Opioid Analgesics in Anesthesia: With Special Reference to Their Use in Cardiovascular Anesthesia


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Summary

Our purpose is to review the use of morphine and other analgesics in current anesthesia practice, particularly anesthesia for patients with cardiovascular disease undergoing cardiovascular operations. The areas of preoperative and postoperative medication will not be considered, nor will mechanisms of action be discussed, as these recently have been well reviewed.¹⁻⁶

The terms narcotic or analgesic are in common usage to describe the compounds that we will discuss. Each of these terms may be misleading when used by itself. A "narcotic" (derived from the Greek word for stupor) was at one time applied to any drug that would induce sleep. It then developed a more restrictive use, referring to morphine-like potent analgesics. It now is used increasingly in a legal context to refer to any substance that can cause dependence. All anesthetic agents, i.e., thiobarbiturates, cause a stuporous or "sleep" state and therefore, can be considered "narcotics," although they are not commonly referred to as such. Aspirin and paracetamol are both analgesics and, in sufficient dosage, render a patient "drowsy," yet they are not classified as narcotic analgesics. For these reasons, we shall either use the terms "opioid" (deriving from, related to, or producing effects like compounds with morphine like action) or "narcotic analgesic" to describe drugs that bind specifically to any of the several subspecies of opioid receptors and produce some opioid agonist actions.

The terms "analgesia" and "anesthesia" often are used interchangeably, describing anesthesia resulting from the use of opioids. We believe this is confusing and incorrect, especially in view of the belief of many that opioids, while capable of producing intense analgesia, do not reliably result in complete amnesia. For clarity in this manuscript, "analgesia" will be defined as a reduced amount or absence of somatic and/or autonomic responses to one or more painful stimuli, and "anesthesia" as all of the above plus unconsciousness and absence of memory (amnesia) of the stimulus and unawareness of all events immediately preceding and following application of the stimulus.

Balanced Anesthesia

The concept of balanced anesthesia dates from 1910, when Geroge Washington Crile, of Cleveland, Ohio,
introduced his theory of anoci association.7 Crile taught that psychic stimuli associated with operations should be prevented by light general anesthesia, while associated painful stimuli could be blocked by local analgesics. The term “balanced anesthesia” was introduced by Lundy in 1926.8 Lundy used a combination of premedication, regional analgesia, and general anesthesia with one or more agents so that unconsciousness and pain relief were obtained via a balance of agents and techniques.

The introduction of curare in 1942 enabled anesthesiologists to obtain relatively controllable muscle relaxation without the need for very deep levels of anesthesia.9 Muscle relaxation was one of the essential components of the anesthetic state, defined as narcosis, analgesia, and muscle relaxation by Gray and Rees.10 This “triad of anesthesia” later was expanded by Woodbridge11 to include the abolition of autonomic reflexes. Several techniques of balanced analgesia were described involving anesthetic induction with sodium thiopental, maintenance with nitrous oxide, and oxygen supplemented with small additional doses of thiopental, and muscle relaxation with d-tubocurare.12,13 However, the combination of thiopental and nitrous oxide provided insufficient analgesia to reliably prevent unwanted sympathetic stimulation during surgery. In other words, not all of the elements of proper “balanced anesthesia” were being achieved. In order to obtain additional analgesia, Neff, Mayer and Perales14 introduced meperidine as a supplement during nitrous oxide anesthesia in 1947 in America. Two years later, a similar technique was introduced in Great Britain by Mushin and Rendell-Baker.15 These techniques rapidly achieved widespread popularity, and many individual variations were described using meperidine16–18 and other opioids.19,20 More recently fentanyl, a synthetic opioid of the 4-amo piperidine series,21 has become popular as an intravenous supplement during general anesthesia with nitrous oxide, other inhalation and intravenous anesthetics, and combinations of intravenous and inhalation anesthetics.22–25 In a double-blind comparison of fentanyl, phenoperidine, and morphone in combination with nitrous oxide for general anesthesia, little difference could be discerned between the drugs.26 This is a characteristic of all opioid compounds when they are combined with other anesthetics, e.g., differences between them with respect to their cardiovascular and other organ system effects tend to be obscured.

