EFFECT OF TETRAETHYLAMMONIUM BROMIDE ON GASTRIC SECRETION AND MOTILITY

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Tetraethylammonium bromide (T.E.A.B.) is known to produce a blockade of the autonomic nervous system, and has been used with this object in the investigation of peripheral vascular disease. The purpose of this paper is to examine its effects on the secretory and motor functions of the stomach.

Pharmacology

The site of action of tetra-alkyl-ammonium compounds is at the ganglionic synapses of the autonomic nervous system, where a blocking effect was first demonstrated by Marshall (1913). T.E.A.B. is a synthetic compound produced by the substitution of four ethyl groups in the ammonium radical of ammonium hydroxide. The chemical relationship of the drug to acetylcholine is:

The site of action of the two compounds is the same and is probably determined by their basic structural relationship; side-chain variants determine their pharmacologically different effects. The blocking effect of T.E.A.B. is probably due to the fact that the drug can replace acetylcholine in the neurohumoral chain at the autonomic synapse, thus excluding it. The transience of its action is probably also due to its similarity to acetylcholine, which is destroyed by cholinesterase.

The pharmacological effects are twofold. Sympathetic blockade leads to release of peripheral vasoconstrictor tone, a fall in blood pressure, and an increase in pulse rate. There is increased blood flow to the extremities, with increased skin temperature. Sweating is inhibited. Parasympathetic blockade leads to inhibition of gastric secretion and motility, inhibition of salivation, paralysis of accommodation, and transient impairment of the power to urinate or defaecate.

Side-effects are noted as follows. After moderate doses (less than 500 mg. intravenously or 20 mg. per kg. of body weight intramuscularly) there is a metallic taste in the mouth, with a sensation of warmth and flushing, transient peripheral numbness, light-headedness, loss of accommodation, and transient difficulty in urination or defaecation. After large doses ptosis, weakness, or even severe collapse may occur. While these severe manifestations are rare, the commoner side-effects make out-patient administration impracticable.

Effect of T.E.A.B. on Gastric Secretion

Published work on the effect of T.E.A.B. on gastric function comes mostly from America. Zweig *et al.* (1948) found that in normal subjects the gastric motility was completely inhibited for a total period of 45–100 minutes after intravenous injection. Unstimulated secretion was reduced

by 85% and histamine-stimulated secretion by 70%; on the contrary, Neligh *et al.* (1947) noted no effect on histamine-stimulated secretion. Brown *et al.* (1948) demonstrated, in duodenal ulcer patients, inhibition of gastric motility and abolition of insulin-stimulated secretion. Ferrer (1948) reported effective reduction of excessive night secretion in patients with peptic ulcer.

1. *Studies by Alcohol Test Meals.*—We have studied the effect of T.E.A.B. on gastric secretion following an alcohol test meal in 20 cases (17 men and three women, eight of them suffering from duodenal ulcer). The method was as follows:

The patients were starved over nine hours, a Ryle's tube was passed at the end of this period and the fasting juice aspirated. Then 50 ml. of 7% alcohol was given and specimens were removed from the stomach every 15 minutes for one and a half hours and titrated. The following day, at the same hour, this procedure was repeated, but in addition 1 g. of T.E.A.B. was given intramuscularly as a 10% solution half an hour before the start of the test meal. The patients were interrogated regarding symptoms following T.E.A.B. administration. Blood-pressure readings were taken throughout. The average values for the 20 test meals are shown in Fig. 1. There is an average reduction of 5–10 clinical units of free HCl. Some reduction in the free HCl was noted in every case. In several the reduction was of the order of 20 units.

FIG. 1.—Effect of T.E.A.B. on gastric secretion after an alcohol test meal (20 cases, average values).

2. *Studies after Insulin Stimulation of Secretion.*—Because of the known pharmacological effect of T.E.A.B. in blocking vagus synapses it was of interest to investigate its action after the administration of insulin. In 1943 Hollander observed copious acid secretion in the gastric pouch of dogs in which he had induced hypoglycaemia; he found a pronounced acid secretion so long as the vagus supply to the stomach was intact and cessation on complete severance of all vagal fibres. This observation led to the development of the insulin test for vagus activity. It was employed as follows in our cases.

The alcohol test-meal technique already described was followed in 10 patients, with the modification that one and a half hours after the meal in each case 20 units of soluble insulin

FIG. 2.—Effect of T.E.A.B. on gastric secretion after administration of insulin (10 cases, average values).

was given intramuscularly. A similar procedure was adopted in the same patients (on a subsequent occasion) after the administration of T.E.A.B. (The patients were all adults, eight males and two females, four of them suffering from duodenal ulcer.) The blood sugar in all cases fell below 55 mg. per 100 ml. The symptoms noted included weakness, hunger, and emptiness. The average of the 10 test meals is shown in Fig. 2. It will be seen that after T.E.A.B. the production of insulin hypoglycaemia failed to stimulate the secretion of gastric juice.

