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# THE EFFECT OF TETRAETHYLAMMONIUM ON THE SMALL BOWEL OF MAN

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Present evidence indicates that tetraethylammonium ion blocks autonomic effector systems at their ganglia. Injection of the drug prevents the passage through the superior cervical ganglion of nerve impulses to the nictitating membrane of the cat (1). Similarly, there occurs inhibition of the effect on the decentralized heart of preganglionic stimulation of either vagal cardio-inhibitory fibers or of the cardio-accelerators (2). The sharp fall in arterial blood pressure accompanying intravenous injection results from ganglionic blockade of the sympathetic vasoconstrictor nerves (2).

The action of tetraethylammonium has been extensively studied in man by Lyons and his associates (3 to 5). After single intravenous injection of 200 to 300 mgm. of the chloride salt there is a fall in blood pressure and a rise in heart rate. These values have usually returned to normal in 10 to 15 minutes after injection. There is an accompanying sensation of tingling and warmth of the face and extremities and sometimes drowsiness and momentary paralysis of accommodation. Serious reactions have not been reported. After giving nearly 100 injections of the drug we observed 1 marked reaction. This patient (Case 4) had an alarming and persistent tachycardia and fall in blood pressure which lasted for 5 days (6).

The action of tetraethylammonium on the gastrointestinal tract has received relatively little attention. Lyons has reported that after intramuscular injection marked diminution in contractions occurs. His patients with peptic ulcer have received dramatic but temporary relief from ulcer pain. Cessation of gastro-intestinal motility has been observed fluoroscopically after ingestion of a barium meal, and abdominal cramps and diarrhea have been abolished. Gastric acidity is said to be diminished (4).

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This report concerns the effect of tetraethylammonium ion on the intestinal tract of 8 patients as observed by the multiple balloon technique. Three patients were hypertensive. Of these 1 had a duodenal ulcer and another had had a lumbo-dorsal sympathectomy 4 years previously without striking change in her blood pressure. Three of our patients had intractable abdominal pain, presumably intestinal in origin. One had gastritis and 1 had rheumatoid arthritis.

In 2 patients the amount of balloon distension of the intestine essential to elicit beginning pain was determined before and during the action of the drug. The purpose of this observation was to find out whether tetraethylammonium affects the sensory impulses arising in the intestine and thereby relieves intestinal pain.

## METHOD

Patients were studied in the fasting state. The motility of the duodenum and jejunum was recorded by means of a 4-channel tube. Balloons were separated at 4-inch intervals, each balloon being connected to a separate U-shaped water manometer (7). Ink writers from each manometer were placed so that contractions were recorded simultaneously in a vertical line. The balloons and tubes were introduced under fluoroscopic control. Each balloon was of the same size and was filled with 20 cc. of air. This was found to be sufficient to fill the intestinal lumen but was well below the amount necessary to elicit pain from stretching of smooth muscle fibers. Chest movements were recorded from a blood pressure cuff taped around the chest wall. The kymograph moved at a rate of about 3 cm. per minute. Blood pressure and pulse were recorded at 2- to 3-minute intervals for 15 minutes before the injection and for 30 to 45 minutes afterward. Tetraethylammonium was administered intravenously at a rate of approximately 200 mgm. per minute. It should be noted that in tetraethylammonium content 390 mgm. of the chloride salt is approximately equivalent to 500 mgm. of the bromide salt. During and following the injection, signs and symptoms which developed were noted. Adrenalin and neosynephrin were always on hand in case of untoward reactions.

TABLE I

Case No.	Diagnosis	Dose	Onset of action after start of inject.	Changes in intestinal activity		Partial return of activity		Full return of activity		Effect on symptoms
				Tone	Contractions*	Tone	Contractions*	Tone	Contractions*	
1. 534560	Rheumatoid arthritis	500	30	Decrease	Decrease only	30	30	45	45	
2. 538260	Intractable pain	500	45	Decrease	Brief decrease only	Only 15' tracing after injection				
3. 114951	Hypertension; lumbodorsal sympathectomy 4 years ago	300	60	Decrease	Absent†	30	20	75 (Return not yet complete)	75	
4. 370990	Intractable pain	230	45	Decrease	Absent†	40	39	65 (Return not yet complete)	65	Pain disappeared with cessation of contractions
5. 190980	Duodenal ulcer and hypertension	400	45	Decrease	Absent†	35	35	55	55	
6. 537908	Hypertension	300	45	Decrease	Absent†	55	30	60 (Return not yet complete)	60	
7. 175870	Gastritis	400	35	No decrease	Absent‡				56 (Sudden and complete return)	
8. 544965	Intractable pain	300	None	No decrease	No decrease					
	(45 min. later)	400	120	Decrease	Decreased and absent§	35	43	53	51	Pain disappeared

\* Refers to both ring-like contractions and propulsive movements.

† Contractions eliminated in all 4 balloons.

‡ Only 2 balloons in duodenum. Contractions eliminated.

§ Only 3 balloons in duodenum. Contractions eliminated in 2, decreased in the third.