The inclusion of an opioid as a component of balanced anesthesia offers several advantages.22,26,27 The course of anesthesia tends to be associated with less fluctuation in cardiovascular dynamics. In addition, opioids decrease requirements for inhalation anesthetics28 and provide increased postoperative analgesia. The use of opioids is particularly advantageous in operations that involve sudden painful manipulations, e.g., pulling on visceral organs during intraabdominal surgery. Anticipation of these events and prior supplementation with a small dose of an opioid, (e.g., 50–100 µg fentanyl intravenously) often will be sufficient to prevent increases of arterial blood pressure and heart rate associated with these manipulations. However, it is important that the timing and the dose of supplemental opioid be tailored to the specific pathology of the patient and the expected duration of the operation in order to avoid postoperative problems. In addition, it should be appreciated that the duration of action of an opioid is determined not only by its pharmacokinetic properties but also by the timing, dosage, and interaction of the drug with other compounds being used. Giving a large dose of any opioid shortly before the end of surgery is very likely to result in postoperative respiratory depression. Similarly, giving opioids and benzodiazepines concurrently tends to potentiate and prolong the duration of respiratory depression produced by the opioid.29

Neuroleptanalgesia

In 1949, Laborit introduced the concept of an anesthetic technique that blocked not only cerebral cortical responses but also some cellular, endocrine, and autonomic mechanisms usually activated by surgical stimulation.26 This state was called “gangloeplégia” or “neuroplegia” (artificial hibernation) and was achieved by the use of a “lytic cocktail” consisting of chlorpromazine, promethazine, and meperidine. From this idea, De Castro derived the concept of neuroleptanalgesia,27 the combination of a major tranquilizer, usually a butyrophenone, droperidol, and a potent opioid analgesic, fentanyl or phenoperidine, to produce a detached, pain-free state of immobility and insensitivity to pain. Neuroleptanalgesia is characterized by analgesia, absence of clinically apparent motor activity, suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in some but not all patients.

Combinations of drugs such as droperidol, which may have a duration of action of up to 24 h, with fentanyl, which, at least in the doses usually used in neuroleptanalgesia (3–5 µg/kg), lasts for 30–60 min, are not usually considered desirable.30 The reason for this is that the effects of the tranquilizer may last much longer than the analgesic and result in a patient who is apparently calm yet may be suffering from restlessness and mental agitation.30 In addition, droperidol in doses of 0.1 mg/kg and above occasionally results in prolonged postoperative somnolence. Nonetheless, the commercial preparation of droperidol and fentanyl (Innovar®) has gained widespread popularity, both in the United States and in Europe, as the principal component of a balanced an-
esthetic technique, which also usually employs N₂O. The most important reason for the continued popularity of Innovar is probably related to the associated intraperative cardiovascular stability and relatively event-free recovery from anesthesia. Morgan and colleagues found doses of droperidol of 5–20 mg and of fentanyl of 0.1–0.8 mg necessary for induction of anesthesia using neuroleptanalgesia in combination with muscle relaxants for major surgery. N₂O/O₂ was used during controlled ventilation and fentanyl (mean dose 0.1 mg/hr) administered for maintenance of anesthesia. The features of the technique were cardiovascular stability (with the exception of occasional hypotension on induction of anesthesia) and a patient who was awake and cooperative at the end of the procedure. Other workers found similar results using neuroleptanalgesia for cardiovascular and other major surgical procedures.24,33 Neuroleptanalgesia has also been used effectively in neurosurgery where it produces a reduction of cerebral spinal fluid pressure in patients with and without space-occupying lesions.34

Opioid Anesthesia

MORPHINE

The use of opioid analgesics as anesthetics has achieved much popularity recently, especially for patients undergoing cardiac surgery. The first reported controlled attempt to use an opioid as an anesthetic was by Schneiderlein in 1900.35 He administered up to 2.5 mg scopolamine and 70 mg of morphine intramuscularly within 75 min. Patients anesthetized with morphine/scopolamine were oblivious to pain and recovered with no recollection of the procedure. However, 70% of patients required some restraint during surgery.36 Unfortunately, these techniques were associated with a number of deaths and soon were abandoned.37

