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Urinary Excretion of Morphine during and after Valvular and Coronary-artery Surgery

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The urines of 34 patients anesthetized with morphine for mitral-valve or aortic-valve replacement operations or for coronary-artery disease revascularization procedures were analyzed for morphine and morphine-3-glucuronide before, during and for two hours after operation. Patients who had coronary-artery disease had higher urinary flow rates and excreted greater proportions of the administered morphine during induction of anesthesia, throughout operation, and for two hours postoperatively than patients with valvular heart disease. Correlation of total urinary output with total free morphine excreted after two hours in the recovery room was high, r = .84. Urinary morphine in the glucuronide form increased progressively from the time of induction of anesthesia to the postoperative period and was >91 per cent for all patients after two hours in the recovery room. Patients who had coronary-artery disease required mechanical postoperative ventilation for significantly shorter periods than did those with valvular heart disease. The duration of postoperative ventilation was negatively correlated with total urinary output and total free morphine excreted in the urine from induction of anesthesia until two hours postoperatively (r = .80 and r = .77, respectively). The data demonstrate that urinary excretion of free morphine and morphine-3-glucuronide during and early after operation is greater in patients who have coronary-artery disease than in those with valvular heart disease. The findings also suggest that duration of mechanical ventilation after morphine anesthesia and operation is inversely related to urinary output and excretion of free morphine. (Key words: Analgesics, narcotic, morphine; Biotransformation (drug), morphine.)

ADMINISTRATION OF LARGE DOSES of morphine (0.5–4.0 mg/kg), intravenously, plus oxygen is a popular anesthetic technique for critically ill patients undergoing open-heart surgery.[1,2] While the fate (metabolism and excretion) of large doses of morphine has been studied in drug addicts,[3,4] it has not been investigated in patients during and after heart operations. In this study 50 patients undergoing aortic-valve or mitral-valve replacement operations or coronary-artery disease (CAD) revascularization procedures with morphine and oxygen anesthesia had their urines analyzed for morphine and morphine-3-glucuronide before, during, and after anesthesia and operation.

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Methods

None of the patients in the study had a history of drug addiction or had been taking narcotics or barbiturates preoperatively. Premedication consisted of atropine (0.005 mg/kg, im) and pentobarbital (1 mg/kg, im) 90 minutes before the scheduled time of operation. A catheter was placed in the bladder at the time of premedication and urine was collected from then until anesthesia was begun (study period 1). Urine was also collected during induction of anesthesia (study period 2), hourly throughout the operation (study period 3), and for two hours postoperatively (study period 4). Intraoperative urine specimens were combined. One milliliter of 0.5 N HCl was added to 20 ml of urine obtained from each of the four study periods and the resulting solutions were frozen until analyzed for morphine and morphine-3-glucuronide by electron-capture gas–liquid chromatography.[5]‡

Preoperative preparation and intraoperative blood and fluid administration were managed as previously described.[6,7] Average urinary flow rate during each of the four study periods was determined by dividing urinary output by time.

Postoperatively all patients were given 100 per cent oxygen to breathe and ventilation was assisted or controlled to keep Pa_{CO_2} at 38–44 torr for two hours. Thereafter, each patient had his endotracheal tube attached to a T-piece apparatus every two hours. Seven to 15 liters/min of humidified 100 per cent oxygen were administered through the T-piece and the patients allowed to breathe spontaneously without mechanical assistance for 20 minutes. Arterial blood samples were analyzed for Pa_{CO_2} every 5 minutes. When Pa_{CO_2} remained <50 torr for 20 minutes spontaneous ventilation was continued with an inspired oxygen concentration that was sufficient to maintain Pa_{O_2} > 100 torr. When Pa_{CO_2} was maintained <50 torr and Pa_{O_2} > 100 torr with an inspired oxygen concentration of 40 per cent or less for two hours, extubation of the trachea was considered. Extubation was accomplished when, in addition to maintaining the above-mentioned blood-gas tensions, each patient could sustain a tidal volume >5 ml/kg and vital capacity >15 ml/kg (as measured by a Wright spirometer attached to the endotracheal tube) and when arterial blood pressure had not changed by more than 15 per cent in the preceding hour.