The threshold of beginning intestinal pain was obtained by inflating the balloon in the duodenum at a rate of a 4- to 6-cm. rise in water pressure per second until pain was first felt. The average of 5 consecutive determinations was taken to be the pain threshold level. The determinations were repeated 5 minutes after the drug had been given.

#### RESULTS

Table I contains a summary of the results obtained in the 8 patients. In all except Case 8 contractions began to decrease in 30 to 60 seconds from the start of the injection. In 60 seconds no more than 200 mgm. of the salt had been given. In Case 8 abdominal muscular contractions which accompanied the patient's pain obscured the intestinal movements as recorded by the balloons.

After receiving 300 mgm. of the chloride salt this patient reported practically no relief of pain and showed only slight decrease in contractions of the abdominal muscles. Forty-five minutes later she received a second injection of 400 mgm., at the completion of which she said that she was free of pain. Abdominal muscle contractions almost completely ceased. For the next 43 minutes no movements were recorded from the balloons in her duodenum and jejunum other than artifacts resulting from coughing, body movements and respirations. This fact suggested that intestinal contractions disappeared following the second injection.

In 5 out of 8 patients, including Case 8 following her second injection, ring-like contractions as well

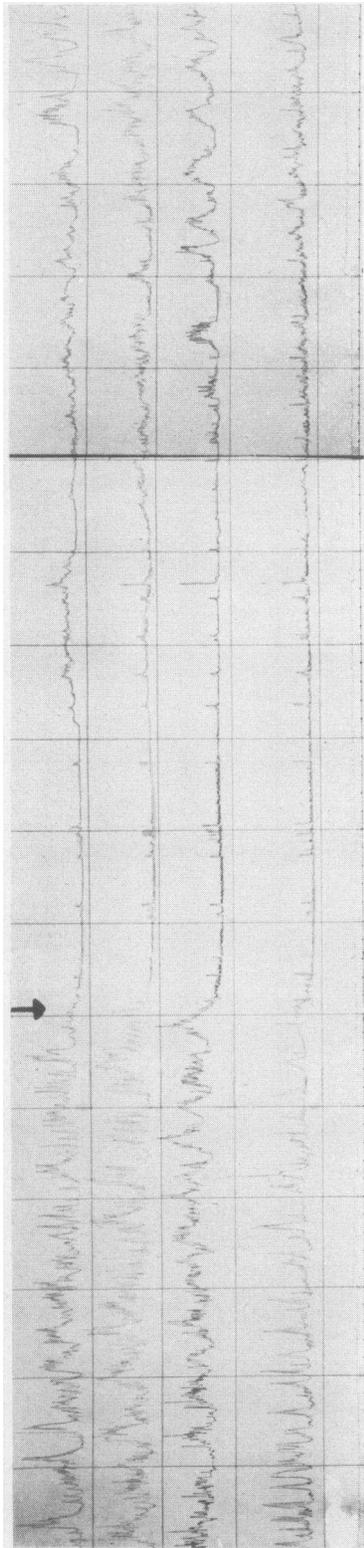


FIG. 1. TRACING OF THE UPPER SMALL INTESTINE

This shows the fall in the baseline and disappearance of contractions 45 seconds following the injection of tetraethylammonium 400 mgm. I.V. Ring-like contractions and propulsive waves were absent except in the top tracing for 35 minutes, at which time both types of contractions began to return along with a beginning elevation of the baseline. Intestinal activity was back to the pre-drug level 55 minutes following the injection. The top, or No. 1, tracing is from the distal balloon and the second, third and fourth tracings are recordings of activity at successive proximal levels. Chest movements are recorded at the bottom tracing. The vertical lines represent 5-minute intervals.

as propulsive movements were abolished (Figure 1) much as they were by atropine (Figure 2). The ring-like contractions are represented by the regularly occurring waves as shown in the figures. Propulsive movements are represented by the sustained elevation of the base of the contraction waves. When the contractions disappeared the baseline of the tracing fell, suggesting a decrease in smooth muscle tone. Certain technical factors made it difficult to quantitate this fall. Transmitted pressure from the abdominal wall contributed to the height of the baseline. Also, distension of the gut by the balloon itself increased contractions and raised the baseline. Since neither of these factors could be measured we are unable to interpret baseline changes in quantitative terms, but only to indicate trends. In all patients except 1 the disappearance of contractions was accompanied by a fall in the baseline of the tracing.

Resumption of activity began between 20 and 43 minutes following the injection, although the contractions did not appear from all 4 balloons simultaneously. In Case 4 the failure of return of activity before 40 minutes might not have been accountable by the effect of tetraethylammonium alone. By this time this patient had already received large doses of epinephrine and neosynephrin intravenously. In 3 patients who were studied until there was complete return of activity the contractions were back to normal in 45 to 56 minutes. Three patients were studied for 60, 65 and 75 minutes, respectively. At these times their contractions had not entirely returned to normal. Three of our patients were hospitalized for study of severe abdominal pain of obscure origin. Two of these patients were complaining of this pain at the time of the injection. In both there was a disappearance of pain following the injection with simultaneous abolition of contractions in 1 patient and marked reduction of contractions in the other.