The opioids were not used again as anesthetics in the United States until the observations of Lowenstein et al.,38 were reported. These investigators showed that 0.5–3.0 mg/kg of morphine administered intravenously during ventilation with 100% oxygen did not alter cardiovascular dynamics in patients without heart disease and improved them in patients with aortic valve disease. They suggested that doses of morphine in excess of 1 mg/kg were necessary to produce “anesthesia” in most patients undergoing open heart surgery. At the same time, de Castro,39 in Europe, proposed “analgesic anesthesia” with large doses of fentanyl, an anesthetic technique that virtually was ignored by most clinicians for 8 years.

Lowenstein’s observations led to many additional studies evaluating morphine as an anesthetic, and the technique gained considerable popularity for cardiac surgery.40–45 However, it soon became apparent that morphine anesthesia did have significant disadvantages. Many problems were reported that included the following: incomplete amnesia, occasional histamine-related reactions (cutaneous flushing, hypotension, bronchoconstriction), marked increases in intraoperative and postoperative blood and fluid requirements, and prolonged postoperative respiratory depression.40–44 In addition, cardiovascular stability was not always complete; bradycardia, hypotension, and hypertension often occurred, and the addition of nitrous oxide caused cardiovascular depression.40–43 Difficulties with high doses of morphine were most evident when the technique was used for patients undergoing coronary artery surgery, particularly when the patients did not have a history of heart failure.45,46,47 The problems associated with high-dose morphine and other opioid anesthetic techniques will be discussed in detail in a later section.

MEPERIDINE AND ALPHAPROPRIDINE

Because of the problems associated with morphine’s use as an anesthetic, attempts were made to find a suitable alternative among existing opioids. Meperidine was studied in isolated cardiac preparations, intact dogs and humans in a variety of experimental conditions by a number of investigators.46–52 Unfortunately, meperidine resulted in decreases in myocardial contractility in heart muscle preparations and, even in low doses (2–2.5 mg/kg), caused significant decreases in arterial blood pressure and cardiac output often accompanied by tachycardia in intact animals46,48,51 and humans.49,50 Anesthetic doses of meperidine (10 mg/kg, intravenously) were associated with marked decreases in cardiac output (fig. 1) and frequently caused cardiac arrest in dogs.46 The cardiovascular depression seen with meperidine in animal experiments appeared to be due to a combination of peripheral vasodilation and a decrease in myocardial contractility.45,48,51,52 When equianalgesic doses of meperidine were compared with morphine, meperidine was 20 times more depressant to the contractile element of the isolated cat papillary muscle than morphine52 (table 1). All of these studies suggested the meperidine was not a suitable alternative to morphine as an anesthetic in patients with significant cardiovascular disease. Alphaprodine, a methyl substitute derivative of the reversed ester of meperidine, also possesses the cardiovascular depressing properties of meperidine.53 Similar findings have been reported with piritramide, an opioid commonly used in Europe for postoperative analgesia.54

FENTANYL

Because of the problems with morphine and meperidine as “anesthetics,” investigators interested in opioid
anesthesia then studied fentanyl. In early studies, fentanyl (25–50 μg/kg) resulted in an increase or (30–160 μg/kg) no change in dP/dt max, or aortic blood pressure. Pretreatment with fentanyl (50 μg/kg) abolished atrial fibrillation and reduced the depressive cardiac effects associated with left circumflex coronary artery occlusion in an investigation on experimentally induced myocardial infarction. These data suggested that fentanyl might be of value in patients with ischemic coronary artery disease. In studies in which fentanyl was given to animals anesthetized with other anesthetics, only minor changes in cardiovascular function were found. Indeed, fentanyl (30–100 μg/kg) given to ventilated dogs anesthetized with halothane only caused a small decrease in blood pressure and little or no change in ventricular performance. Some investigators, impressed with these findings, studied enormous doses of fentanyl in dogs. In these studies, doses of fentanyl of up to 3

mg/kg were found to produce a dose-dependent decrease in heart rate, but only small reductions in cardiac output, peripheral resistance, and arterial pressure, and an increase in stroke volume in dogs basally anesthetized with barbiturates. These investigations in animals were very encouraging and suggested fentanyl might have a place as an “anesthetic” in humans.

