Effects of Some Psychotropic Drugs Upon Urinary Water Output. (28860)

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Several reports have appeared which indicate that certain psychotropic drugs, particularly the phenothiazines, have antidiuretic effects(1-5). We therefore decided to examine several of the newer drugs of this type for their effects upon urinary excretion of water. In addition to 2 phenothiazine derivatives, the drugs included a thioxanthene, a dibenzazepine, a dibenzocycloheptadiene, and two benzodiazepine derivatives, members of a new class of highly potent psychodepressants(6,7).

Methods. Intact male rats obtained from Laboratory Animals Corp., Plainfield, N. J., were used. Body weights ranged from 125-150 g. Food and drinking water were removed 24 hours before injection of drugs. Compounds were dissolved or suspended in distilled water and administered intraperitoneally in a volume of 2 ml/kg body weight. All compounds, except diazepam, were soluble in distilled water. Chlorprothixene solutions were prepared by dilution of commercial Taractan® parenteral material with distilled water. Diazepam was administered as a suspension. Control animals were injected with distilled water. Exactly one hour after drug administration each rat was given 5 ml/100 g body weight distilled water by gastric tube, and immediately placed in an individual metabolism cage. Urine was collected for 90 minutes after administration of the water load. This time interval was selected because preliminary studies indicated that control animals consistently were able to excrete 50% of their water load in 90 minutes.

Results and discussion. All the compounds tested, except diazepam, produced antidiuretic effects when sufficient doses were administered (Table I). Chlorpromazine and thioridazine were equally potent in their ability to depress urinary water output. Chlorprothixene required approximately twice the dosage of the phenothiazines to cause equivalent depression of urinary water. Two thymoleptic compounds, imipramine and amitriptyline, manifested antidiuretic effects at dosages approximately 4 times that of chlorpromazine. Imipramine was biphasic in its effect. Lower doses were diuretic while higher doses were antidiuretic. Chlordiazepoxide showed antidiuretic effects at a dosage 8 times that required with chlorpromazine. Diazepam had no effect on urinary water output at 16 times the antidiuretic dose of chlorpromazine.

Insufficient evidence is available to classify the mechanism of the antidiuretic effects with psychotropic drugs. The dosages required to elicit antidiuretic activity were much greater than those necessary to produce significant behavioral depression(8). Hence, marked central depression occurred at antidiuretic dosages. The antidiuretic effect appeared to be related to the severity of CNS depression. The different chemical structures of the compounds which produce antidiuretic effects indicate that the mechanism involved is rather non-specific in molecular configuration.

Other authors(1-5) have suggested that the depression of urinary water output by psychotropic drugs is caused by stimulation of antidiuretic hormone (ADH) secretion. In our view such a conclusion is not justified solely on the basis of depressed urinary output. We would not conclude, for example, that the biphasic activity of imipramine was due first to inhibition of ADH secretion followed by stimulation of ADH release as dosage of imipramine was increased. It is conceivable that the antidiuretic effects with high doses of psychodepressants may be related to alterations in renal function secondary to CNS depression. Insufficient evidence is available to attribute these effects in whole or in part to the action of antidiuretic hormone.

Summary. Chlorpromazine, thioridazine,

TABLE I. Effects of Psychotropic Drugs on Urinary Water Output.

Compound	Dose, mg/kg	No. of rats	Mean ± S.E. Proportion of water load excreted in urine in 90 min*	"t" test†
Water	—	136	.52 ± .02	—
Chlorpromazine • HCl	4	10	.59 ± .05	N.S.
	8	10	.28 ± .06	$p < .001$
	16	10	.14 ± .04	$p < .001$
Thioridazine • HCl	4	10	.47 ± .06	N.S.
	8	10	.29 ± .04	$p < .001$
	16	10	.09 ± .03	$p < .001$
Chlorprothixene	8	9	.41 ± .07	N.S.
	16	10	.22 ± .04	$p < .001$
	32	8	.16 ± .07	$p < .001$
Imipramine • HCl	4	10	.80 ± .04	$p < .001$
	8	10	.76 ± .04	$p < .001$
	16	20	.83 ± .03	$p < .001$
	32	20	.39 ± .06	$p < .01$
	64	18	.05 ± .02	$p < .001$
Amitriptyline • HCl	16	8	.59 ± .07	N.S.
	32	10	.19 ± .05	$p < .001$
	64	9	.12 ± .04	$p < .001$
Chlordiazepoxide • HCl	32	8	.50 ± .06	N.S.
	64	10	.27 ± .07	$p < .001$
	128	10	.04 ± .03	$p < .001$
Diazepam	32	10	.46 ± .07	N.S.
	64	10	.42 ± .06	N.S.
	128	10	.48 ± .04	N.S.

* 90 min urine vol/water load vol.

† "t" test based upon comparison with controls run concurrently, usually 10 rats, and not upon control value listed in table which is a composite value for entire study.

chlorprothixene, imipramine, amitriptyline, and chlordiazepoxide all manifested antidiuretic activity when a sufficient dose was administered. Diazepam failed to show either diuretic or antidiuretic activity at dosages up to and including 128 mg/kg.

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