretion is evident between 6 a.m. and mid-day, except for a tendency to rise at meal hours. Figs. 2 and 3 show the effect of 25 mg. and 50 mg. injections of Ro3-0484 on the secretion of free HCl. No increase in the incidence of achlorhydria was obtained with a dose of 100 mg. No attempt was made to determine the maximum duration of effect with any particular dose as this would require a very large number of patients and excessively long fasting. If gastric stasis precedes depression of acid secretion, the first juice aspirated may contain free HCl even if it is withdrawn an hour or more after injection of the drug. This may explain the apparent delayed response in some cases in Fig. 3. On the other hand achlorhydria was frequently present when the tube was removed six hours after the injection of 50 mg. of the drug. This compares very favourably with the results charted after 100 mg. of hexamethonium by Kay and Smith (1950).

The superimposed curves of Figs. 2 and 3 obscure the fact that depression of free HCl secretion was produced in over 90% of cases with 50 mg. Ro3-0484. Where the juice spontaneously secreted was of low free acidity, achlorhydria could be regularly produced (Fig. 4), but even when it was high the level of free HCl could usually be lowered, though not always to achlorhydria (Fig. 5). In one case the fasting gastric juice contained no free HCl as estimated by Topfer's reagent, but the presence of free HCl was proved with Gunzburg's reagent. It seemed of interest to observe the effect of Ro3-0484 on this stomach. ' Achlorhydria ' persisted during repeated sampling for three hours after 100 mg. Ro3-0484 intramuscularly but free HCl could always be demonstrated with the Gunzburg reagent. After three hours 0.5 mg. histamine intramuscularly produced a prompt secretion of juice containing 20 clinical units of free HCl. In the light of this experience one should perhaps qualify the statement that ' achlorhydria was produced ' by the clause ' as judged by Topfer's reagent.' The fact that Ro3-0484 blocked neurogenic but not chemical secretion of HCl was demonstrated. Vagal stimulation by 20 units of soluble insulin intramuscularly was blocked by 50 mg. Ro3-0484 intramuscularly ; there may even be achlorhydria up to two hours later (Fig. 6). The normal secretion of free HCl in response to histamine injection was not blocked even if spontaneous achlorhydria were present (Fig. 7).

The volume of gastric juice secreted in 30 minutes was significantly reduced by Ro3-0484 in doses of 50 mg. and over (Fig. 8). The average of all cases has been charted so as to even out inconsistencies due to

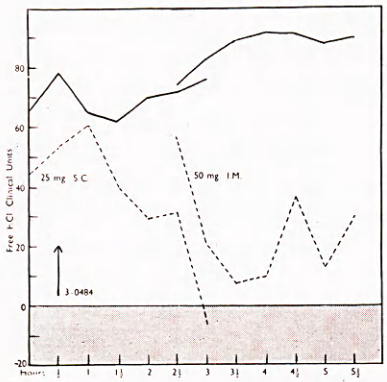


Fig. 5. Depression of free HCl in two cases with high acidity in control test.
——— control.
-------- after Ro3-0484
both injections at the time indicated.

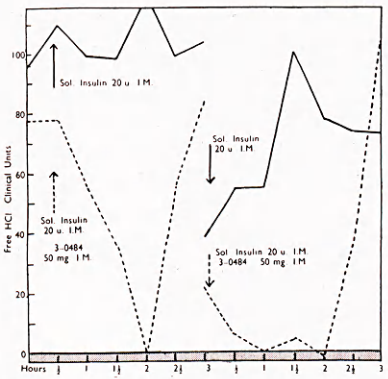


Fig. 6. Inhibition of insulin-stimulated secretion of free HCl.
——— after insulin alone.
-------- after insulin and Ro3-0484.