3. Studies after Histamine Stimulation of Secretion.—The response of the stomach to administration of histamine was studied by the method already described for insulin, an injection of 1 mg. of histamine being given at the end of 1½ hours in each case. In view of the effect of histamine on blood pressure no patient was used in this series whose

FIG. 3.—Effect of T.E.A.B. on gastric secretion after histamine stimulation (10 cases, average values).

T.E.A.B. the injection of histamine stimulated the secretion of gastric juice, but the response was not so great as in the control series.

4. Studies on Spontaneous Night Secretion.—Much attention has recently been devoted to the secretion of the stomach during interdigestive phases, and particularly at night. It is claimed that the nocturnal secretion is large in volume and highly acid, and that this unbuffered secretion expelled rapidly into the duodenum is of importance in the production of duodenal ulcer. Investigations of the action of T.E.A.B. upon the nocturnal secretion in 10 patients were made as follows.

The patients had nothing to eat or drink after 5 p.m. A duodenal tube with multiple perforations at its tip was passed at 8 p.m., the stomach emptied of its contents, and the secretion aspirated till 8 a.m. by means of constant suction set up by means of an electric pump. Narcotics were withheld. The following evening the experiment was repeated, giving 1 g. of T.E.A.B. four-hourly to a total of 3 g.

Night Secretion Tests (8 p.m.—8 a.m. Continuous Suction). Total Dosage = 3 g. of T.E.A.B.

Without T.E.A.B.			With T.E.A.B.			Average Reduction in Milli-equivalents/Hr.
Volume	Free HCl	Total Acid	Volume	Free HCl	Total Acid	
630	36	57	400	12.5	26.5	79%
105	12	22	55	0	6	100%
595	42	58	400	20	34	70%
750	56	66	305	33	46	76%
410	36	52	300	12	28	75%
640	9	19	274	9	30	60%
740	48	60	480	20	28	69%
1,170	28	34	372	15	33	84%
220	14	32	104	0	6	100%
692	13	22	165	4	24	91%

In 10 cases the volume of secretion was reduced, as was the acidity. The accompanying Table shows that T.E.A.B. brought about an average reduction of 309 ml. in the volume of the night secretion and a reduction of 80% in milli-equivalents per hour of the night secretion. All patients were cases of duodenal ulcer with severe symptoms. None complained of dyspepsia during the administration of T.E.A.B.

Effect of T.E.A.B. on Gastric Motor Functions

This was studied in five patients by means of gastrograms according to the technique described by Kay (1947). After a 12-hour fast the patients (all of whom were cases of duodenal ulcer proved later at operation) swallowed two Ryle tubes fastened together, one having an inflatable balloon attached at its tip.

The balloon was inflated to a standard pressure of 5–10 ml. of water and the column of air was connected to a tambour kymograph unit recording variations in intragastric pressure; the other Ryle tube may be used for aspiration of secretion or performance of the “water test” (Kay, 1947).

In normal individuals the gastrogram has four components (Johnson, 1948): (1) Postural tonus, characteristic of hollow viscera, fairly constant and independent of its degree of distension. (2) Tonus waves: these are regular gentle undulations of postural tone, which may be peristaltic in nature, with a frequency of three a minute. (3) True gastric contractions which are spastic contractions of the whole stomach, considerably increasing intragastric pressure. They are represented by sharp-topped waves lasting 30 seconds, and occur in normal individuals in bursts at intervals of 1½–2 hours with a frequency of 1–2 minutes. They are present in hunger pains and are greatly increased in amplitude and frequency in duodenal ulcer patients. (4) Cardio-respiratory effects: these are frequent small oscillations superimposed on the above intrinsic waves. They are due to respiratory movements of the diaphragm and cardiac pulsations; they occur with a frequency of 20 a minute. In five patients showing frequent true gastric contractions after a control period of 20 minutes, 1 g. of T.E.A.B. was injected intramuscularly. After a latent period of 15–30 minutes tonus waves and true gastric contractions were abolished and postural tonus diminished: the effect persisted for 1–1½ hours, tonus waves returning before gastric contractions. There is a striking similarity between the gastrogram shown and that following vagotomy: in four of five patients this inhibition of vagal activity was found, the remaining case showing for 1½ hours diminished frequency, amplitude, and duration of contractions (Fig. 4).

FIG. 4.—Gastrograms in normal duodenal ulcers, after injection of T.E.A.B., and after vagotomy.

