The Diuretic and Antidiuretic Effect of Morphine Sulphate in Rats[1] (34676)

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Recently, Marchand and Denis (1) showed that chronic morphine treatment in rats is associated with an osmotic diuresis characterized by an increase in electrolyte and urea excretion. These observations contrasted with the classical notion that an acute dose of morphine causes a decrease in urinary output. The antidiuretic effect is believed to be mediated through release of antidiuretic hormone or, possibly, by a direct effect of the narcotic on the kidney (2). A survey of the literature on the antidiruetic effect of morphine revealed that nearly all these experiments were conducted in animals or patients pre-loaded with water. The present experiments were undertaken to study the effect of acute doses of morphine under physiological conditions of hydration.

Methods. Sprague-Dawley female rats, weighing between 200 and 250 g, were anesthetized with ether and the bladder was surgically exteriorized according to the method of Czaczkes *et al.* (3). Three days after surgery, the rats were housed in metabolism cages in groups of four. Food and water were offered *ad libitum* until a few minutes before subcutaneous administration of various doses of morphine or a 0.9% saline solution in control rats. In another series of experiments, the animals received, by gavage, a volume of warm tap water equivalent to 5% of their body weight, immediately after the morphine injection. The urine was collected and measured every hour in tubes that were graduated to 0.05 ml; after 4 hr of collection, the samples were frozen for later determinations. In Table I, the combined 4-hr urine volume

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TABLE I. Effect of Morphine Sulfate on the Urinary Volume, Urea, and Electrolyte Excretion in Nonhydrated and Hydrated Rats over a 4-hr Period Following Saline or Morphine Injection. Each value represents the mean ± standard error of 5 groups, 4 rats in each group.

Morphine sulfate (mg/kg)	Urine				
	Vol (μl/hr/100 g)	Urea (mg/hr/100 g)	Sodium (μeq/hr/100 g)	Potassium (μeq/hr/100 g)	Calcium (μg/hr/100 g)
	Nonhydrated				
Saline	30.9 ± 11.5	1.0 ± 1.4	3.6 ± 1.1	8.8 ± 3.4	2.8 ± 0.5
3	81.4 ± 11.6[a]	2.7 ± 0.4[a]	6.6 ± 2.1	9.8 ± 2.2	5.9 ± 1.0[a]
6	55.8 ± 11.2	1.9 ± 0.4	3.4 ± 0.5	7.5 ± 1.2	4.1 ± 1.0
12	48.2 ± 13.1	1.3 ± 0.2	1.9 ± 0.5	3.2 ± 0.8[a]	2.8 ± 0.5
	Hydrated				
Saline	482.3 ± 40.5	10.5 ± 1.4	11.3 ± 0.9	24.8 ± 3.5	11.4 ± 0.8
3	354.5 ± 36.6[a]	9.5 ± 0.6	9.4 ± 1.4	19.6 ± 3.5	8.1 ± 0.8[a]
6	269.6 ± 58.6[a]	5.9 ± 1.1	5.0 ± 0.9	19.7 ± 1.9	10.9 ± 0.6
12	225.5 ± 64.5[a]	7.5 ± 2.2	9.4 ± 2.2	15.3 ± 3.6	7.0 ± 2.2

[a] $p < .05$.

was calculated as (μl/hr/100 g) in order to have a uniform basis for expression with the other variables measured. Sodium and potassium were measured with a flame photometer, calcium, with an atomic absorption spectrophotometer, and urea according to the method of Friedman (4).

Significance of the difference between control and treated rats was assessed by the *t* test and a *p* value of .05 or less was considered significant.

Results. The effect of morphine on the urinary output of nonhydrated rats is shown in Table I; the urinary volumes represent collection periods of 4 hr following saline or morphine injection. Following administration of 3 mg/kg, there is a diuretic effect. With increasing doses of the narcotic, this diuresis shows a tendency to progressively disappear. Since chronic morphine treatment in rats is associated with an osmotic diuresis, urea and electrolytes were measured. The diuresis provoked by administration of 3 mg/kg of morphine sulfate, in the nonhydrated rats, was associated with a significant increase in urinary urea; sodium and potassium excretion seemed to be augmented, but no significant difference could be established. Calcium excretion, which is known to be markedly enhanced during chronic morphine treatment (1), was also significantly increased after a single injection of 3 mg/kg of morphine sulfate. It must be pointed out that, as the diuretic effect decreases with augmentation of the dose of morphine, the urea and electrolyte excretion follows a similar pattern.

