Anesthesiology
V 38, No 6, June 1973

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024

The Effects of High-dose Morphine on Fluid and Blood Requirements in Open-heart Operations

Theodore H. Stanley, M.D., Maj, MC, Neal H. Gray, M.D., Maj, MC,† William Stanford, M.D., Col, MC,‡ Raymond Armstrong, M.D., LtC, MC ‡*

The effects of large (2.7 ± 0.3 mg/kg) and very large (9.3 ± 0.7 mg/kg) anesthetic doses of morphine were compared in 17 patients undergoing elective open-heart surgery. Patients who received a mean of 514 mg needed significantly more blood during bypass, during the entire operative procedure, and for the first 24 hours postoperatively than those who received a mean of 179 mg. Although all patients received equal volumes of crystalloid during operation, patients who received very large doses of morphine produced significantly less urine during bypass and needed significantly more sodium bicarbonate to avoid base deficits. Postoperatively, these patients were edematous and plum-colored, and they needed significantly more crystalloid to maintain urinary output. (Key words: Morphine; Fluid balance; Transfusion; Renal function; Open-heart surgery.)

THE USE of large doses of morphine (0.5–3.0 mg/kg, iv) as the sole anesthetic has been suggested as a safe method of anesthetizing critically ill patients for cardiac operations.[1, 2] Hemodynamic stability, profound analgesia, and amnesia have been reported to be produced by morphine in critically ill patients. Healthier patients, however, have not always been amnesic with these amounts, and supplemental anesthesia has been used.[3] The supplemental agents have included scopolamine, alcohol, droperidol, thiopental, diazepam, and low concentrations of nitrous oxide or halothane.[3-6] Since some of these supplemental agents can attenuate the benign circulatory response to morphine,[4] the rationale of adding them in order to make morphine a complete anesthetic has been questioned.[3] The alternative, using morphine in amounts greater than 3 mg/kg to produce complete anesthesia, has been proposed but not fully evaluated. This study was conducted in order to compare the effects of large (3 mg/kg) and very large (8–11 mg/kg) doses of morphine in patients undergoing cardiac operations.

Methods

Seventeen patients scheduled for elective open-heart correction of a variety of congenital and acquired cardiac lesions were arbitrarily assigned to two groups. Group I, the high-dose group, was given morphine intravenously until either consciousness was lost or a maximum of 3 mg/kg had been reached. When still responsive after 3 mg/kg, these patients were then given 2.5-mg increments of diazepam or droperidol intravenously until unresponsive to verbal command and/or pin-prick stimulation. Group II, the very-high-dose group, received sufficient morphine to produce an unresponsive state.

The study was approved by the Medical Center Human Study Committee. Informed, written consent was obtained from every patient at the preoperative visit. Premedication included a barbiturate (1 mg/kg) or diazepam (1 mg/10 kg), morphine (1 mg/10 kg), and atropine (0.05 mg/10 kg), one and a half hours before the scheduled operation. Before anesthesia was begun, two intravenous lines were started in the upper extremities, a central venous pressure catheter was placed in the antecubital fossa and threaded to the right atrium, and a radial-artery catheter was inserted. A catheter was also inserted into the

* Staff Anesthesiologist, Anesthesiology Service.
† Resident in Anesthesiology.
‡ Staff Thoracic Surgeon, Thoracic Surgery Service.

Received from the Anesthesiology and Thoracic Surgery Services, Department of Surgery, Wilford Hall USAF Medical Center (AFSC), Lackland AFB, Texas 78236. Accepted for publication January 11, 1973. Presented at the Annual Meeting of the American Society of Anesthesiologists, Boston, October 1972.

Dr. Stanley's present address is: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, Utah 84112.

TABLE 1. Mean Preoperative Data in the Two Study Groups

	Number of Patients	A.S.A. Class	Age (Years)	Cardiac Output (l/min)	Weight (kg)
Group I, high dose	9	2.9	37	4.0	66
Group II, very high dose	8	2.3	29	4.3	56

urinary bladder and standard electrocardiograph leads applied to the extremities.