In the 2 patients whose thresholds for beginning pain were measured by balloon distension, the number of centimeters of water pressure essential to elicit pain was unchanged 5 minutes after the drug had been given. The first patient's pre-drug threshold averaged 70 cm. of water pressure and post-drug threshold, 72 cm. The second patient's pre-drug threshold averaged 84 cm. of water pressure. After the drug the threshold level averaged 80 cm. of water pressure.

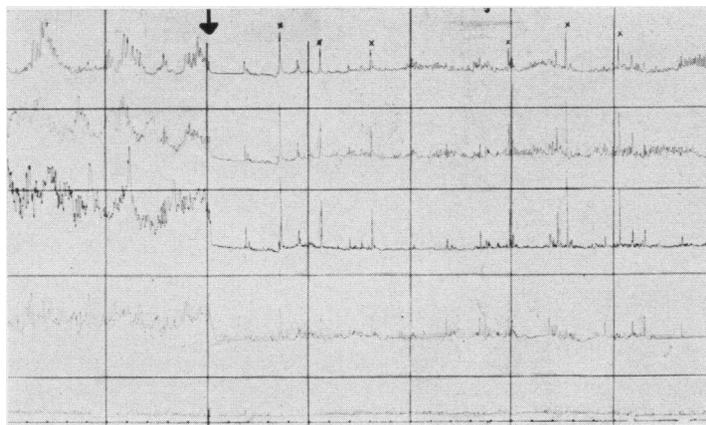


FIG. 2. EFFECT OF 0.6 MG.M. OF ATROPINE SULFATE I.V.

The same subject as in Figure 1 was given 0.6 mgm. of atropine sulfate I.V. over a 30-second interval. At the end of injection there was a fall in the baseline, a disappearance of propulsive waves and abolition of ring-like contractions. The movements noted following the injection are artifacts due to body movements and respirations. From 10 to 15 minutes following the injection there was a slight return of ring-like contractions. It is apparent from this tracing that the effect on intestinal motility is much the same as that following the injection of tetraethylammonium. The balloon arrangement and positions are the same as in Figure 1.

#### DISCUSSION

Tetraethylammonium causes an immediate cessation, or marked decrease, of motility of the upper small bowel. This effect is more prolonged than the fall in blood pressure or rise in pulse which the drug induces. It is possible that buffer reflexes for the circulation are more highly developed and account for the more rapid return of blood pressure to normal. Within the limitations of our method the effect on the intestine is identical to that of atropine.

The control of the activity of the small bowel is exceedingly complex and poorly understood. Not only is this activity under the partial control of sympathetic fibers and the vagus but the myenteric plexus of Auerbach, the plexus of Meissner, and the smooth muscle fibers themselves contribute to the regulation of intestinal activity. If tetraethylammonium blocks vagal and sympathetic impulses to the gut at the respective ganglia, as one might expect from analogy to results obtained in other autonomic effector systems, then injection of the drug might be expected to produce effects similar to those obtained by section of autonomic fibers. In the dog, rabbit and cat under alcohol-chloro-

form-ether anesthesia soon after a combined splanchnicectomy and vagotomy, the bowel is found to be quite active (8, 9). Pendular movements as well as progressive ring-like contractions are still present. Unless the splanchnics are cut the small intestine is found to be in a profound state of inhibition when the abdomen is opened, and this inhibition is released only when the splanchnic fibers are sectioned. Conversely, section of the vagi causes no further change in the contractions. In the combined operation, stimulation of the peripheral end of the cut splanchnics leads to complete inhibition whereas prolonged and repetitive stimulation of the peripheral end of the cut vagus is followed by enhanced contraction of the small bowel, except only that the first part of the duodenum responds more quickly and seems to be more directly under vagal control. Such vagal effects can be blocked by small doses of nicotine but not by large doses of atropine in animals. However, in man large doses of atropine continue to decrease intestinal contractions following vagus resection. Procaine block of the lumbar sympathetic ganglia supplying the gut in man leads to augmented contractions of the small bowel and colon (10).

Three days after transthoracic vagotomy the ring-like contractions of the bowel are decreased (observation in 1 subject). This effect may in part be due to trauma of operation (10). Observations immediately postoperative have not yet been made. *In vitro*, the longitudinal contractions of the rabbit intestine are enhanced by tetraethylammonium (11), but no studies on the circular component have been made.

These considerations suggest that the mechanism of action of tetraethylammonium on the small intestine is not solely that of an autonomic blocking agent. Perhaps this drug has an additional action on the intrinsic neuronal structure or on the smooth muscle itself which are responsible for the continued activity following surgical denervation.

The fact that the thresholds for intestinal pain elicited by balloon distension were unchanged following the administration of tetraethylammonium suggests that this drug has no significant action on the sensory innervation of the intestine. Its pain-relieving effect must, therefore, depend on the anti-spasmodic action.

If continued use demonstrates its reasonable safety, tetraethylammonium may have diagnostic value in implicating smooth muscle spasm as responsible for the features of certain cases of obscure abdominal pain. Its value as a relaxing agent in such conditions as ulcerative colitis and intractable peptic ulcer is limited, at least at present, by its brief duration of action.

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