Comparative Study of Morphine and Dromoran as Antidiuretic Agents in the Dog.* (18056)

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The influence of morphine on renal function has been the subject of investigation for many years. Experimental results have not been conclusive and controversy still exists regarding the exact mechanisms involved.

Stimulated by earlier clinical observations and speculations, Fee(1) noted that morphine inhibited water diuresis in decorticated and decerebrated dogs and cats. Stehle and Bourne(2) studied the effects of morphine on kidney function in dogs with bladder fistulae. They observed minimal anti-diuretic effects of morphine when urinary flows were normal or low, however, in the presence of high urinary flows morphine exerted a marked anti-diuretic effect. Chloride excretion was also studied and in most cases chloride excretion was reduced by morphine although the results were variable.

Fee(3) employed himself as an experimental subject and noted that the administration of morphine produced an anti-diuretic effect accompanied by chloruresis. Having eliminated cortical and cerebral effects in his previous experiments in the dog, he concluded that the posterior pituitary gland was responsible for regulation of the renal excretion of water and chlorides. It remained for Ranson and his co-workers(4) to definitely establish this concept.

The nature and mechanism of morphine effect on renal function was further investigated by De Bodo(5,6,7) in normal and diabetes insipidus dogs. He concluded that morphine owed its anti-diuretic and chloruretic effects to stimulation of the neurohypophysis with release of the anti-diuretic hormone.

Handley(8) recently studied changes in renal hemodynamics produced by morphine and reported a reduction in glomerular filtration rate, renal plasma flow, and Tm_G both in normal and in diabetes insipidus dogs. He concluded that morphine could reduce urine output by either reducing the number of active nephrons or by causing the liberation of anti-diuretic hormone.

Clinical reports on the anti-diuretic effects of morphine have been less decisive. Boyd and Scherf(9) found that although morphine was anti-diuretic in the normal human, it caused diuresis presumably through extra-renal factors in patients with cardiac decompensation. Ferrer and Sokoloff(10) confirmed the anti-diuretic and chloruretic action of morphine in normal humans, but noted anti-diuresis with reduced chloride excretion in 3 out of 9 cardiac patients receiving mercurial diuretics in addition to morphine. More recently, Kraushaar *et al.*(11) reported that although morphine was anti-diuretic in pregnant and non-pregnant women, it caused a

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reduction of urinary chloride excretion in 4 out of 6 patients. In contrast to morphine, pitressin produced chloruresis in this series. Since morphine produced an anti-diuretic effect in 2 patients with clinical diabetes insipidus, although to a lesser degree than in normals, the authors concluded that morphine anti-diuresis was not mediated through the stimulation of the neuro-hypophysis in man. Brown, Hodges and Bradbury(12) observed that in the human, morphine effected a reduction in renal plasma flow, did not affect glomerular filtration rate, and increased the tubular resorption of water.

The anti-diuretic properties of morphine may be undesirable in clinical conditions of oliguria and edema associated with salt and water retention. Recently, a morphine substitute, 3-hydroxy-N-methyl morphinan hydrobromide (Dromoran†) has been reported to be an effective analgesic with fewer side reactions than morphine(13,14,15). The purpose of this investigation was to study the possible anti-diuretic effects of Dromoran in the dog and to compare its renotropic effects with those of morphine.

Methods. All experiments were performed on trained, unanesthetized female dogs in the fasting state. Essentially the same procedures as reported by De Bodo(5) were used. Each experiment consisted of 2 consecutive diuresis periods of 3 hours duration. The animals were hydrated with tapwater (40 cc/kg) by stomach tube at the start of each period. Urine samples were collected by means of indwelling urethral catheters. Total urine volumes for each period were recorded and aliquots were taken for chloride analysis which were done by the method of Schales(16). Control runs were made to determine the normal diuretic response to the doses of water administered in Periods I and II.

TABLE I.
Control Diuretic Responses Following Second Hydration During Period II.

Dog	Hydration vol. (total cc)	Urine vol. (cc/3 hr)	% retention
Ev.	920	790	13.7
Br.	800	720	10.0
Tr.	650	550	15.3
Qu.	650	576	11.4
Co.	640	555	13.3
Sp.	800	615	23.1
Mean	—	—	14.5

All drugs were administered during Period II. Since morphine occasionally produced emesis, it was routinely injected 40 minutes after the second hydration which initiated Period II. In this way, no appreciable loss of the hydration dose occurred, since complete absorption of this dose of water has been shown to occur within a 40 minute period(5). The volume of urine output during Period II was divided by the hydration volume to obtain the per cent of water returned. Any anti-diuretic effect was calculated by arbitrarily subtracting the per cent of water return from the ideal return of 100%.

Morphine sulphate was administered subcutaneously in doses of 0.5, 0.75, 1.0, 2.5 and 5.0 mg/kg. Dromoran was injected subcutaneously in doses of 0.25, 0.5 and 1.0 mg/kg. The responses to these doses were plotted to obtain the anti-diuretic dose which would produce 50% inhibition of water diuresis (AD_{50}).

Results. Table I summarizes the diuretic responses following hydration in the dog under controlled conditions. In Period II approximately 85% of the administered water was excreted, yielding an average "inhibition" of 15%. These data compare favorably with those of De Bodo. The anti-diuretic responses to increasing doses of Dromoran and morphine are presented in Table II. It is evident that both drugs are anti-diuretic in the doses employed, although the variability

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† Dromoran Hydrobromide is the trademark of this compound which is also reported in the literature as "Nu-2206."

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TABLE II.
Effect of Morphine and Dromoran on Water Diuresis in the Normal Dog.

