Hemodynamic effects of narcotics

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In intact animals and nonaddicted supine patients, morphine and fentanyl and some new, as yet unreleased narcotics, e.g., sulfentanil, produce minimal changes in cardiovascular dynamics.[1-3] Indeed, Lowenstein et al[1] observed that the introduction of large (anesthetic) doses of morphine (as much as 1 mg/kg) intravenously as the sole or principal anesthetic did not cause significant circulatory changes in patients without cardiac disease. In patients with aortic valvular disease, stroke volume and cardiac output increased. Yet several investigators observed depression of myocardial contractility by narcotics when isolated myocardial muscle and heart-lung preparations were perfused with saline solution.[4] When blood was substituted as the perfusing solution, no depressant effect was observed with as much as 30 mg/kg morphine in dog and cat heart-lung preparations.[5] Apparently, fentanyl also does not change myocardial mechanics in blood-perfused preparations, whereas meperidine does cause considerable myocardial depression.[6]

Myocardial depression does not occur after morphine administration in intact animals or man. Schmidt and Livingston[7] found no evidence of cardiac depression in awake dogs given as much as 100 mg/kg morphine. Vasco et al[8] found that morphine had a positive inotropic effect in dogs, which

was dependent on endogenous catecholamine release and blocked by beta-adrenergic blocking agents or previous surgical adrenalectomy. Morphine also increases the concentrations of catecholamines in both blood and urine of human subjects.[9-11] Endogenous catecholamine secretion appears to be dependent on the functional state of the cardiovascular system and plasma concentrations of morphine.[9, 10] Liu et al[12] have shown that elevated plasma and urinary concentrations of epinephrine and norepinephrine also occur after administration of large doses (0.5 to 30 mg/kg) of fentanyl to dogs. However, recently we found that anesthetic doses of fentanyl do not alter plasma catecholamine concentrations in man.[13]

The potential for cardiovascular stability and anesthesia with large doses of morphine has made it a popular drug in modern anesthesia, especially in critically ill patients with little cardiovascular reserve.[14, 15] However, morphine may not always be benign with respect to circulatory dynamics. Bradycardia, tachycardia, hypotension, and hypertension have been observed in both man and experimental animals after administration of morphine.[15-19] Therefore, certain precautions must be taken during the induction and maintenance of anesthesia with morphine.

Hypotension can occur during and after administration of even relatively small doses of morphine.[17] Due to arterial and venous dilation and increased vagal activity with cardiac slowing, hypotension most often occurs in hypovolemic, hypertensive patients and in those with high vagal tone or during rapid administration of morphine. Hypotension is less common (a) when morphine is given slowly (5 mg/min or slower), (b) when a rapid infusion of intravenous fluids is given concurrently, (c) in patients who are in a slight Trendelenburg (head down) position, and (d) in patients with congestive heart failure. The latter findings suggest that a large component of hypotension observed after morphine is given is secondary to venodilation. Experiments in animals[7] and man[14, 17, 20] have confirmed the arterial and venodilating ability of morphine, with the latter property being more dominant. Ward et al[21] have shown that the differential arterial and venous actions of morphine may be due to a selective venous alpha adrenergic blocking effect. However, Zelis et al[22, 23] and Flaim et al[24] found that morphine selectively impairs certain sympathetic reflexes involving peripheral veins; they concluded that this was caused by the action of the drug on the central nervous system. Apparently venoconstriction to tilting or inhalation of carbon dioxide is impaired by morphine, whereas venoconstriction to a single deep breath is not. Whatever the mechanism, we found that venodilation after morphine is dose-related and results in occasional hypotension during induction and increases in blood requirements during and after surgery when compared to patients anesthetized with halothane.[25] There is evidence that venodilation and increased blood requirements do not occur with lower doses of morphine (<0.5 mg/kg plus N_2O). (Unpublished data.)

Arterial vasodilation after morphine, in contrast to venovasodilation, lasts for only a short period of time (15 to 30 minutes)[26] and is related to histamine release[27] and the direct effects of morphine on vascular smooth muscle.[7] Histamine release following morphine varies, although dose and rate of morphine administration undoubtedly have some influence. Hypotension secondary to histamine release can be corrected by vasopressors; however, administration

of antihistamines either before or after morphine-induced hypotension is of no benefit.

Hypotension also occurs after the intravenous administration of meperidine (Demerol).[7] Hypotension occurs more frequently after meperidine and is more profound than after comparable doses of morphine. This is due to a significant negative inotropic effect of meperidine[7, 28, 29] as well as a marked reduction in systemic vascular resistance. As a result, meperidine has had little value as a "complete" anesthetic, although it is still popular as a supplement in nitrous oxide-narcotic "balanced" anesthesia.[30] Meperidine, in contrast to morphine, rarely results in bradycardia but can cause tachycardia.[31] This may be related to the structural similarity of meperidine to atropine.