Large doses of fentanyl plus oxygen then were evaluated as an anesthetic in humans. Initial unpublished observations in 52 unpremedicated patients breathing 100% oxygen and undergoing a variety of cardiac and noncardiac operations indicated that if given in sufficient dosage fentanyl would produce unconsciousness (Stanley TH, unpublished data). Unfortunately, it was impossible to predict a “sleep dose” of the drug as some patients became unconscious and nonresponsive with as little as 6 μg/kg (given as an infusion of 50–200 μg/min) and others required as much as 40 μg/kg. Furthermore, following paralysis with succinylcholine and endotracheal intubation, some patients would open their eyes on command following return of neuromuscular function 5–10 min after anesthetic induction. Injection of additional fentanyl always resulted in the return of nonresponsiveness, and patients never remembered the event when intensively questioned postoperatively. Nonetheless, these findings suggested that if fentanyl were to be used as an anesthetic, that frequent supplementation probably would be required throughout operation, and thus it would be difficult to predict what dose should be used for induction of anesthesia or at what frequency additional supplements should be administered. The initial observations were encouraging because arterial and pulmonary artery blood pressures and cardiac output appeared unchanged throughout anesthesia and operation, patients seemed to rapidly recover consciousness (3–6 h after operation), and no patient remembered any aspect of the anesthetic induction or operation, even when repeatedly interviewed throughout their postoperative course. However, it was felt that because of the variable response of patients to fentanyl, especially with induction, the drug should be used cautiously with the following recommendations. First, that atropine or some belladonna or belladonna-like drug always should be used for premedication or given intravenously immediately before administration of fentanyl because of occasional profound decreases in heart rate during anesthetic induction. Second, that succinylcholine always should be used as the relaxant for endotracheal intubation so that reevaluation of the patient’s ability to respond to sound (commands) could be accomplished before surgical stimulation. Third, that liberal use of additional fentanyl was necessary in response to even the slightest suggestion of inadequate anesthesia (pupillary dilation, conjunctival or face flushing, tearing, frowning, any movement or

![Graph showing cardiac output (mean ± SD) before and after meperidine (10 mg/kg, iv) in nine basally anesthetized (sodium thiopental) mongrel dogs. *P < 0.01, one-way analysis of variance (Stanley, TH, unpublished data).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931417/)
the slightest increase in arterial blood pressure or cardiac output. Finally, that careful attention (including talking to the patient) was advisable at all times during operation. Following these uncontrolled trials, a number of more carefully designed studies was initiated to evaluate fentanyl in selected patient populations.

The first studies were accomplished in patients undergoing mitral valve\textsuperscript{54} and coronary artery surgery.\textsuperscript{55} For mitral valve surgery, an average of 11 μg/kg of fentanyl resulted in unconsciousness, and 74 μg/kg was required for the entire operation. However, there were, as in the original observations, marked differences between patients. Nonetheless, changes in cardiovascular dynamics with induction (20 μg/kg) in these patients were small and consisted of small decreases in heart rate and arterial blood pressure (fig. 2). All other cardiovascular variables studied, including cardiac output, remained unchanged (fig. 2). No further changes were found with additional fentanyl of up to 50 μg/kg. Interestingly, addition of diazepam (10 mg, iv) after fentanyl resulted in significant decreases in stroke volume, cardiac output and arterial blood pressure, and increases in central venous pressure.\textsuperscript{58} Results have been the same in other studies irrespective of the dosage or sequence of fentanyl or diazepam administration.\textsuperscript{60–62} A recent study suggests that the combination of diazepam and fentanyl results in impressive decreases in myocardial contractility.\textsuperscript{63} Significant decreases in arterial blood pressure have been reported following addition of diazepam after large doses of morphine,\textsuperscript{64} suggesting that combinations of opioids plus diazepam, and probably all of the benzodiazepines, should be used cautiously, especially in patients with cardiac disease.