Drug	Dose, mg/kg s.c.	No. of dogs	% inhibition of water diuresis (mean)	Standard deviation*
Morphine	5.0	4	66.5	8.44
	2.5	6	66.1	15.7
	1.0	7	52.9	13.3
	0.75	5	42.2	8.07
	0.5	5	17.8	7.30
Dromoran	1.0	5	60.4	8.71
	0.5	5	60.6	7.0
	0.25	5	30.9	17.1

* Estimated from range/σ.

TABLE III.
Effects of Water Diuresis on Chloride Excretion.

Dog	Total urinary chlorides (milliequivalents)			Relative chloride concentration (milliequivalents/liter)		
	Period I	Period II	Difference	Period I	Period II	Difference
Co.	1.47	1.06	0.41	8.14	3.41	4.73
Qu.	3.22	1.61	1.61	5.89	3.20	2.69
Za.	0.75	0.72	0.03	2.98	1.33	1.65
Sh.	2.46	0.85	1.61	8.47	1.71	6.76
Br.	0.88	0.53	0.35	1.97	1.48	0.49
Mean difference			0.80			5.26
Probability value (P)			0.05			0.08

TABLE IV.
Effects of Morphine and Dromoran on Urinary Chloride Excretion During Water Diuresis in the Dog.

Drug	Dose, mg/kg s.c.	No. of animals	Mean decrease in urinary chloride excretion			
			Total meq.	S.D.	Meq./l	S.D.
Control	—	5	0.80	0.75	3.26	2.65
Dromoran	0.25	4	1.35	1.72	2.84	2.85
	0.50	5	1.88	1.86	2.22	2.64
	1.00	5	2.74	1.55	3.86	2.74
Morphine	0.50	5	0.93	0.86	2.22	2.12
	0.75	5	4.50	3.59	13.55	16.16
	1.0	4	1.45	1.56	3.39	4.34
	2.50	5	1.52	1.45	1.92	4.09

in the results is quite marked. The AD_{50} dose for morphine was 0.9 mg/kg and for Dromoran, 0.4 mg/kg. The decrease in chloride excretion caused by hydration under controlled conditions is summarized in Table III. The difference between Periods I and II in terms of total milliequivalents of urinary chloride was statistically significant. The differences in relative chloride concentrations in meq./liter between Periods I and II just exceeded the probability level of statistical significance. In view of the variable effects of water diuresis on chloride excretion, had more experiments been run, the 5% probability level would, in all likelihood, have been satisfied insofar as the relative chloride concentration was concerned. The effects of morphine and Dromoran on chloride excretion are tabulated in Table IV. It is apparent that neither drug effected chloruresis and that the decrease in chloride excretion in Period II is probably a hydration phenomenon.

During the course of the experiments the

side-effects of the two drugs were noted. Animals receiving Dromoran showed a lower incidence of emesis and diarrhea than with morphine.

Summary. The results indicate that Dromoran, as well as morphine, has anti-diuretic activity in the range of doses studied. Comparison of the relative anti-diuretic potencies of the two drugs must of necessity take into consideration their analgesic potencies. Clinical studies indicate that Dromoran is approximately 4 times as potent an analgesic as morphine in the human(15). Since no data are available on Dromoran's analgesic potency in the dog, the AD_{50} doses of Dromoran and morphine obtained in the dog were arbitrarily related to the analgesic potency of these drugs in man.

If the following ratio is computed:

$$\frac{\text{Equivalent analgesic dose (man)}}{AD_{50}\text{ (dog)}} = \text{Anti-diuretic index (A.D.I.)}$$

it is apparent that for equivalent analgesic effects, the larger the dose required to produce 50% inhibition of water diuresis in the dog, the less the anti-diuretic potency. The quotient of this ratio can be arbitrarily termed an anti-diuretic index (A.D.I.)

$$\text{For morphine } \frac{1}{0.9} = 1.1 \text{ (A.D.I.)}$$

$$\text{For Dromoran } \frac{0.25}{0.40} = 0.6 \text{ (A.D.I.)}$$

At equivalent analgesic doses, it is obvious that Dromoran has a lower anti-diuretic index than morphine.

A review of the literature indicated no dose-response relationships in reference to chloruretic responses to morphine. De Bodo obtained chloruresis in the dog with doses larger than those which we employed. Ferrer and Sokoloff noted chloruresis in 2 human patients using a dose of morphine lower than that used by Kraushaar who reported a depression of chloride excretion by morphine in 4 of 6 patients.

The data reported in this paper do not elucidate the mechanisms involved in the anti-diuretic responses. The inhibition of chloride excretion following the second hydration is consistent with inhibition of the posterior lobe during water diuresis. Neither morphine nor Dromoran effected this inhibition of anti-diuretic hormone secretion. The absence of chloruresis in the presence of anti-diuresis suggests that in the doses used, these drugs produce an anti-diuretic effect through a mechanism other than the release of anti-diuretic hormone from the posterior pituitary.

Conclusions. 1. Dromoran is less anti-diuretic than morphine when anti-diuretic activity is related to analgesic potency. 2. In the range of doses employed in these studies, neither morphine nor Dromoran effected a chloruresis. 3. The lack of chloruresis in the presence of anti-diuretic action suggests that these drugs do not act by liberation of the anti-diuretic hormone.

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Dual Antibody Response to Coxsackie and Poliomyelitis Viruses in Patients with Paralytic Poliomyelitis.* (18057)

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Simultaneous excretion of both Coxsackie (C) and poliomyelitis viruses from the intestinal tract of man during both periods of illness and apparent health(1-3), as well as the simultaneous recovery of these two viruses from flies trapped in poliomyelitis areas(4),

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