With continuous electrocardiographic and arterial and central venous pressure recording, morphine sulfate (Lilly) was given to both groups at rates of 5–15 mg/min. After the patient had received 0.25 mg/kg, oxygen was given via a face mask. Respiration was first assisted and later controlled. In this manner, Pa_{CO_2} was maintained between 35 and 45 torr, as measured in radial-artery blood obtained every 15 minutes. When the patient was unresponsive, succinylcholine (1.5 mg/kg) was slowly given intravenously and the trachea intubated. Controlled ventilation was continued. When succinylcholine paralysis disappeared, the patient was given *d*-tubocurarine (0.5 mg/kg) over a period of 20 minutes and the operation begun. When additional anesthesia was considered necessary (as determined by extremity movement, wrinkling of the forehead or eye opening), Group I received increments of droperidol or diazepam and Group II, additional morphine.

Ringer's lactate solution in dextrose, 5 per cent in water, was administered at a rate of 1,000–1,200 ml/hour during induction of anesthesia, and 50–70 ml/hour during the rest of the procedure. Postoperatively, Ringer's lactate solution or dextrose, 5 per cent in water, was administered at 20–50 ml/hour unless urinary output decreased to less than 20 ml/hour, when the rate was increased to 200 ml/hour. If urinary output then failed to increase within two hours, a diuretic (mannitol) was given.

Whole blood was the only colloid routinely given intraoperatively and during the first 24 hours postoperatively. Blood was not necessary before bypass in either group. During bypass, blood was added to the oxygenator as necessary to maintain a blood flow of at least 40 ml/kg/min. After bypass and in the recovery room, blood was given to maintain preoperative central venous or intraoperative left atrial pressure. No inotropic agent was given. Intraoperative blood loss, although estimated at the end of each procedure, played no part in the operative adminstration of blood. Postoperative chest-tube drainage was measured hourly.

Urinary output was measured hourly during the operation and for the first 24 postoperative hours. During bypass, urinary output was measured each half hour. Bypass urine volume was added to that collected during the rest of the procedure to obtain a total called "intraoperative urine." Postoperative urine volumes are not reported, since they reflect to a large degree the administration or absence of diuretics.

The extracorporeal system (Bentley oxygenator; Sarns roller pump) was primed with 20–25 mg/kg of Ringer's lactate solution. Bypass flow rates were maintained between 40 and 70 ml/kg/min. Radial-artery blood pressures and extracorporeal flow rates were recorded every 15 minutes during bypass. Sodium bicarbonate was given during bypass to half-correct calculated base deficits of 4 mEq/l or more, as determined from arterial blood every 15 minutes.

Intraoperative esophageal temperature was monitored with a Yellow Springs temperature probe and recording pack. All patients except four who had atrial septal defects corrected were cooled to 32 C during extracorporeal support and rewarmed to 37 C at its conclusion.

After bypass the blood remaining in the extracorporeal system was measured and added to the surgical blood loss to obtain a total called "intraoperative blood."

Results

Nine of the 17 patients studied were in the high-dose group (Group I) and eight in the very-high-dose group (Group II) (table 1).

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024

TABLE 2. Intraoperative Data of Group I (High-dose Morphine)

Diagnosis	Morphine		Length of Procedure (Hours)	Blood		Crystalloid		Urine	
	(mg)	(mg/kg)		(ml)	(ml/kg)	(ml)	(ml/kg)	(ml)	(ml/kg)
Mitral stenosis and mitral insufficiency	105	2	5.3	1,500	27	2,000	35.7	152	2.7
Coronary artery disease	165	2	7.7	2,000	22	2,600	29.2	644	7.2
Mitral stenosis	120	3	6.0	500	11	2,500	54.3	209	4.5
Coronary artery disease	200	3	7.0	2,000	28	2,700	37.5	765	10.6
Atrial septal defect and pulmonary stenosis	180	3	3.0	1,000	17	2,300	38.3	200	3.3
Mitral stenosis and mitral insufficiency	190	3	6.5	1,500	24	2,200	34.9	724	11.5
Atrial septal defect	210	3	3.0	1,000	14	2,070	29.6	155	2.2
Coronary artery disease	300	3	4.0	1,000	11	2,860	31.8	249	2.8
Mitral stenosis	140	3	5.5	2,000	44	2,300	51.1	180	3.1
MEAN	179	2.7	5.3	1,389	22	2,392	38.0	364	5.3
SD	17.2	0.3	1.6	163	9.9	275	8.4	248	3.4