‡ This method enables detection of morphine concentrations of 15–20 nanograms in 1–2 ml of urine.

No patient received a narcotic antagonist during operation or postoperatively. Results are based upon data obtained only for patients who did not require inotropic, analgesic or diuretic drugs during the first 12 postoperative hours, who had average urinary outputs >20 ml/hour, and who maintained mean arterial blood pressures >70 torr during the first two postoperative hours.

Results

Thirty-four patients were studied: 11 had mitral-valve replacement; 11, aortic-valve replacement; 12, CAD revascularization. The three groups were similar with respect to age. Patients having mitral-valve replacement weighed slightly less and had lower preoperative cardiac outputs than the other two groups. The amounts of morphine administered were similar in all groups and averaged 2.1 ± 0.7, 1.9 ± 0.5, and 1.7 ± 0.4 mg/kg for patients who had CAD, aortic-valve disease, and mitral-valve disease, respectively.

Although mean arterial blood pressures before anesthesia, during anesthetic induction, and after operation were similar in all groups, patients undergoing CAD operations experienced slightly higher, $P < .05$, blood pressures than the other two groups during operation. Extracorporeal flow rates, times of bypass, total operative times, amounts of crystalloid administered intravenously, and blood losses and replacements during anesthetic induction and operation and for two hours postoperatively were similar in the three groups.

Mean urinary flow rates, cumulative percentages of administered morphine excreted in urine, and percentages of urinary morphine as the glucuronide form appear in tables 1–3. Urinary flow rates were similar in the three groups preanesthetically, but significantly higher in the CAD group in all subsequent study periods. Patients who had mitral-valve or aortic-valve disease did not sustain significant changes in urinary flow rates during any of the subsequent study periods. Patients who had CAD, on the other hand, experienced significantly higher urinary flow rates during induction of anesthesia ($P < .01$) and throughout the entire operation ($P < .05$), compared with preanesthetic values.

Patients who had CAD excreted higher percentages of administered morphine during induction of anesthesia, by the time they reached the recovery room, and after two hours in the recovery room than did those in either of the other two groups (table 2). Mean cumulative amounts of free morphine excreted after two hours in the recovery room were 5.8 ± 1.4, 7.3 ± 2.1 and 18.0 ± 3.6 per cent of those administered in the mitral-valve disease, aortic-valve disease, and CAD groups, respectively. Correlation of total free morphine excreted after two hours in the recovery room with total urinary output from induction to that point, in all three groups combined, was good, r = .84. Urinary morphine in the glucuronide form increased progressively from induction until the postoperative period and was >81 per cent in all patients at the end of operation and >91 per cent after two hours in the recovery room (table 3).

The tracheas of patients who had CAD were extubated an average of 7.3 ± 2.2 hours after operation, while those of patients with mitral-valve and aortic-valve disease were extubated 14.6 ± 3.1 and 20.9 ± 6.3 hours postoperatively. The differences

TABLE 1. Urinary Flow Rates (Mean ± SD)

	Preanesthetic	Induction	Operative	Postoperative
Mitral-valve operations	1.08 ± .19	1.22 ± .15	1.21 ± .12	0.95 ± .14
Aortic-valve operations	1.15 ± .16	1.29 ± .21	1.25 ± .20	1.02 ± .15
Coronary-artery disease	1.22 ± .19	2.33†§ ± .23	1.74†¶ ± .21	1.31* ± .19

* $P < .05$, † $P < .025$, ‡ $P < .01$, Student's t-test for unpaired data, compared with mitral-valve or aortic-valve operation values during the same period.
§ $P < .01$, ¶ $P < .05$, Student's t-test for paired data, compared with preanesthetic values.

