Antidiuretic Effects of Physostigmine and Atropine in the Dog.* (19646)

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Intravenously administered acetylcholine can inhibit water diuresis in the dog, presumably by stimulating the hypothalamo-hypophyseal system to liberate antidiuretic hormone(1). The injection of acetylcholine or physostigmine directly into the region of the supraoptic nuclei of the dog has been shown to produce antidiuresis(2). Atropine, administered subcutaneously, has been employed in conjunction with intravenously injected acetylcholine to eliminate the muscarinic effects of the latter, and physostigmine, administered subcutaneously, has been used to "reinforce" the antidiuretic action of acetylcholine(1-4). It has been reported that large doses of atropine are antidiuretic in mice(5). In dogs this drug is said to inhibit an established water diuresis, or to delay and diminish diuresis(6,7). Ginsberg and Heller are quoted by Heller(8) as being unable to inhibit urine flow in rats with doses as high as 50 mg per animal administered subcutaneously.

During experiments in this laboratory on the antidiuretic effect of acetylcholine, atropine has been routinely used to block muscarinic effects, in doses of 0.05 to 0.15 mg per kg administered subcutaneously at the time of water loading. As in Pickford's work, no difficulty was encountered in achieving a satisfactory water diuresis. It was decided, nevertheless, to investigate the alleged antidiuretic activity of atropine. During attempts to potentiate the antidiuretic activity of 3-hydroxy-2-phenylcinchoninic acid, intravenously injected physostigmine was found capable of inhibiting water diuresis. The latter drug was therefore included in our antidiuretic studies. The data reported in this paper are the results of these investigations.

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Methods. Trained perineotomized female dogs were used for all experiments, urine being collected by catheter at 15-minute intervals. Atropine was injected as the hydrochloride and physostigmine as the sulfate. All doses are calculated as these salts. Each injection was administered intravenously in a volume of 5 ml or less over a period of 30 seconds or less. Doses were usually varied by 2-fold increments. Injections were made after diuresis was established by the administration of 40 ml of water per kg by stomach tube. An antidiuretic effect was considered obtained when an unequivocal decrease in urine flow was observed, followed by a return to higher levels, as described previously(9). In the majority of experiments, the urinary excretion of endogenous creatinine was used to detect changes in glomerular filtration rate, but in 4 experiments the clearance of administered creatinine was used. The method of Folin-Wu as modified by Phillips(10) was employed to determine creatinine.

Results. Ten experiments with physostigmine were performed in 4 dogs. Doses of 0.08 to 0.1 mg per kg were necessary to produce an antidiuresis in all animals. The changes in urine flow were independent of changes in glomerular filtration rate (Fig. 1) and therefore the antidiuretic effect may be

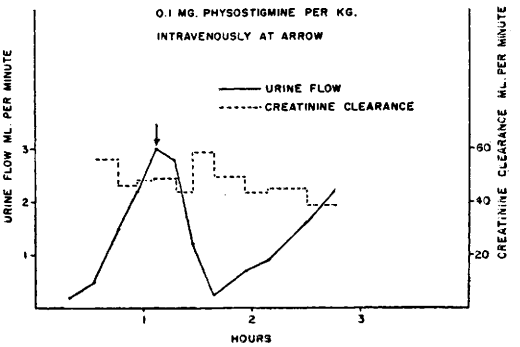

FIG. 1. Effect of physostigmine on water diuresis and creatinine clearance in the dog.

said to represent increased tubular reabsorption of water. Urine flow in almost all instances decreased within 15 minutes after injection of the drug, with the maximal inhibition occurring at approximately 30 minutes. A slow return to pre-injection urine flows followed. Doses of 0.04 to 0.12 mg per kg produced in all dogs tremor of varying severity lasting from 8 to 50 minutes. In one dog, profuse salivation and defecation also occurred.

Eighteen experiments with atropine were performed in 5 dogs. In 3 dogs unequivocal antidiuretic effects were observed with doses of 0.12, 0.25 and 0.5 mg per kg, respectively. As with eserine, the changes in urine flow were independent of changes in glomerular filtration rate. In most instances where an antidiuretic effect was elicited the onset of the effect was delayed 15 to 45 minutes after injection of the drug, and the maximal effect was reached 30 to 60 minutes after injection. Urine flows returned slowly to pre-injection values. In the other 2 dogs no inhibition of urine flow could be detected despite the administration of doses (0.25 to 0.5 mg per kg) sufficient to produce toxicity. Higher doses could not be administered to these particular animals because of the production of excitement or viciousness severe enough to make experiments impossible. Even minimal effective doses were accompanied by marked stimulation of the central nervous system in 2 dogs. This stimulation reached maximum intensity during the period of the antidiuresis. The toxic manifestations seen included restlessness, whining, barking, ataxia, panting, vomiting, mydriasis, and tachycardia.

Discussion. Either of the 2 drugs studied is capable of producing antidiuresis in dogs by increasing the renal tubular reabsorption of water, an effect most probably mediated by release of antidiuretic hormone from the neurohypophysis. The doses necessary to affect the urine flow, however, produce obvious signs of intoxication, although the production of toxic manifestations is not necessarily accompanied by antidiuresis. In the case of atropine, at least, it seems likely that the antidiuretic effect is part of the results of widespread stimulation of the central nervous system. In view of the large doses needed when the drug is given intravenously it seems unlikely that the relatively small doses used subcutaneously to block the muscarinic effects of acetylcholine could have significant effects on urine flow. The results with physostigmine are compatible with the theory of Pickford and associates that acetylcholine is the mediator of stimuli in the hypothalamo-hypophyseal system.

Summary. Physostigmine and atropine produce antidiuresis in the dog by increasing tubular reabsorption of water. The doses required, however, are large and usually accompanied by signs of toxicity.

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