Discussion

The administration of T.E.A.B. leads to a slight fall in gastric acidity as estimated by the alcohol test meal. After T.E.A.B. the induction of insulin hypoglycaemia fails to stimulate a rise in gastric acidity. This indicates the presence of vagal blockade and is in keeping with the known action of the drug. It can be assumed that such secretion as occurs after T.E.A.B. is due to the chemical mechanism of gastric secretion. It is interesting to note that after T.E.A.B. the injection of histamine does stimulate gastric secretion, albeit less than normally. This is interesting on account of the fact that histamine acts directly on the oxyntic cells, and so the reduction in acidity in this case cannot be due to an autonomic blockade. Hollander (1944) asserts that the oxyntic cells secrete acid of a constant strength; but if on histamine stimulation they secrete into a stomach which is comparatively amotile there will result a fair degree of buffering and dilution by alkaline and mucoid elements. This fall in acidity may therefore be attributed to retention, to which Johnson ascribes the same effect following vagotomy. He points out that in the amotile stomach there is difficulty in evacuating serial specimens completely, so that dilution of secretion occurs.

The reduction in night secretion is interesting. Because of the motility effect, it could be held that it was in part due to regurgitation of duodenal contents through a relaxed pylorus. A few experiments were abandoned because of bile-staining of the juices drained off; on the other hand, the 10 cases reported were free from bile in the suction specimen, and the volume in the 12-hour specimen after T.E.A.B. was less than that taken off the previous evening.

The average reduction in milli-equivalents per hour was 80%, comparing not unfavourably with 90% following anatomical section of the vagus.

The motility effect has been shown to be similar to that following vagotomy; but T.E.A.B., as well as inhibiting the parasympathetic supply of the stomach, might be expected to effect gastric function in some way by its action on the sympathetic. There are several records of the effect of splanchnic section on gastric secretion in man and animals. Brown (1933) could find no demonstrable change in free or combined acidity following complete removal of the sympathetic chain or coeliac ganglia in cats, and Ray (1942) investigated and found no change in gastric acidity after bilateral sympathectomy.

It has been claimed by Little *et al.* (1947) that T.E.A.B. is effective in preventing or modifying the course of peptic ulcer produced experimentally in animals. In view of its effects on the gastric secretion and motility, and particularly on the volume and acidity of the nocturnal juice, the hope was raised that it might be of value in the treatment of peptic ulcer in man. It is perhaps worthy of note that all 10 patients submitted to repeated injections of T.E.A.B. were free from pain during the progress of the experiment, whereas previously they had had incapacitating symptoms. T.E.A.B. has, however, certain practical disadvantages, especially in requiring to be given by injection and in giving rise to unpleasant subjective symptoms. It remains for future research to find a means of prolonging its action and minimizing its side-effects.

Summary

The chemistry and pharmacology of T.E.A.B. are described. T.E.A.B. produced a slight fall in gastric acidity in the secretory response to an alcohol test meal.
It negated the secretory response to hypoglycaemia.
It reduced the response to histamine.

It reduced the volume and acidity of the 12-hour spontaneous night secretion.

It produced a vagotomy-like effect on gastric motility.

Its effect on the cephalic and humoral phases of secretion is discussed after its use in 10 patients submitted to insulin and histamine stimulations respectively. The changes in the concentration of the night secretion in 10 ulcer patients and the effects on motility in five ulcer patients are discussed; a comparison is drawn with that following vagotomy. Its disadvantages are enumerated. Experimental use in peptic ulceration in animals is mentioned and suggestions are made for further use.

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NITROGEN MUSTARD THERAPY WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE

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Therapeutic trials with the nitrogen mustards in cases of neoplastic disease were started in the United States in 1942. Rhoads (1946) published the first analysis of results obtained, and many further reports have appeared since. Experiences in this country have been given by ApThomas and Cullumbine (1947), Wilkinson and Fletcher (1947), ApThomas (1948), Boyland *et al.* (1948), and Watson and Pemberton (1948). These reports make no claim that the treatment is any more than palliative. The best results have been obtained in cases of Hodgkin's disease, and moderate but variable remissions in other lymphomata and lymphosarcoma, chronic leukaemia, polycythaemia vera, and mycosis fungoides. In carcinomatous conditions the results have been disappointing except in bronchial growths, where in some cases transient benefit has followed treatment. In April, 1946, a trial supply of the "bis" compound was received. As it is now generally available, this interim report summarizing the benefits and dangers attending its use is being published.

Dosage and Method of Administration

The amount of the drug that can be given is limited by the action on the bone marrow, and the American workers recommended that in a standard course the total dose of the "bis" derivative hydrochloride should be 0.4 mg. per kg. of body weight. This was divided into four doses of 0.1 mg. per kg. given intravenously on consecutive days. The vein used for the injection often becomes thrombosed, and to reduce the demand for veins trials were made with fewer but larger injections. This also