RADIOIMMUNOASSAY OF ANTIDIURETIC HORMONE DURING MORPHINE ANAESTHESIA

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THERE ARE CONFLICTING REPORTS in the literature concerning the effect of morphine on plasma antidiuretic hormone (ADH) levels. Some authors state that morphine and all narcotics stimulate ADH secretion¹ while others suggest that if a decrease in urine flow occurs with morphine administration, it is due to factors other than elevated ADH^{2,3} such as decreased renal blood flow.⁴ Part of the confusion may be due to species differences since morphine is known to stimulate ADH secretion in dogs and rats^{5,6} but direct evidence for this is lacking in man. Further, the previous method of determining plasma ADH levels utilized a biological assay that was both tedious and time-consuming, and thus led to studies in which a less than optimum number of ADH measurements were performed or indirect evidence for ADH levels was used.

This study was undertaken to determine the effect of morphine on plasma levels of ADH in man utilizing a radioimmunoassay which allowed for multiple determinations.

METHODS

Seven adult patients scheduled for elective open heart operations were selected for study. Table I lists patient characteristics. Informed consent was obtained after detailed discussion of the procedure. All patients were premedicated with scopolamine 0.4 mg and morphine 0.1 mg/kg given intramuscularly approximately one hour prior to arrival in the induction room.

Each patient had monitoring electrocardiogram (ECG) leads placed, and a percutaneous radial artery cannula, a CVP line, and a 16-gauge volume line were introduced under local analgesia. Pressures and ECG were recorded continuously on an eight channel Hewlett Packard monitor with an oscilloscope. A Foley indwelling urinary catheter was placed after induction of anaesthesia and connected to a collecting bag.

The study was divided into three periods: (1) control – following placement of monitoring lines before induction of anaesthesia; (2) anaesthesia – following induction with morphine and before the skin incision; (3) operation – following skin incision. Measurements obtained in periods 2 and 3 were at 15 and 30 minute intervals. During each period the following variables were measured or recorded:

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TABLE I
PATIENT CHARACTERISTICS

Patient	Age	Sex	Disease	Operation
J.R.	64	F	A.S. M.S.	Aortic valve replacement Mitral valve replacement
D.A.	58	M	A.S. CAD	Aortic valve replacement Coronary bypass graft to LAD
G.D.	59	M	A.S. CAD	Aortic valve replacement Coronary bypass graft to LAD and circumflex
M.F.	64	F	M.S. T.I.	Mitral valve replacement Tricuspid valve replacement
A.C.	48	M	A.S.	Aortic valve replacement
W.W.	56	M	A.S.	Aortic valve replacement
M.T.	62	F	A.S. A.I.	Aortic valve replacement

A.S. = Aortic stenosis.

M.S. = Mitral stenosis.

T.I. = Tricuspid insufficiency.

CAD = Coronary artery disease.

LAD = Left anterior descending coronary artery.

A.I. = Aortic insufficiency.

(1) mean arterial and central venous pressures; (2) heart rate and electrocardiogram; (3) cardiac output; (4) urine flow; (5) arterial blood gases and serum sodium; (6) serum and urine osmolality; (7) plasma ADH levels.

Cardiac output was determined in duplicate by standard dye dilution techniques utilizing Indocyanine green dye and a Beckman cardiodensitometer with sampling from the radial artery. Serum and urine osmolalities were measured by the freezing point technique using a 3W Advanced osmometer.

Plasma ADH determinations involved the collection of 5 ml of blood in heparin and this was immediately iced. Specimens were centrifuged within 15 minutes and the plasma frozen until assayed. Antibodies to arginine vasopressin, the anti-diuretic hormone in man, were produced in rabbits in response to immunization with a co-polymer of arginine vasopressin and succinylated poly-L-lysine in Freund's adjuvant. The labelled hormone was produced by the iodination of vasopressin with I^{131} by a modification of the Hunter and Greenwood method⁷ in which the bisulfate step is omitted. Acetone was added to 1 ml plasma samples to precipitate plasma proteins and the supernate extracted with ether. Incubation of the aqueous phase with labelled hormone and antibody for 48 hours and separation of bound and free phases by Dextran-coated charcoal⁸ resulted in the measurement of plasma vasopressin with an overall recovery of 50 per cent.