TABLE 2. Cumulative Percentages of Administered Morphine Excreted in Urine (Mean ± SD)

	Preanesthetic	Induction	Operative	Postoperative
Mitral-valve operations	—	17 ± 5	22 ± 6	26 ± 4
Aortic-valve operations	—	20 ± 4	26 ± 5	27 ± 3
Coronary-artery disease	—	36* ± 8	40* ± 7	46* ± 6

* $P < .01$, Student's t-test for unpaired data, compared with mitral-valve or aortic-valve operation values during the same period.

TABLE 3. Percentages of Urinary Morphine in the Glucuronide Form (Mean ± SD)

	Preanesthetic	Induction	Operative	Postoperative
Mitral-valve operations	—	71 ± 8	91 ± 3	96 ± 1
Aortic-valve operations	—	65 ± 7	89 ± 2	96 ± 1
Coronary-artery disease	—	49* ± 9	89 ± 3	95 ± 1

* $P < .05$, Student's t-test for unpaired data, with mitral-valve or aortic-valve operation values during the same period.

between patients who had CAD and the other two groups were statistically significant, $P < .05$. Seven of twelve patients with CAD had respiratory dynamics that enabled them to have their tracheas extubated between the third and sixth postoperative hours. These patients had higher ($P < .05$) urinary outputs and excreted significantly ($P < .025$) greater percentages of administered morphine (54 versus 33 per cent) after two hours in the recovery room than CAD patients whose tracheas could not be extubated after six postoperative hours. None of the patients with mitral-valve or aortic-valve disease had excreted more than 34 per cent of the morphine administered to them after two hours in the recovery room, and none could have the trachea extubated before the tenth postoperative hour. Hours of postoperative mechanical ventilation were strongly negatively correlated with total urinary output and total free morphine excreted in the urine from induction of anesthesia until two hours postoperatively in all patients combined, r = .80 and r = .77, respectively.

Discussion

Morphine addicts receiving large daily doses (4 mg/kg) of morphine sulfate subcutaneously excrete 5–15 per cent of the compound in the urine in its free form, 60–80 per cent as morphine-3-glucuronide, and 3–7 per cent as free or conjugated normorphine in 24 hours.[4] Urinary excretion of total morphine administered is linearly related to the volume of daily urinary output in these patients. Results of the present investigation suggest that nonaddicted patients receiving anesthetic doses of morphine intravenously for open-heart operations excrete the compound and its glucuronide conjugation product in a manner similar to that observed in individuals who are addicted to morphine. In addition, our findings indicate that duration of respiratory depression after morphine anesthesia is inversely related to urinary flow rate and urinary free morphine excretion during anesthesia, operation, and the early postoperative period.

In this study, patients with CAD having revascularization procedures had greater urinary flow rates, excreted more morphine, and required postoperative mechanical ventilation for shorter periods than patients having valvular replacement operations. Why the urinary flow rates were greater in patients with CAD than in those with valvular disease is unknown. The most likely explanation for this finding is that CAD patients had greater cardiac outputs and hence, greater hepatic and renal blood flows. Since morphine is conjugated in the liver and excreted in the urine, the rates at which these two events occur depend upon hepatic and renal blood flows. However, other possible explanations could include increased plasma concentrations of antidiuretic hormone secondary to elevated left atrial pressure in patients with valvular heart disease[8] or increased renal vascular resistance and hence reduced renal blood flows in patients with mitral-valve or aortic-valve disease secondary to elevated plasma levels of norepinephrine.[9] Unfortunately, since we could not measure cardiac output, renal blood flow, or renal vascular resistance, or plasma concentrations of norepinephrine or antidiuretic hormone, during this study, our data do not elucidate the mechanism(s) involved.