TABLE 3. Intraoperative Data of Group II (Very-high-dose Morphine)

Diagnosis	Morphine		Length of Procedure (Hours)	Blood		Crystalloid		Urine	
	(mg)	(mg/kg)		(ml)	(ml/kg)	(ml)	(ml/kg)	(ml)	(ml/kg)
Tetralogy of Fallot	190	8.6	6.5	3,000	136	1,350	61.4	210	9.5
Coronary artery disease	740	9.0	5.7	2,500	30	1,350	16.3	238	2.9
Atrial septal defect	200	9.0	3.6	450	20	1,000	43.5	190	8.3
Atrial septal defect	450	9.0	4.0	500	10	3,100	62.0	100	2.0
Aortic stenosis and aortic insufficiency	940	9.6	4.5	3,000	31	2,350	23.9	339	3.5
Coronary artery disease	760	9.8	8.5	3,000	39	2,300	29.5	959	12.3
Ventricular septal disease	230	11.0	5.0	2,000	95	2,000	95.2	300	14.3
Aortic stenosis and aortic insufficiency	600	8.3	6.0	1,400	21	2,300	31.9	340	4.7
MEAN	514	9.3	5.5	1,994	48	1,969	45.4	335	7.2
SD	271	0.7	1.5	1,009	13.1	193	24.3	248	4.3

TABLE 4. Mean Bypass Data in the Two Study Groups

	Number of Patients	Pressure (mm Hg)	Flow (ml/kg)	Time (min)	Blood* (ml)	Urine* (ml)	HCO_3* (mEq)
Group I, high dose	9						
Mean		61	61	90	556	122	20
SD		12	12	19	217	140	13
Group II, very high dose	8						
Mean		60	56	108	1431	40	72
SD		26	5	19	1135	29	101

* $P < .001$, Student's t test.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024

Patients in Group I received an average of 179 mg, or 2.7 ± 0.3 mg/kg, of morphine, while those in Group II needed a mean of 514 mg, or 9.3 ± 0.7 mg/kg, of morphine ($P < 0.001$). Blood pressure and heart rate did not change more than 15 per cent from preoperative values after any dose of morphine in any patient of either group. There were, however, transient episodes of hypotension during cannulation of the great vessels or immediately after bypass in some patients of both groups.

The lengths of the operation and the durations of bypass were similar in the two groups (tables 2, 3, and 4). Patients in Group II, however, needed significantly ($P < 0.001$) more blood during bypass, during the entire operative procedure ($P < 0.001$) and during the first 24 hours postoperatively ($P < 0.001$) than those in Group I (table 5). Mean measured operative and 24-hour postoperative blood losses were 990 and 615 ml, respectively, in Group I, and 1,015 and 590 ml, respectively, in Group II. The differences between the two groups were not significant.

There was no significant difference between the amounts of crystalloid administered intravenously in the intraoperative period (table 5). Postoperatively, however, patients in Group II needed an average of 1,505 ml of crystalloid during the first 24 hours to maintain urinary output. This was more than twice the amount needed by patients of Group I ($P < 0.001$).

Urinary outputs of the two groups during operation were similar, averaging 69 ml/hour in Group I and 61 ml/hour in Group II. However, during bypass, in spite of similar arterial pressures and blood flow rates, the mean total urinary output of Group II was less than a third of that of Group I ($P < 0.01$) (table 5). In addition, Group II patients needed an average of 73 mEq sodium bicarbonate, or more than three times the amount received by patients of Group I ($P < 0.001$), to maintain normal blood *p*H (table 5). Six of eight patients of this group, compared with two of nine of Group I, needed mannitol to increase postoperative urinary output to >20 ml/hour. Postoperatively, Group II patients were edematous, plum-colored, and prone to hypotension, especially on change of position. All patients survived the operation and were eventually discharged from the hospital. No patient in either group had any abnormal postoperative motor movements, psychotic behavior, or memory of the operative procedure.

