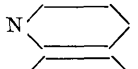
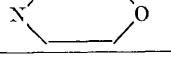
Diuretic Effects of Some Mercurated Substituted N-n-propylurea Derivatives. (23312)

HARRY ROSEN, ALBERT BLUMENTHAL, MARY H. NEAD, RICHARD TISLOW AND JOSEPH SEIFTER
Wyeth Institute for Medical Research, Radnor, Pa.

Since the observation by Vogl(1), that organic mercurials had a diuretic effect, their use as parenteral diuretics has become well established. Recently, considerable effort has been expended toward the development of orally active organomercurials and in this paper we are reporting studies with 6 such mercurial compounds tested for their diuretic effects when administered by the oral route in dogs.

Methods. Various test animals and numerous methods have been used to determine diuretic and antidiuretic properties of drugs(2-6) and the dog appears to have become the test object of choice for evaluating mercurial diuretics(7-10). The animals used in this study were healthy mongrel dogs of both sexes maintained on a standard diet in air-conditioned quarters. They were fasted for 18 hours prior to use, but permitted water *ad lib.* On the morning of the experiment, each dog was given an oral load of 0.9% saline, 25 ml per kg, and one hour later was anesthetized with sodium pentobarbital, 40 mg/kg i.p. The level of anesthesia was kept constant with supplementary doses, as needed. Each dog was catheterized as soon as anesthetized and the bladder emptied by light compression. The catheter remained in the bladder until conclusion of the experiment. Female urethral catheters (12 F.) were used for the female animals and graduated ureteral catheters with a whistle tip (7 or 9 F.) for the male dogs. Collection of urine for experimental purposes was started 2 hours after the saline load and was measured at 15 minute intervals for a total of 5 hours. Each dog was tested twice, thereby serving as his own control. The control experiment was made first and 7 days later, the test experiment was made with the drug under investigation or with a second control. In this way, we have accumulated data which show the urine output that can be expected from the second test without a diuretic. A 2-fold increase in urine output per kg per 5 hours over and above the control output indicated diuresis. Test compounds were administered orally in capsules 60 minutes after the saline load and just prior to anesthesia. Six mercurated substituted-N-n-propylurea derivatives synthesized by Dr. Gerhard Wendt, and listed in Table I by code numbers and corresponding chemical configurations, were all tested at doses equivalent to 2, 4 and 8 mg mercury/kg dog.

TABLE I. Compounds Tested.*
$NH_2CONHCH_2CHRCH_2HgCl$.

Wyeth No.	R
1031	$N(CH_3)_2$
864	$N(CH_2CH_3)_2$
1032	$N(CH_2CH_2CH_3)_2$
935	
774	
775	

* The clinical diuretic efficacy of Wy-864 and 935 was reported by David Baden, Thomas Lau, Richard Borreson and Don W. Chapman, Am. Soc. Pharm. & Exp. Therap., French Lick, Ind., Nov. 8-10, 1956.

Results. One hundred and thirty-seven dogs of both sexes ranging in weight from 4.0 to 16.2 kg were used in this study. The average weight of all dogs for the initial control run was 10.36 kg $\pm$ 2.01. For the test run, 7 days later, the average weight was 10.16 kg $\pm$ 2.19.

Table II shows hourly and total 5 hour urine output for all dogs during the initial control determinations. The averages for males (72) and females (65) as well as combined averages are shown. As time elapsed, hourly output increased for both sexes and average total urine volume was somewhat greater in females.

TABLE II. Control Urine Values in ml/kg.

Collection period	♂ (72) Mean	S.D.	♀ (65) Mean	S.D.	Combined (137) Mean	S.D.
1st hr	.6	.45	.8	.40	.7	.43
2nd	.7	.50	.9	.56	.8	.54
3rd	.8	.48	1.0	.63	.9	.57
4th	.9	.55	1.2	.69	1.1	.64
5th	1.0	.56	1.3	.66	1.1	.62
5 hours	4.0	2.08	5.2	2.44	4.6	2.32

During these experiments we accumulated data on 29 dogs (14 males and 15 females) used as double controls; an initial control run and 7 days later another control run without a test drug. Diuretic values were obtained by subtracting the first 5 hour volume of urine in ml per kg from the second 5 hour volume of urine and then dividing the initial volume into this difference. The mean values for males were 0.002 $\pm$ a standard deviation of 0.3440 and for females—0.123 $\pm$ 0.3636. The differences are negligible and an analysis of variance(11) showed no significant difference between males and females or within the groups themselves ($P = >0.2$). Therefore the data on males and females were combined. A *t* test was made comparing this combined mean diuretic value with an expected mean of zero. In this case $P = >0.3$, showing that both control runs, 7 days apart, are equivalent in urine output.

TABLE III. Summary of Diuretic Results. No. dogs positive/No. dogs used.

Wyeth No.	Dose (mg mercury/kg dog) 8	4	2
774	4/4	0/ 4	2/4
775	2/4*	3/ 4	2/4*
864	3/4	18/24*	2/4*
935	4/4	18/24*	3/4
1031	2/2	4/ 4	3/4
1032	1/2	2/ 4*	0/4

* One dog, considered as negative, gave a diuretic value between 1.0 and 1.4.

Table III is a summation of the results obtained with each compound. All dogs recorded as positive gave a diuretic value of 2 or greater. Of the 108 dogs included in this table, only 6 as indicated, resulted in questionable diuresis as determined by our standards. The diuretic values for these were between 1 and 1.4, which we considered as a mild diuresis and for our purposes were listed as negative.

Summary. 1) A method for testing mercurial diuretics by the oral route of administration in dogs has been presented. 2) Six mercurated substituted-N-n-propylurea derivatives have been tested by this method and found to be active diuretics.

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