Alphaprodine (Nisentil) is structurally similar to meperidine and has had limited use as an analgesic supplement in patients in the operating room and delivery suite. Unfortunately, although alphaprodine is somewhat shorter acting than meperidine, it possesses all of the cardiovascular depressant qualities of the latter.[32] Large anesthetic doses (50 to 100 μg/kg) in man and small analgesic doses (5 to 10 μg/kg) of fentanyl also reduce arterial blood pressure but rarely below 90 torr systolic.[2, 33] Hypotension, when it occurs after fentanyl administration, is primarily due to bradycardia, and can be reversed with atropine, ephedrine, or even large doses of pancuronium.[34]

Hypertension, occasionally severe enough to necessitate the use of vasodilators, has been found with narcotic-oxygen anesthesia or narcotic-nitrous oxide balanced anesthesia.[15, 16, 35, 36] This complication is a frequent and especially serious problem in patients with coronary artery disease.[18] However, it most often occurs in healthy patients or those with only minimal impairment of cardiovascular reserve and is much less common in patients with valvular heart disease or in those who are severely ill irrespective of the primary pathology.[37] Hypertension during and after coronary artery surgery may be related to operative manipulation of the coronary arteries or to the type of patient who acquires coronary artery disease rather than to morphine or the other opioids.[18] Perhaps the primary cause of hypertension during opioid anesthesia may be inadequate analgesia or narcosis or both.[16, 38] This belief is supported by occasional awareness when opioids are the major component of the anesthetic technique.[16] Also hypertension rarely occurs before endotracheal tube intubation or surgical stimulation.[36] Both sympathetic nervous stimulation and renin-angiotensin responses are probably not blocked by morphine in doses of 1 to 3 mg/kg.[10, 39] However, larger doses of morphine, 4 mg/kg or higher, block increases in circulating catecholamine levels in response to surgical stimulus.[9] Hypertension produced during narcotic anesthesia is often difficult to treat. Higher doses of morphine, other narcotics, and even potent inhalation agents may not be effective in restoring blood pressure when noxious stimulation has elevated it. In these situations, vasodilators or adrenergic blockers may be required to treat hypertension. In addition, increased doses of morphine, a variety of intravenous hypnotics, or low concentrations of inhalation anesthetics may also be needed to suppress awareness.[16]

As mentioned, bradycardia often occurs following the intravenous administration of morphine, fentanyl, and some of the other narcotics.[2, 40, 41] Although bradycardia almost always accompanies

induction of anesthesia with narcotics during breathing of oxygen, it occurs less frequently when nitrous oxide is also used for induction.[2, 40, 42] This may be due to a possible stimulating effect of nitrous oxide on the sympathetic nervous system. Although premedication with the belladonna drugs or glycopyrrolate minimizes bradycardia after morphine and fentanyl have been given intravenously, these drugs do not always eliminate bradycardia.[42] Also, treatment of narcotic-induced bradycardia with atropine (0.4 to 0.8 mg, intravenously) is usually, but not always effective. On occasion even large doses of atropine (1 to 2 mg, intravenously) are ineffective in treating narcotic-induced bradycardia. In these situations ephedrine (15 to 25 mg, intravenously) is almost always effective.

Anesthesiologists experienced with narcotic anesthesia are usually not concerned with bradycardia accompanying induction of anesthesia as long as arterial blood pressure or cardiac output or both remain unchanged or are only moderately reduced. This is especially true when patients are brought to the operating room with low heart rates secondary to chronic use of propranolol. Thus, narcotic-induced bradycardia is not usually detrimental to myocardial function and indeed may be advantageous in patients with ischemic cardiac disease. Furthermore, bradycardia from narcotics is relatively transient, usually lasting only 10 to 20 minutes. Most experimental evidence indicates that bradycardia following the use of morphine is caused by stimulation of the vagal nucleus in the medulla of the brain.[41, 43] However, morphine may also have a direct effect on the sinoatrial node[44] and depress atrioventricular conduction.[45] Although narcotics usually do not cause arrhythmias, large doses of morphine and probably other narcotics used as anesthetics can cause increasing sinoatrial and atrioventricular block and decrease the duration of the refractory phase of atrial depolarization.[45] Theoretically, this could lead to the development of reentry type arrhythmias, but this rarely occurs. In a recent study it was found that the doses of epinephrine necessary to induce arrhythmias in dogs are not any greater during narcotic-nitrous oxide anesthesia than during halothane, enflurane, or nitrous oxide anesthesia. However, these authors reported that the incidence of malignant arrhythmias (ventricular tachycardia and ventricular fibrillation) was much less with narcotics plus nitrous oxide than with most potent inhalation anesthetics.[46] Despite these data many clinicians are of the opinion that patients anesthetized with narcotics are less susceptible to catecholamine-induced arrhythmias than patients anesthetized with halogenated compounds, and that the absence of dangerous arrhythmias is the strongest reason for considering narcotic anesthesia in patients with cardiac problems.