After control measurements had been obtained, anaesthesia was induced with one mg/kg of morphine given intravenously at the rate of 5 to 10 mg/min. while the patients were breathing 50 per cent oxygen and 50 per cent nitrous oxide. The trachea was intubated during induction with relaxation provided by a 0.2 per cent succinylcholine drip. Following induction, measurements were obtained at 15 and 30 minutes and then repeated at 15 and 30 minutes following the skin incision.

Intravenous fluids consisted of lactated Ringer's solution administered at a rate of 5 ml/kg/hr during the study period.

Osmolar clearance (Cosm) and free water clearance (CH_2O) were calculated according to the following formula:

$$\text{Cosm} = \text{Uosm} (\dot{V}) / \text{Posm}$$

$$\text{CH}_2\text{O} = \dot{V} - \text{Cosm}$$

where Uosm is urinary osmolality (m.osm/kg), Posm is plasma osmolality (m.osm/kg) and $\dot{V}$ is urinary flow (ml/min)

RESULTS

Tables II and III summarize the data obtained during each period. There were no significant changes in any of the parameters measured at 15 and 30 minutes following the morphine induction. At 15 minutes after the skin incision there

TABLE II*
EFFECT OF MORPHINE ANAESTHESIA ON ADH AND URINARY FUNCTION

	Control	Anaesthesia		Operation	
		15 min	30 min	15 min	30 min
ADH $\mu\text{u/ml}$	3.21 ± 0.1	4.42 ± 2.6	4.14 ± 2.2	$12.05 \pm 0.4^\dagger$	8.29 ± 2.9
Serum Osm. m.osm/kg	289 ± 3	289 ± 4	290 ± 4	289 ± 3	289 ± 3
Urine osm. m.osm/kg	691 ± 142	685 ± 129	693 ± 100	686 ± 86	660 ± 93
C osm ml/min		6.85 ± 4.6	1.64 ± 0.7	9.87 ± 8.6	1.98 ± 0.8
CH_2O ml/min		-3.76 ± 2.5	-0.79 ± 0.4	-4.14 ± 3.5	-1.1 ± 0.6

*Mean $\pm$ standard error of the mean.

$^\dagger P < 0.05$ (students t-test).

TABLE III*
CARDIOVASCULAR EFFECTS OF MORPHINE ANAESTHESIA

	Control	Anaesthesia		Operation	
		15 min	30 min	15 min	30 min
BP mm/Hg	74 ± 2	74 ± 5	73 ± 6	$85 \pm 4^\dagger$	72 ± 3
Pulse beats/min	78 ± 5	77 ± 4	78 ± 4	81 ± 3	82 ± 3
PaO_2 mmHg	72 ± 6	196 ± 4	198 ± 5	198 ± 4	201 ± 5
PaCO_2 mmHg	39 ± 4	41 ± 3	41 ± 4	39 ± 3	39 ± 4
Serum Na mEq/L	141 ± 1.5	138 ± 0.9	138 ± 1.1	138 ± 0.8	139 ± 0.7
C.I. L/min/m ²	3.04 ± 0.5	2.84 ± 0.3	3.02 ± 0.9	2.37 ± 0.2	2.60 ± 3

*Mean $\pm$ standard error of the mean.

$^\dagger p < 0.02$ (student t-test).

FIGURE 1. Graphic illustration of changes in mean blood pressure and plasma ADH with surgical stimulation during morphine anaesthesia.

were significant changes in mean blood pressure and plasma ADH which is shown graphically in Figure 1. Plasma ADH rose to 373 per cent of the control value but at 30 minutes was declining. The increase in blood pressure at 15 minutes after skin incision was significant, but had returned to base line values at 30 minutes. The serum sodium, serum osmolality, and urine osmolality did not change significantly throughout the study period.

Because the Foley catheter was not inserted until after induction had started, the urine osmolality for the control period represents a residual bladder specimen and osmolar and free water clearances were not calculated. Subsequent measurements demonstrated a wide but not significant variation.

The initial blood gases were obtained during spontaneous breathing of room air and all were within normal limits. Subsequent samples were obtained during controlled ventilation with 50 per cent oxygen and 50 per cent nitrous oxide and did not significantly change during the course of the study. There were no significant changes in cardiac index.