Discussion

Although it is well established that 1–3-mg/kg doses of morphine have little effect on cardiovascular dynamics in supine, normovolemic man,[1, 4, 7] the effects of doses greater than 3 mg/kg have not been carefully evaluated. The results of this study demonstrate that very large doses of morphine (8–11 mg/kg) impose,

TABLE 5. Mean Intraoperative, Bypass and 24-hour Postoperative Totals in the Two Study Groups

	Intraoperative		Bypass		Postoperative	
	(ml)	(ml/kg)	(ml)	(ml/kg)	(ml)	(ml/kg)
Blood						
Group I	1,389*	22.0*	556*	7.5*	744*	14.3*
Group II	1,994	47.7	1,431	31.6	1,523	37.7
Crystalloid						
Group I	2,392	38.0	92	1.4	695*	11.8*
Group II	1,969	45.4	102	1.8	1,505	39.0
Urine					(*Diuretics*)	
Group I	⌜ 364	5.3	122*	3.3*	2 of 9	
Group II	⌞ 335	7.2	40	0.7	6 of 8	
HCO_3^-			(mEq)	(mEq/kg)		
Group I			20*	0.3*		
Group II			72	1.3		

* $P < 0.001$, Student's t test.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024

as defined by our criteria for blood replacement, an additional requirement for blood upon patients undergoing cardiac surgery with cardiopulmonary bypass. In addition, these patients have lower postoperative urinary outputs, need diuretics more frequently, and are more prone to postoperative hypotension than those receiving 1–3 mg/kg. These results suggest that very large doses of morphine cause significant blood pooling and secondarily reduce effective blood volume.

Morphine has been shown to be a significant arterial dilator in man.[7, 8] Studies of animals have suggested that its action on venous tone may be similar.[9, 10] Henney *et al.*[9] showed that 400 ml of blood are pooled and lost from the circulating blood volume of dogs after 1 mg/kg morphine. They also found that, while arterial tone returned to normal within 30 minutes of morphine administration, venous capacitance remained elevated for much longer periods. Ward *et al.*[10] found that 0.25 mg/kg morphine caused marked, selective attenuation of the venoconstrictor responses to both neural and humoral adrenergic stimulation, and suggested that the drug acts as a venous adrenergic blocking agent. Drew *et al.*[11] demonstrated that as little as 10–30 mg could cause enough vasodilation and peripheral pooling in man to result in vascular collapse on passive tilting or sitting. While the effects of larger doses of morphine on vascular capacitance are unknown, the plethoric appearance and increased blood requirements of our Group II patients, compared with Group I, suggest that vasodilation and sequestration of blood are dose-related.

Another cause of vasodilation after these doses of morphine could be the preservatives used in the diluent of the commercial preparation. The Lilly preparation of morphine used in this study contains the preservatives chlorobutanol (0.5 per cent) and sodium bisulfite (0.1 per cent). Our patients received as much as 310 mg of the former and 62 mg of the latter in the morphine they were given. Both drugs have been shown to have negative inotropic effects on cardiac tissue and have been implicated in the hypotension sometimes seen after rapid intravenous administration of *d*-tubocurarine.[12, 13] Longnecker *et al.*[14] showed in man that this hypotension is primarily due to a reduction in systemic vascular resistance, which they attributed to an increase in capacitance-vessel volume or a loss of fluid from the intravascular compartment. It was not demonstrated whether this effect was caused by *d*-tubocurarine or one of its preservatives; however, Stoelting[15] has shown that 50 mg chlorobutanol and 10 mg sodium bisulfite have no effect on mean arterial blood pressure in man. Since larger doses of these drugs have not been evaluated in man or animals, their effects in this study cannot be determined.

Finally, the plethora and blood sequestration observed postoperatively in Group II patients might be attributable to overtransfusion rather than vasodilation. However, while total blood volumes may have been elevated in this group (blood volumes were not measured), their oliguria, absence of elevated left atrial and central venous pressures, and frequent hypotension suggest that effective (circulating) blood volumes were diminished.

