Contribution to the Pharmacology of Apoatropine and Its Methyl Bromide. (21150)

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Apoatropine is found to a limited extent in belladonna root(1). It is an anhydride of atropine (with respect to the tropic acid moiety of the molecule) and is prepared from atropine by the action of dehydrating agents (2). There are several fragmentary studies of its pharmacology recorded during the past half-century. Apoatropine differs from atropine in that it elicits only a mild mydriatic response(3). It was found that in larger doses it evokes increased respiratory activity and finally convulsive seizures. Our interest in this compound stems from the studies of Kreitmair and Wolfes(4), who observed that apoatropine was 5 times more potent than atropine in relaxing a barium ion-induced spasm in the isolated intestinal strip of the rabbit. These investigators confirmed the previously-mentioned action of apoatropine on the central nervous system. They also observed that its acute toxicity to mice was 20 times greater than that of atropine. We considered it interesting to study apoatropine as an antispasmodic and also to compare it with its methyl bromide, which to our knowledge has never been compared.

Materials. The apoatropine used in these studies was prepared for us by Dr. Verne C. Bidlack, Jr.,* by dehydrating atropine with sulfuric acid. The compound melted between 256 and 257°C. The hydrochloride was found to contain 11.72% chlorine (theory 11.85%). Apoatropine methyl bromide prepared from this sample of apoatropine melted between 253 and 256°C.

Acute toxicity. Upon intraperitoneal injection in the mouse the LD_{50} for apoatropine was 14.1 mg/kg with 95% confidence limits of 17.5 mg/kg and 11.4 mg/kg. Under the same conditions the values reported for atropine in the literature are between 200 and 300 mg/kg. Apoatropine was much less toxic to the mouse when administered orally. The LD_{50} orally was found to be 160 mg/kg with 95% confidence limits of 115.1 mg/kg and 222.4 mg/kg.

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TABLE I. Oral Administration of Apoatropine to 4 Dogs.

Wt, kg	Dose, mg/kg	24 hr	48 hr	72 hr
14.2	40	X and M*	Recovery	
12.1	80	*Idem*	Dead	
9.6	160	" & emesis		Dead
5.4	320	*Idem* with convulsions	Recovery	

* X and M = Xerostomia and mydriasis.

Chronic toxicity. Apoatropine was given by stomach tube to mongrel dogs weighing between 6 and 10 kg. The effect and dosage levels are given in Table I.

Three groups of 6 rats were given apoatropine orally each day for 5 days at dosage levels of 20, 40 and 80 mg/kg. Each animal appeared to tolerate the drug without symptoms. Weight gains were not retarded and none of the animals succumbed to the treatment.

Circulatory effects of apoatropine. Apoatropine was injected intravenously into 3 dogs anesthetized with ether. Blood pressure recordings and electrocardiograms were made.

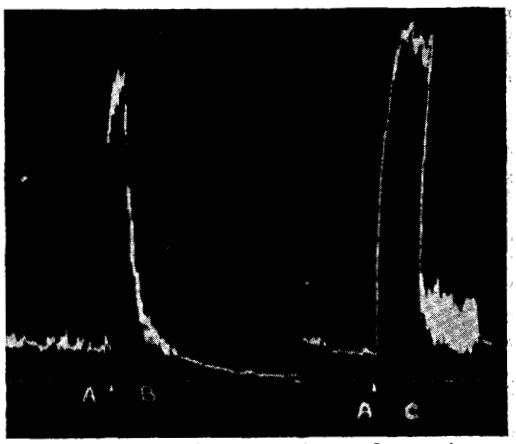

FIG. 1. Action of apoatropine and atropine on the isolated strip of the rat's intestine. L. Apoatropine. R. Atropine. A. 1 mg barium chloride. B. 0.5 mg apoatropine. C. 1 mg atropine. Volume of bath 30 ml.

TABLE II. Passage of Charcoal Mixture.

Drugs administered	No. of rats	% of intestine through which charcoal passed	P value
Control	8	81.3	
Atropine sulfate, 0.5 mg/kg	5	50.0	<0.01
Apoatropine hydrochloride, 20 mg/kg	10	41.2	<0.01

In dosage levels from 2 to 5 mg/kg the following findings were observed. A precipitous fall in blood pressure occurred immediately upon injection. There was a concomitant bradycardia and depression of the rate and amplitude of respiration. Mydriasis was present. The cardiac vagus was blocked to faradic stimulation. The bradycardia was progressive. In one animal in which death occurred the respiration continued for a short period after the cessation of the heart beat. The electrocardiographic findings were depression of the R-spike, depression of the heart rate and increase in the P-R interval.

Intestinal motility of the rat in vitro. Our principal interest in apoatropine stemmed from its possible availability as an anti-spasmodic. On smooth muscle we were able to confirm the work of Kreitmair and Wolfes(4) in that the antispasmodic action was similar to that of atropine. With 7 strips of rat's intestine, the rat's uterus and rabbit's intestine, our findings indicate that atropine and apoatropine evoke about the same degree of antispasmodic action. The antispasmodic action of apoatropine obliterated most of the rhythmic contractions of the muscle. The action of atropine, however, invariably was followed by diminished rhythmic contractions. The respective antispasmodic actions of the 2 compounds are shown in Fig. 1.

Intestinal motility of the rat in situ. Apoatropine and atropine were compared on the intestinal motility of the rat by the method of Van Liere(5). The method depends upon the relative distance traveled by a charcoal acacia mixture from the pyloris along the intestine in a period of 40 minutes after its oral administration. The drugs are administered intraperitoneally 10 minutes prior to the charcoal mixture. The data are shown in Table II. This dosage of apoatropine produced convulsive seizures in half of the animals. The experiment was repeated using 5 rats at a 2.5 mg/kg dosage level. No diminution of the rate of intestinal propulsion was observed.

Apoatropine methyl bromide. By quaternizing the nitrogen atom in homatropine the useful antispasmodic and less toxic homatropine methyl bromide is formed. Accordingly we studied the corresponding quaternized apoatropine. Toxicity was enhanced. The intraperitoneal LD_{50} in the mouse was 0.76 mg/kg with confidence limits of 1.36 mg/kg and 0.42 mg/kg. Employing approximately this dose in the rat, 0.7 mg/kg, in 8 rats the intestinal motility was reduced to 58%. Many of the animals manifested toxic symptoms. It is obvious that by quaternizing apoatropine one enhances the toxicity approximately 20-fold, with no widening of the margin of safety as an antispasmodic as measured by the action on the rat's intestine.

Summary and conclusions. 1. Apoatropine is about 20 times more acutely toxic than atropine. 2. On the isolated rat's intestine atropine and apoatropine elicit about the same degree of antispasmodic action. 3. In the intact rat, apoatropine is approximately one-fortieth as active as atropine in producing the tranquilization of the small intestine. 4. Apoatropine is a potent cardiac depressant in the dog. 5. By quaternizing apoatropine one enhances markedly its toxicity without appreciable effect upon its antispasmodic action.

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Received May 27, 1954. P.S.E.B.M., 1954, v86.