In a recent report, Bedford and Wollman[10] showed that the ventilatory response to increasing concentrations of inspired carbon dioxide is less in patients receiving morphine anesthesia for mitral-valve replacement than in those having morphine for CAD revascularization procedures. In another study, Lecky *et al.*§ demonstrated that morphine, compared with halothane anesthesia, did not significantly increase the period of postoperative ventilatory support in patients undergoing CAD revascularization procedures, but did in patients having mitral-valve operations. Neither of these groups could explain why morphine produces longer-lasting postoperative respiratory depression in patients with mitral-valve disease than in those with CAD. While there are numerous possible explanations for this phenomenon, including greater preoperative and postoperative pulmonary function abnormalities, more significant mechanical circulatory problems, and greater morphine sensitivity in mitral-valve disease than in CAD, our data suggest that an additional mechanism may be that patients with mitral-valve disease have higher concentrations of morphine in plasma and/or tissue secondary to diminished urinary excretion of the opiate. Plasma levels of morphine were not routinely measured in this study because of the extensive blood sampling necessary. However, preliminary results (Stanley, unpublished data) from another series of three CAD and four mitral-valve disease patients undergoing operation with somewhat higher doses of morphine (2.5–4.0 mg/kg) suggest that plasma levels of free morphine are slightly higher (3–5 per cent) in patients having mitral-valve replacement operations than in those having revascularization procedures after six hours in the recovery room. Even more impressive is the additional finding that mitral-valve disease patients have plasma morphine-3-glucuronide concentrations that range from 12 to 16 per cent above those of patients who have CAD in the recovery period. The latter finding raises the serious question of whether morphine-3-glucuronide, the principal metabolite of morphine, has respiratory depressant actions of its own. To our knowledge, the influence of the glucuronide conjugate of morphine on respiratory rate, tidal volume,

§ Lecky J, Ominsky A, Wollman H: Personal communication.

ventilatory response to increased inspired tensions of carbon dioxide, or any other determinant of medullary respiratory sensitivity is not known.

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Obstetric Anesthesia

LOCAL ANESTHETICS AND THE NEWBORN Four newborn infants were studied following maternal epidurnal block with lidocaine or mepivacaine. Each of these neonates, born with umbilical-vein blood *p*H values of 7.23 or less, showed an elevated fetal-to-maternal concentration ratio. This may be a manifestation of ion tapping of a weak base. (*Brown WU Jr, and others: Acidosis, local anesthetics, and the newborn. Obstet Gynecol 48:27–30, 1976.*)

EPIDURAL ANESTHESIA, EPINEPHRINE AND LABOR Because of the unresolved controversy regarding the effects of epidural anesthesia and epinephrine upon uterine contractility, it was decided to study their effects on a small number of patients. Intrauterine and intra-arterial pressures, fetal heart rate, and maternal heart rate were measured continuously from at least 20 minutes before administration of the epidural anesthetic until complete dilatation had occurred. Nineteen patients were in spontaneous labor, and 18 had labor stimulated with oxytocin. Lidocaine alone (1.0–1.5 per cent) was used in 12 patients (30 observations), and lidocaine with epinephrine, 1:200,000, was used in 12 patients (30 observations), and lidocaine with epinephrine, 1:200,000, was used in 26 patients (51 observations). Uterine contractions were calculated in Montevideo units for 60 minutes following the epidural anesthetic. The changes, if any, in the two groups were compared. There was a significant decrease in uterine activity when epinephrine was added to the anesthetic solution, mainly a lessening of intensity. This decrease was not seen in a control group of patients to whom plain lidocaine had been administered. There were comparable decreases in systolic and diastolic blood pressures in the two groups, and tachycardia was observed. In one case, severe hypertension was observed following administration of lidocaine with epinephrine. It was concluded that the addition of epinephrine to the anesthetic solution predictably produces diminution of uterine activity. In addition, the epinephrine does not give "cardiovascular support" to the patient in labor. (*Matadial L, and others: The effect of epidural anesthesia on uterine activity and blood pressure. Am J Obstet Gynecol 125:846–854, 1976.*)