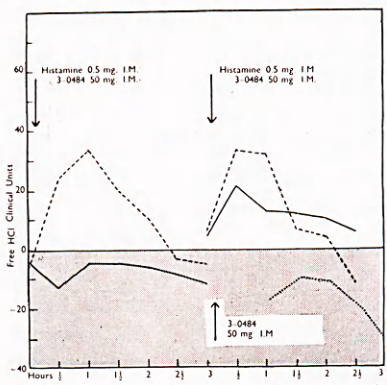


Fig. 7. Failure to inhibit histamine stimulated HCl secretion, even in a case with achlorhydria
——— control.
-------- after histamine and Ro3-0484.
..... after Ro3-0484 alone.

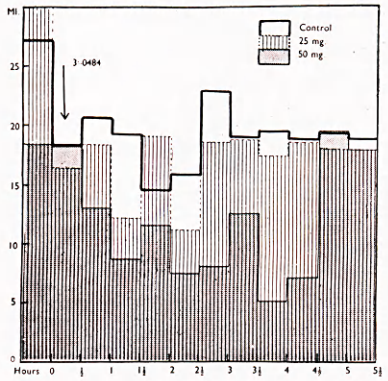


Fig. 8. Effect of Ro3-0484 on rate of secretion of gastric juice.

inadequate aspiration or timing. It will be seen that the ' spontaneous ' secretion is at a fairly steady rate. The first aspiration samples vary widely as the juice collected may have been secreted over a long period. For the same reason, the first sample withdrawn has been excluded from the averages where this was made after the administration of the drug. In some cases after injection of Ro3-0484 great difficulty was found in aspirating any juice, and this often seemed to consist entirely of mucus. Indeed the impression was gained that the secretion of mucus was often inversely proportional to the secretion of HCl. It was certainly not blocked by the drug.

Gastric motility was significantly inhibited by Ro3-0484. The normal gastrogram shows phasic activity of contraction waves of about 30 seconds

duration. Quiescence of the fasting stomach rarely lasts for more than 30 minutes in patients with duodenal ulcer (Kay & Smith, 1950) and activity is readily induced by swallowing milk. Fig. 9 shows stasis lasting for 80 minutes after subcutaneous injection of 25 mg. Ro3-0484 in a patient with active duodenal ulcer. Stasis persisted despite milk feeds and psychic stimulation by encouraging the patient to think of his favourite meal and permitting him to smell appetising food. With 50 mg. Ro3-0484, gastric stasis has been observed to be present more than three hours after injection.

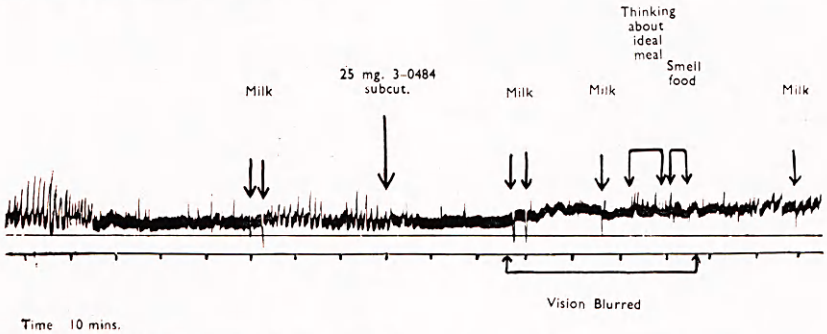


Fig. 9. Gastric stasis after 25 mg. Ro3-0484 subcutaneously in a patient with duodenal ulcer.

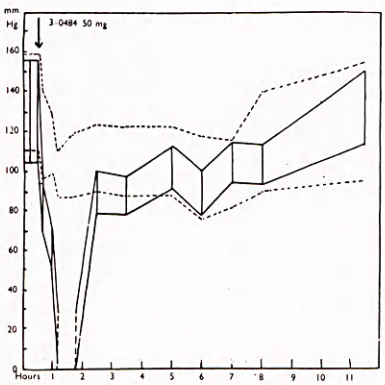


Fig. 10. Depression of blood pressure by Ro3-0484 in a typical case of moderate hypertension.

