Plasma Antidiuretic Hormone Levels in Cardiac Surgical Patients during Morphine and Halothane Anesthesia

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The effects of halothane and morphine anesthesia on plasma antidiuretic hormone (ADH) levels and urinary flow were determined in 18 patients undergoing elective open-heart operations. Patients were divided into three groups of six each: Group I, halothane, 0.5 per cent; Group II, morphine, 1 mg/kg; Group III, morphine, 2 mg/kg. In addition, all patients received nitrous oxide–oxygen, 50 per cent each. Measurements of mean blood pressure; heart rate; urinary flow, osmolality and electrolytes; and plasma ADH (by radiimmunoassay) were made prior to induction of anesthesia, 15 and 30 min after induction, and 15 and 30 min after surgical incision. Control values received from the Cambridge Antidiuretic Hormone Group in all groups (about 3 pg/ml). There was no significant change in any group after induction of anesthesia. After surgical incision ADH levels increased significantly in Group I (102 ± 29 pg/ml), and Group II (42.6 ± 25 pg/ml), but not in Group III (14.5 ± 7 pg/ml). The increase of plasma ADH was significantly higher in Group I than in Group II or III. Variations in urinary flow were not significant ADH related throughout the study. These data demonstrate that neither morphine nor light halothane anesthesia stimulates high levels of ADH secretion. They suggest that the increase in ADH with surgical stimulation is a stress response that can be attenuated by deeper morphine anesthesia. The ADH levels are beyond the physiologic range for antidiuretic action on the kidney, and may represent a vasopressor response. Variations in urinary flow were not ADH-related. (Key words: Anesthetics, volatile: halothane. Anesthetics, intravenous: morphine. Anesthesia, cardiovascular. Hormones: antidiuretic. Kidney: urine.)

The effects of narcotic drugs and general anesthetics on plasma antidiuretic hormone (ADH) levels are somewhat confusing. Some reports state that all narcotics and inhalation anesthetics stimulate ADH secretion, leading to decreased urinary output, while others suggest that any observed decrease in urinary flow is not ADH-related. Recent studies have failed to detect a significant change in plasma ADH with the use of morphine or other general anesthetics. This study was undertaken to determine the effects of morphine in anesthetic doses and light halothane anesthesia on plasma ADH levels and urinary flow in patients undergoing elective open-heart operations.

Methods

Eighteen adult male patients scheduled for elective open-heart operations were selected for study and assigned randomly to three groups. Ages ranged from 48 to 73 years (59 ± 8). Informed consent was obtained from all patients, and approval was granted by the Human Studies Committee at the Massachusetts General Hospital. The patients in Group I had primarily coronary-artery operations, while patients in Groups II and III had mitral-valve or aortic-valve replacement or coronary-artery operations. All patients were premedicated with scopolamine, 0.4 mg, intramuscularly, an hour prior to arrival in the induction room. In addition, patients in Group I received morphine, 0.1 mg/kg, as part of their premedication.

Each patient had monitoring electrocardiographic (ECG) leads placed and a percutaneous radial-artery catheter, central venous pressure catheter, and 16-gauge intravenous catheter introduced with local anesthesia. Arterial and central venous pressure values and ECG were recorded continuously on an eight-channel Hewlett-Packard monitor with oscilloscope. A Foley indwelling urinary catheter was placed after induction of anesthesia and connected to a collecting bag.

The study was divided into three periods: 1) control, following placement of monitoring lines but prior to induction of anesthesia; 2) anesthesia, 15 and 30 min after induction of anesthesia but prior to skin incision; 3) operation, 15 and 30 min following incision and median sternotomy but before institution of cardiopulmonary bypass. During each period the following variables were measured or recorded: mean arterial and central venous pressures; heart rate and ECG; urinary flow, osmolality, and electrolyte values; plasma ADH level. Plasma ADH determinations utilized a radiimmunoassay technique previously reported. Serum and urinary osmolalities were measured by a freezing-point technique utilizing a 3W Advanced osmometer.

After control measurements were obtained, anesthesia was induced according to the following protocol: Group I, thiopental, 2 mg/kg, and halothane.
0.5 per cent; Group II, morphine, 1 mg/kg, intravenously, at a rate of 5–10 mg/min; Group III, morphine, 2 mg/kg, intravenously, at a rate of 5–10 mg/min. All patients received nitrous oxide–oxygen, 50 per cent each. Lactated Ringer’s solution was administered at a rate of 5 ml/kg/hr during the study period. The trachea of each patient was intubated following induction of anesthesia, with relaxation provided by an infusion of succinylcholine, 0.2 per cent. Ventilation was controlled following induction to maintain arterial P\textsubscript{\text{ET}}\text{CO\textsubscript{2}} at 38 ± 6 torr. Arterial oxygen partial pressure averaged 70 ± 8 torr during the awake control period and 190 ± 10 torr during anesthesia while breathing 50 per cent oxygen.

Intragroup data were analyzed by correlated t test and intergroup data by uncorrelated t test.