In initial studies in patients with coronary artery disease breathing oxygen and premedicated with atropine and diazepam, loss of consciousness occurred after 18–24 μg/kg of fentanyl, but the cardiovascular dynamics were similar to those observed in patients undergoing mitral valve surgery.\textsuperscript{59,65} The marked differences in narcotic requirements for unconsciousness and entire operations observed in individual patients in these later studies again indicated that it was difficult to predict narcotic requirements prior to induction of anesthesia. As a result, today many clinicians routinely add nitrous oxide during or after administration of large doses of fentanyl. Unfortunately, addition of nitrous oxide to the inspired gas after large doses of fentanyl produces significant decreases in cardiac output and increases in peripheral and pulmonary vascular resistances and heart rate that may be undesirable in many patients with cardiac disease.\textsuperscript{59} Similar results have been reported following combination of nitrous oxide with all other pure agonist opioids.\textsuperscript{41,44,49,66} The mechanism(s) by which combinations of benzodiazepines and/or N\textsubscript{2}O plus opioids result in myocardial and cardiovascular depression is unknown.

Alternative anesthetic techniques involving a single "bolus" injection or more rapid infusion of fentanyl for patients undergoing coronary artery surgery also have been reported.\textsuperscript{67–72} Following a variety of premedicants and with or without a small dose of pancuronium given as pretreatment (to reduce the incidence of chest wall rigidity), large doses of fentanyl (50–100 μg/kg) have been administered rapidly followed by paralysis with large doses of a nondepolarizing muscle relaxant (usually pancuronium). Little or no cardiovascular depression (hypotension, bradycardia) usually is observed with induction of anesthesia in these studies.\textsuperscript{67–72} However, some investigators have reported hypertension and/or tachycardia during or immediately after induction with this approach.\textsuperscript{71,72}

Some question the wisdom of using a single large "bolus" dose of fentanyl followed by a large dose of pancuronium at the beginning of anesthetic induction because of the risk of fentanyl-induced bradycardia and hypotension or pancuronium-induced tachycardia and hypertension. Some authors indicate that these changes have occurred infrequently, at least during and immediately after anesthetic induction.\textsuperscript{67,68} On the other hand, other investigators not only have experienced these problems during anesthetic induction\textsuperscript{71,72} but with initial surgical stimulation and at other times during surgery.\textsuperscript{69,70,72} Another controversial question is whether plasma fentanyl concentrations remain sufficiently high after a single large bolus to insure amnesia throughout

![Figure 2](attachment:figure2.png)

**Fig. 2.** Cardiac output (●) and mean arterial (○) blood pressure before and after large doses of fentanyl and fentanyl plus diazepam (mean ± SD). *p < 0.05, **p < 0.01, one-way analysis of variance. Reprinted from Stanley TH, Webster LR: Anesth Analg 57:411–416, 1978, with permission of the International Anesthesia Research Society.
operation. Undoubtedly, the duration of surgery, as well as the dose and kind of premedicants or other drugs (relaxants) used, are important factors that make the issue a difficult one to resolve. If there is any clinical suggestion that anesthesia may be insufficient (patient movement, sweating, flushing, tearing, pupillary dilatation, etc.), some clinicians simply administer additional fentanyl\textsuperscript{58,65,67} while others use a variety of other supplements.\textsuperscript{60,72} The merits and problems of both approaches will be addressed later.

Fentanyl (30–50 μg/kg) given over 1 min in conjunction with pancuronium also has been used successfully as the sole anesthetic for ligation of patent ductus arteriosus in premature infants.\textsuperscript{73} No significant changes in cardiovascular dynamics were found, and the infants were awake within 1 h of the end of surgery.