In contrast to the nonhydrated rats, the hydrated animals responded to the same doses of morphine by a diminution in urine output that was dose dependent (Table I). The gradual decrease in urinary volume seemed to be associated with a parallel diminution in urea and electrolyte excretion, but this relationship was not as striking as in nonhydrated rats.

In order to assess the time effect relationship in these experiments, the urinary volume was measured 1, 2, 3, and 4 hr after injection (Table II). In nonhydrated animals, the diuretic effect was most apparent within the first hour that followed morphine administration. In hydrated rats, the antidiuretic effect of the narcotic was more marked during the first 2 hr that followed treatment with the narcotic.

Discussion. The antidiuretic effect of morphine observed here in hydrated rats confirms previous observations (5-7). De Bodo (8) was the first to show that morphine released antidiuretic hormone. In his experiments, the animals were pre-loaded with water. Whether they wanted to show that

TABLE II. Effect of Morphine Sulfate on the Urinary Volume (ml/hr) in Nonhydrated and Hydrated Times After Morphine Injection.

Each value represents the mean ± standard error of 5 groups, 4 rats in each group.

Morphine sulfate (mg/kg)	(hr): 1	2	3	4
		Nonhydrated		
Saline	0.16 ± 0.05	0.36 ± 0.14	0.17 ± 0.09	0.25 ± 0.11
3	1.00 ± 0.33[a]	0.48 ± 0.11	0.42 ± 0.11	0.70 ± 0.17
6	0.12 ± 0.07	0.36 ± 0.10	0.50 ± 0.28	0.85 ± 0.19[a]
12	0.10 ± 0.08	0.98 ± 0.47	0.18 ± 0.07	0.26 ± 0.15
		Hydrated		
Saline	4.62 ± 0.87	8.42 ± 0.34	1.26 ± 0.32	0.58 ± 0.12
3	2.14 ± 0.65[a]	3.26 ± 0.37[a]	2.96 ± 1.03	1.24 ± 0.38
6	1.16 ± 0.44[a]	1.17 ± 0.71[a]	1.82 ± 0.28	4.13 ± 2.02[a]
12	1.76 ± 0.56[a]	3.15 ± 1.02[a]	1.12 ± 0.50	0.62 ± 0.13

[a] $p < .05$.

narcotics cause antidiuresis through release of ADH or through a direct action on the kidney, subsequent investigators always loaded patients or animals with water (5, 9–16). It seems, then, that conclusions concerning the effect of morphine on urinary volume were drawn under special conditions, namely, in hydrated patients or animals. Furthermore, the importance of the dose of morphine in assessing the effect of the narcotic on the urine output has been stressed by George and Way (9). These investigators showed that, at small doses, the antidiuretic effect of morphine is probably due to a release of ADH, whereas, at high doses, the narcotic may exert a direct influence on the kidney.

On the other hand, the present experiments reveal that, in nonhydrated animals, morphine acts as a diuretic. This diuresis is characterized by an augmentation of urinary electrolyte and urea excretion. In this respect, the acute effect of morphine differs only on a quantitative basis from that of chronic treatment reported previously (1). As a speculation, it may still be possible that the diuretic effect is mediated through ADH. It is known that the action of ADH on the urine output is dependent on the state of hydration. ADH has caused saluresis with a concomitant increase in urinary output in animals perfused with saline (17, 18). These experimental states may hardly be physiologically comparable.

Although the present observations in the rat are not necessarily relevant to man, they serve to question the commonly held opinion that morphine is an antidiuretic agent (2, 19). Furthermore, there have been recent reports indicating that morphine potentiates the diuretic effect of furosemide in patients with pulmonary edema (20). These observations and the recent work of Inturrisi *et al.* (21) in chickens indicate that the effects of morphine on the diuresis must be reevaluated. On the other hand, the notion among physicians that morphine is antidiuretic in nonhydrated patients should be carefully considered. The retention of urine observed clinically may be caused by the known effect of morphine on the bladder (22). This condition could mask the presence of a diuretic state. Laparotomy performed 1 hr after administration of morphine usually reveals a full bladder in rats.

Summary. Administration of morphine sulfate in water-loaded rats exerts an antidiuretic effect that is dose dependent. In animals not waterloaded, the narcotic exerts a diuretic effect at a dose of 3 mg/kg sc but not at 6 and 12 mg/kg. The diuresis is characterized by an increase in urea and calcium excretion. Since, in the past, experiments dealing with the antidiuretic effect of morphine were usually carried out under hydrated conditions, the clinical significance of the effect of the narcotic on urine must be reevaluated, especially under nonwater-loading conditions.

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