**Results**

**Group I: Halothane**

Following incision of the skin there were marked increases in plasma ADH levels over control values at 15 and 30 min (Table 1). Mean arterial blood pressure, urinary sodium content and urinary flow, heart rate, and central venous pressure did not change significantly.

**Group II: Morphine, 1 mg/kg**

There was no significant change in any variable measured following induction of anesthesia. Plasma ADH levels were significantly increased both 15 and 30 min after the start of operation, representing 228 per cent and 1,000 per cent of control values, respectively, with no change in other variables (Table 1).

**Group III: Morphine, 2 mg/kg**

No significant change in any variable was found. The data for all three groups indicated that the increase in plasma ADH that followed surgical incision was greatest in Group I and significantly more than corresponding increases in Groups II and III (Fig. 1). The increase in Group II was also significantly greater than that in Group III (Table 1).

**Discussion**

The apparent disagreement in the literature surrounding the effects of narcotics and anesthetics on plasma ADH levels may be attributed to two major causes. First, much of the original work was done in laboratory animals, particularly the dog. Subsequent evidence suggests that there may be considerable species differences. Second, and perhaps more important, the previously used biological assay for ADH was tedious, time-consuming, and often nonspecific. This led to studies in which only small numbers of samples were analyzed or indirect evidence for changes in ADH levels, such as urinary flow, was used. Even with these limitations in mind, many investigators who have utilized similar indirect evidence have suggested that any decrease in urinary flow following induction of anesthesia was probably not ADH-related. This approach is necessary since the response time...
and half-life of ADH are relatively short (10–20 min). In this study, sampling at 15-min intervals in all groups should have detected any significant increase in ADH level following induction of anesthesia. The lack of such a change demonstrates that at least under these conditions, neither halothane nor morphine significantly alters plasma ADH.

The control values for ADH in these three groups of patients were slightly higher than usually accepted as normal for healthy man. When it is considered that these patients had all been without fluids since the night before operation and were anticipating major cardiac operations, the values obtained become acceptable. The slight but not significant variations in plasma ADH following induction of anesthesia probably reflect to some extent the varying patient responses to stimulation. During this period every patient had both an indwelling Foley urinary bladder catheter and an endotracheal tube inserted, and the surgical preparation of the skin was performed, as well as draping. For this reason, control urinary flows were not obtained, and control urinary osmolality and electrolytes reported are those obtained from the initial bladder sample. The voided specimen of urine was not utilized, since in most instances it was obtained 90 to 120 min prior to arrival in the operating room.

The morphine premedication in Group I was omitted in Groups II and III to determine the effect of this small dose on the control ADH values. Absence of a significant difference among the three groups suggests that morphine in small doses does not have a “lasting” effect on ADH secretion. However, we cannot preclude a small ADH response, since the interval of 90 min between injection and sampling was sufficient to allow for a response and return to the control level.

The marked increase in plasma ADH concentration that occurred with surgical stimulation in Groups I and II was demonstrated in previous studies, but not in the cardiac surgical patient. The concentrations of ADH obtained in Group I are among the highest reported for man, and are considerably above the physiologic range for an antidiuretic action on the kidney. The maximum antidiuretic effect is exerted at concentrations of less than 20 pg/ml. Once maximum concentration of urine is achieved higher vaso-pressin levels either will have no effect or may exert some inhibitory action on urinary concentration secondary to hemodynamic effects. At high concentrations the vasoconstrictor effect of vaso-pressin may become significant; it is one of the most potent endogenous vasoconstrictors in man, and more potent than angiotensin because of its direct action on the smooth muscle of vascular beds. At these high concentrations urinary flow may be independent of ADH present and reflect the status of hemodynamic events.

The apparent lesser response in Group II compared with Group I, and more interestingly, the lack of a significant increase of plasma ADH in Group III with surgical stimulation, suggest that this may indeed be a stress reaction. It would appear that deeper levels of anesthesia (as in Group III) can effectively obtund this response. Unfortunately, deeper halothane anesthesia could not be studied in these patients because of the untoward side effects. In all of these studies, induction of anesthesia necessitated the administration of nitrous oxide, 50 per cent, which confirms our previous observations about its lack of effect on ADH level. With induction of anesthesia the change from spontaneous to controlled ventilation also did not affect ADH concentrations, as was reported previously.

The possibility exists that morphine, aside from the depth of anesthesia produced, possesses a specific ADH-inhibiting effect. This seems unlikely. It is more probable that deeper halothane anesthesia would result in the same lack of response to surgical stimulation, but the data to substantiate this are lacking.

We conclude that morphine administered in anes-
thesia doses in excess of 1 mg/kg and light halothane
anesthesia do not measurably affect plasma ADH
level. A decrease in urinary flow found under these
circumstances may not be ADH-related, and may be
due to a change in cardiac output or renal blood
flow. Surgical stimulation can produce marked in-
creases in plasma ADH or vasopressin. The extent
of this response may be related to the depth of anes-
esthesia, and may result in concentrations in excess of
the physiologic range from an effective renal anti-
diuretic action. This may represent a stress response
to the operation rather than the anesthetic, and vasopre-
sassin may in fact deserve its name, functioning as
an endogenous vasoconstrictor released in response
to this stress.

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