——— sitting B.P.
-------- lying B.P.

No depression of the blood pressure of normotensive subjects was observed with doses up to 50 mg., whether lying or sitting. In patients with hypertension, significant hypotension could usually be produced. In the majority this was present when sitting upright and in many when lying flat, but a few patients required to stand before the postural effect was seen. In one case no response could be obtained, but the effect of

single doses greater than 100 mg. intramuscularly and of repeated doses have not been investigated. Fig. 10 shows a typical response in a sensitive case. Provided some response was found, suitable posturing could usually bring the pressure down to a level at which it became unrecordable and syncope threatened. This was rapidly countered by placing the patient flat. Hypertensive subjects certainly seemed to react more readily than did the normotensives. The main difference observed with increasing dosage was that the return to the pre-injection pressure was delayed (Table 2). In many cases the pulse rate increased by 5-20 beats per minute, during the period of greatest depression of the blood pressure.

No muscular weakness was noted as the result of questioning and of a few trials of grip-strength with a dynamometer. Moderate dryness of the mouth was sometimes found, and occasionally a feeling of drowsiness, but the only consistent effect otherwise noted was difficulty in visual accommodation. An attempt was made to estimate the incidence and duration of accommodation paralysis by requesting all patients to read throughout the test and to report the presence of difficulty in reading. The results are shown in Table 2 but this is probably an underestimate. This was not realised by the writer until he had personally experienced the effect of 100 mg. of Ro3-0484 intramuscularly. Reading was quite comfortably performed when the paper was held at the writer's (rather long) reading-distance, but he was unable to read a paper placed 5 or 6 inches from the eyes, although normally he could do this with ease. Changes in pupil diameter were considered too variable to record as there was no control over the environmental lighting conditions. The subjective estimation of visual disturbance was not directly related to inhibition of gastric secretion. The author has pointed out in the previous paper (Simpson, 1953) that the response of any particular parasympathetic ganglion to a blocking drug is no criterion that another parasympathetic ganglion will be equally responsive.

DISCUSSION.

In the previous paper (Simpson, 1953) the author has reviewed the development of the search for potent ganglion blocking drugs and stressed that the most urgent clinical requirement is for drugs which will selectively block sympathetic or parasympathetic ganglia. It was shown that the bis(trimethylammonium) compounds, exemplified by hexamethonium, were very potent blocking agents but were non-selective (as thus defined). A review of the literature suggested that selective block was possible but that the effect of any particular drug in the human subject could not be accurately predicted. It was concluded that clinical trial should be given to any promising drug, though the initial selection for trial must perforce be suggested by animal assay.

The high therapeutic ratio shown by Ro3-0484 in the pharmacological laboratory of Roche Products suggested that clinical trials should be carried out. Further interest was given by the fact that 2-methyl-3 thiapentamethylene-1 : 5-bis (trimethylammonium iodide) resembles penta- and hexamethonium iodide in its methonium groups separated by a chain of similar length but with a thio group instead of a methylene group at one point in the chain. Previous workers have noted that activity of bis-onium compounds varies with the nature of the terminal groupings and the chain length (Paton & Zaimis, 1949, and review by Simpson, 1953). It seemed of interest to observe the effect of alteration of the inter-methonium chain structure without altering its length.

This clinical trial, which is summarized in Table 2, shows that, as in the rabbit, the effect of Ro3-0484 in human patients is similar in all respects to that of hexamethonium. It may be rather more effective in small doses than the latter drug, but the extent of the trial is too small to be confident of this. Certainly there is no evidence of selective block.

SUMMARY.

2-methyl-3 thiapentamethylene-1 : 5 bis(trimethylammonium iodide) is a potent ganglion blocking agent.

There is no evidence of selective blockade of specific ganglia.

The clinical value of the compound is similar to that of hexamethonium.

ACKNOWLEDGEMENT.

Roche Products Limited kindly supplied Ro3-0484 tor clinical trials.

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