The most common arrhythmia noted during narcotic anesthetic administration other than bradycardia, is supraventricular tachycardia.[36] This occurs more often during or immediately after endotracheal intubation or surgical stimulation and, therefore, is probably evidence of inadequate anesthesia rather than a direct effect of the narcotic. However, there are certain patients who experience supraventricular tachycardias during narcotic anesthetic induction without concurrent noxious stimulation. This is especially true following the use of large doses of meperidine and alpha-prodine but also occurs with the use of morphine. Although tachycardia following the administra-

tion of meperidine and alpha-prodine may be attributed to the structural similarity of these compounds to atropine, tachycardia following morphine cannot. Tachycardia, when it occurs during induction with morphine, is usually accompanied by facial and upper torso flushing. This suggests that increased circulation concentrations of histamine or catecholamines or both may be the explanation for this infrequent but certainly not uncommon finding.

The pulmonary vascular effects of narcotic administration have not been nearly as well studied as have the systemic vascular actions. However, there are data that demonstrate that morphine significantly increases pulmonary artery blood pressure and decreases pulmonary blood volume.[40, 47] Hug (unpublished data) has found that large doses of fentanyl intravenously can also occasionally dramatically increase pulmonary artery pressure in man. The mechanism(s) involved in producing these changes have not been elucidated.

As noted, narcotics are usually used along with other drugs (supplements) during anesthesia. The most common supplement used with intravenous narcotics is nitrous oxide. Although nitrous oxide alone has minimal effects on myocardial mechanics[48] and cardiovascular dynamics,[49] when given to patients receiving intravenous narcotics, myocardial depression frequently occurs,[14, 50, 51] McDermott and Stanley[50] found that after administration of morphine (2 mg/kg), nitrous oxide produces concentration-dependent decreases in stroke volume, cardiac output, and arterial blood pressure and increases in systemic vascular resistances. Impairment of cardiac output was always greater than the reduction in blood pressure because of an increase in peripheral vascular resistance. Heart rate was usually little changed by addition of nitrous oxide. This could lead to a reduction in total blood flow before the variables that are usually monitored (arterial blood pressure and heart rate) are changed enough to alert the anesthesiologist to the impending danger. Similar decreases in stroke volume and cardiac output and increases in peripheral vascular resistances have resulted from lower doses of morphine,[36] other narcotics plus nitrous oxide,[30, 33, 52] and also with Innovar-nitrous oxide anesthesia. Surprisingly, cardiovascular depression during nitrous oxide-narcotic anesthesia appears not to be related to the plasma concentration of the narcotic.[52]

A variety of other intravenous supplements are often combined with narcotics during anesthesia to increase analgesia, ensure adequate hypnosis and amnesia, and correct undesirable cardiovascular alterations (usually hypertension). This therapy is effective, but it is usually achieved at the expense of significant cardiovascular depression. Stoelting[53] has demonstrated, for example, that when a barbiturate has been given for induction of anesthesia, thiamylal (4 mg/kg intravenously), morphine (1 mg/kg intravenously), reduced cardiac output and stroke volume 30% to 40% and decreased blood pressure 16%; systemic vascular resistance was increased 35%. Similarly, diazepam (5 to 10 mg intravenously), a compound with little cardiovascular effects when employed alone, results in marked cardiovascular depression when added after morphine, fentanyl, and probably most narcotics.[2, 54] Of the intravenous compounds that have been studied it appears that only scopolamine and droperidol do *not* produce significant cardiovascular depression when combined with intravenously administered narcotics.[35, 54]

Morphine, meperidine, and more re-

cently fentanyl have also been combined with potent anesthetics.[55, 56] These techniques have varied from the addition of narcotics to patients who were primarily anesthetized with potent inhalation anesthetics[55] and vice versa.[56] These procedures have frequently included numerous other intravenous supplements as well. The rationale for this practice is based on the minimal effects of narcotics on cardiovascular dynamics, their presumed ability to decrease the MAC of the inhalation anesthetics and the belief that use of these combinations produces deep anesthesia without marked cardiovascular depression.[1, 55, 57] Although all of the above seem reasonable, there are, unfortunately, little data that these combinations have any more benign effect on cardiovascular dynamics than the use of any of the compounds alone or that there are not more potential problems from drug interactions than advantages. Stoelting et al[56] have shown that addition of low to moderate concentrations of halothane after large doses of morphine produces severe cardiovascular depression. Bennett and Stanley[55] have found that the same changes occur when fentanyl (200 μg intravenously) is added during enflurane-nitrous oxide anesthesia, but that lower doses of fentanyl (50 to 100 μg) produced little change in cardiovascular dynamics during enflurane-nitrous oxide anesthesia.

Narcotic compounds decrease cerebral blood flow and intracranial pressure.[58, 59] For this reason nitrous oxide-narcotic anesthesia with or without other supplements is a popular technique for patients with increases in intracranial pressure. Some narcotics can decrease the consumption of cerebral oxygen, but the reduction is transient and usually less than the corresponding reduction in cerebral blood flow, at least in dogs.[58, 60, 61] Although there is no evidence that narcotic-induced decreases in cerebral flow are dangerous in man, some anesthesiologists are reluctant to use narcotic techniques in patients with marginal cerebral circulation.

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