DISCUSSION

The comparative ease of the radioimmunoassay for plasma ADH levels as compared to the biological assay allowed us to obtain samples at the fairly frequent intervals of 15 minutes. This is necessary since the response time and half-life of

ADH are relatively short (10 to 20 minutes). The control values obtained in our subjects ($3.21 \pm 0.1 \mu\text{u/ml}$) are in agreement with those reported in the literature utilizing a biological assay.^{9,10} The magnitude of response to surgical stimulation which we have demonstrated is also in agreement with reports in the literature.^{11,12}

Our data indicate that in anaesthetic doses morphine does not stimulate ADH secretion or produce significantly elevated levels of plasma ADH. Samples obtained at 15 and 30 minutes following induction demonstrate this. The increase in the standard error of these measurements, as compared to the control, more than likely is the result of the varying response to laryngoscopy, intubation, bladder catheterization and surgical skin preparation, all of which were done during this period. Previous work in the literature also has suggested that morphine in therapeutic doses does not stimulate ADH secretion, except in unusual circumstances (i.e., nausea and vomiting^{4,9}). Our data confirm the speculation of previous investigators who did not measure ADH directly,^{2,3,4} but correctly concluded that decreases in urine flow with high dose morphine were not ADH related.

It is interesting to note that the control ADH levels were obtained during spontaneous respiration while those following induction with morphine were obtained during controlled ventilation. This was necessary to maintain adequate oxygenation and prevent carbon dioxide accumulation which could itself stimulate ADH secretion.¹⁴ It is apparent that the use of controlled ventilation itself did not significantly affect the ADH levels and this is in agreement with previous work.¹⁵

In this study the induction with morphine was associated with the administration of nitrous oxide. We can therefore conclude that nitrous oxide at least in 50 per cent concentration also does not stimulate ADH secretion. We did not observe the rise in urine osmolality with nitrous oxide previously reported by Stanley,² but we were using a smaller dose of morphine and a lower concentration of nitrous oxide. The protocol of this study does not allow us to differentiate between the effects of morphine and those of nitrous oxide on renal function and this may be responsible for the variations obtained in osmolar and free water clearances. This may also be explained on the basis of patient variability since all had had some degree of congestive heart failure in the past, were digitalized, and in varying states of hydration prior to induction. Since no measurement of urine flow could be made until the Foley catheter had been placed during induction, no attempts was made to achieve a constant flow prior to the start of the study.

We conclude from these data that morphine anaesthesia in doses of one mg/kg does not decrease urinary output by stimulating the release of ADH nor does nitrous oxide in 50 per cent concentrations. ADH changes previously attributed to morphine may be due to surgical stimulation, possibly through a catecholamine release phenomenon resulting in a decrease in urinary output. Alterations in renal blood flow may also occur, resulting in a decrease in urine production previously attributed to elevated ADH levels.

SUMMARY

The effect of morphine anaesthesia on plasma antidiuretic hormone levels was studied in seven adult patients. Measurements of ADH showed no significant change with morphine and 50 per cent nitrous oxide. Significant elevation occurred

with surgical stimulation as previously reported. Changes in urine flow with high doses of morphine are then not ADH related.

RÉSUMÉ

Une étude des taux plasmatiques d'hormone antidiurétique a été effectuée par technique radio-immunologique, chez sept patients anesthésiés à la morphine (1 mg/kg) et au protoxyde d'azote à 50 pour cent chirurgie à cœur ouvert.

Quinze et trente minutes après administration de la morphine, les taux plasmatiques s'établissaient respectivement à $4.42 \pm 2.6 \mu\text{u/ml}$ et à $4.14 \pm 2.2 \mu\text{u/ml}$, taux qui ne différaient pas de façon significative de ceux des contrôles faits avant administration de la morphine ($3.21 \pm 0.1 \mu\text{u/ml}$).

Ces taux se sont cependant élevés de façon significative 15 minutes après le début de la chirurgie ($12.05 \pm 0.4 \mu\text{u/ml}$) et demeuraient élevés ($8.29 \pm 2.9 \mu\text{u/ml}$) bien que plus bas après 30 minutes de chirurgie.

Donc la morphine à doses anesthésiques combinée au protoxyde d'azote à 50 pour cent ne stimule pas la sécrétion d'HAD et les modifications du débit urinaire observées durant une anesthésie à la morphine ne sont pas liées à une stimulation de la sécrétion d'HAD par cet agent.

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