The effects of morphine on the kidney have been extensively studied in man and other animals,[16] but dose–response effects of the drug on renal function have not been done. The significantly decreased postoperative urinary outputs of Group II patients compared with Group I suggest that impairment of renal function after morphine may also be dose-related. In order to maintain urinary volumes greater than 20 ml/hour during the first 24 hours postoperatively, Group II patients received almost three times the volume of intravenous crystalloid solution received by Group I. In spite of this, six of eight of the former needed mannitol. Decreases in urinary flow following morphine have been attributed to both a stimulation of ADH release and a reduction in renal blood flow.[16] Which of these mechanisms was more responsible for the postoperaitve differences between the two groups was not determined. However, the similarity and adequacy (>60 ml/hour) of mean urinary outputs in the two groups intraoperatively, when morphine blood levels are likely to be highest, suggest that the postoperative oliguria of Group II patients may not have been a direct effect of morphine, but rather was an indirect effect, perhaps secondary to pooling of peripheral blood, reduced venous return, and diminished cardiac output. Unfortunately, this

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024

could not be confirmed, as cardiac outputs of these patients were not measured.

Lack of amnesia after 1–3 mg/kg anesthetic doses of morphine is not uncommon, especially in patients with relatively normal cardiac outputs.[3] The patients in this study were incompletely paralyzed and could open their eyes and wrinkle their foreheads when aware or when painfully stimulated. On these occasions, in order to insure amnesia, Group I patients were given increments of diazepam or droperidol and Group II patients, additional morphine. No patient in either group had any memory of intubation or the surgical procedure. While this does not document the reliability of 8–11 mg/kg doses of morphine for producing amnesia in all patients, it does suggest that when large doses are insufficient, very large doses of morphine will produce loss of consciousness. We doubt, however, that the amnesia achieved with such doses of morphine is worth the increased blood requirements and postoperative vaso-instability that accompanies them.

The authors gratefully acknowledge the help of Dr. Edward Lowenstein in the preparation of the manuscript.

References

1. Lowenstein E, Hallowell P, Levine FH, et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389–1393, 1969
2. Hasbrouck JD: Morphine anesthesia for open heart surgery. Ann Thorac Surg 10:364–368, 1970
3. Lowenstein E: Morphine "anesthesia"—a perspective. ANESTHESIOLOGY 35:563–565, 1971
4. Martin WE, Hornbein TF, Freund FG, et al: Cardiovascular effects of morphine–O_2 and morphine–N_2O in man. Abstracts of Scientific Papers, 1970 Annual Meeting, American Society of Anesthesiologists, pp 127–128
5. Lowenstein E: Personal communication
6. Mannheimer WH: The use of morphine and intravenous alcohol in the anesthetic management of open heart surgery. South Med J 64:1125–1127, 1971
7. Ryan TJ, Brand E, Ramaswamy L: Effects of morphine on ventricular function of man. Clin Res 14:260, 1966
8. Jaffee JH: Narcotic analgesics, The Pharmacological Basis of Therapeutics. Third edition. Edited by LS Goodman and A Gilman. New York, MacMillan, 1965, pp 255–256
9. Henney RP, Vasko JS, Brawley RK, et al: The effects of morphine on the resistance and capacitance vessels of the peripheral circulation. Am Heart J 72:242–250, 1966
10. Ward JM, McGrath RL, Weil JV: Effect of morphine on the peripheral vascular response to sympathetic stimulation. Am J Cardiol 29:659–666, 1972
11. Drew JH, Dripps RD, Comroe JH: Clinical studies on morphine. II. The effect of morphine upon the circulation of man and upon the circulatory and respiratory responses to tilting. ANESTHESIOLOGY 7:44–61, 1946
12. Carrier O, Murphy JC: The effects of *d*-tubocurarine and its commercial vehicles on cardiac function. ANESTHESIOLOGY 33:627–634, 1970
13. Dowdy EG, Holland WC, Yamanaka I, et al: Cardioactive properties of *d*-tubocurarine with and without preservatives. ANESTHESIOLOGY 34:256–261, 1971
14. Longnecker E, Stoelting RK, Morrow AG: Cardiac and peripheral vascular effects of *d*-tubocurarine in man. Anesth Analg (Cleve) 42: 660–665, 1970
15. Stoelting RK: Blood-pressure responses to *d*-tubocurarine and its preservatives in anesthetized patients. ANESTHESIOLOGY 35:315–317, 1971
16. Papper S, Papper EM: The effects of preanesthetic, anesthetic and postoperative drugs on renal function. Clin Pharmacol Ther 5:205–215, 1964

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/38/6/536/293677/0000542-197306000-00006.pdf by guest on 03 April 2024