**NEUROPHYSIOLOGIC EFFECTS OF NARCOTIC ANALGESICS**

The neurophysiologic state obtained by use of large doses of opioid analgesics is not the same as the "general anesthetic" state resulting from the use of volatile inhalational anesthetic agents.\textsuperscript{74} "General anesthetics" produce a dose-related generalized depression of the central nervous system, while opioid analgesics are more selective in action. High-dose fentanyl anesthesia produces a reproducible electroencephalographic response characterized by high-voltage slow delta waves.\textsuperscript{74} A similar EEG pattern has been reported after the administration of meperidine 400 mg.\textsuperscript{75} The EEG with fentanyl is not altered by the addition of N\textsubscript{2}O or surgical stimulus and is consistent with surgical anesthesia.\textsuperscript{74} As the "anesthetic" effects of a high dose of an opioid decrease, the EEG waves become more frequent and of lower amplitude, suggesting recovery from anesthesia.\textsuperscript{76} However, a strong cause-and-effect relationship between EEG changes and depth of anesthesia is yet to be established. Increasing dosage with conventional anesthetic agents produce a continuum of EEG changes, resulting in burst suppression and a flat EEG with overdosage. In contrast, a "ceiling effect" is reached with fentanyl. Increasing the dosage from 50 to 150 μg/kg does not affect the EEG further (Sebel PS, Bovil JG, unpublished data).\textsuperscript{76} Furthermore, some patients have EEG recordings that only slowly return toward "control," even though plasma and presumably brain concentrations are decreasing rapidly. In spite of these problems, recent work by Scott et al.\textsuperscript{76} suggests that computer-assisted analysis of the EEG during high-dose fentanyl or other opioid anesthesia may be of value in determining depth of anesthesia. While the electroencephalographic effects of doses of fentanyl above 150 μg/kg have not been studied in humans, existing data suggest that opioids have a different neurophysiologic mechanism of action, possibly producing anesthesia by blocking afferent input into the nervous system rather than by generalized central nervous system depression.\textsuperscript{74,76}

Another feature of the general anesthetic state associated with potent inhalation anesthetics is muscle relaxation. Opioid analgesics do not produce any muscle relaxation. On the contrary, they result in an increase in muscle tone, sometimes resulting in "lead pipe" rigidity.\textsuperscript{52} The mechanism by which this occurs in unknown; however, neuromuscular blocking agents can be used to block this action of opioids or treat it once it occurs.\textsuperscript{62,65,66,71}

**HORMONAL RESPONSES TO OPIOIDS**

Considerable interest has been expressed in recent years in possible anesthetic modification of the hormonal and associated metabolic responses to surgical trauma. The so-called surgical stress response consists of increases in plasma concentrations of the catecholamines, cortisol, antidiuretic hormone (ADH), human growth hormone, glucose, lactate, pyruvate, and sometimes other hormones and metabolites. Increases in plasma concentrations of the stress hormones occur during general anesthesia with most inhalation and intravenous agents and are increased further with operation.\textsuperscript{65,77–79} Surgically induced increases in the majority of the stress hormones are related to the severity of the operative trauma,\textsuperscript{77} being much greater during intraabdominal surgery than body surface procedures,\textsuperscript{78,79} and are considered undesirable because they promote hemodynamic instability and intraoperative and postoperative metabolic catabolism. Cardiac surgery with cardiopulmonary bypass produces profound endocrine and metabolic changes.\textsuperscript{65}

**MORPHINE**

Analysis of hormonal data from a number of studies suggests that morphine modifies hormonal responses to surgical trauma in a dose-related fashion.\textsuperscript{80–85} Morphine, even in small doses, inhibits ACTH release and blocks at least part of the pituitary–adrenal response to surgical stress.\textsuperscript{80,81} After morphine (0.33 mg/kg), significant decreases in blood lactate occur, however, pyruvate concentrations remain unchanged.\textsuperscript{82} Morphine (1 mg/kg) suppresses surgically induced increases in plasma cortisol but not human growth hormone during major abdominal operations.\textsuperscript{83} During cardiac surgery with morphine (4 mg/kg) anesthesia, plasma concentrations of cortisol and human growth hormone are not increased in the prebypass period but are during bypass.\textsuperscript{83–85} Increases in plasma concentrations of these hormones continue into the period after bypass and postoperatively.\textsuperscript{84}
Morphine also has been shown to increase some stress-responding hormones. Plasma catecholamine levels are increased after morphine in dogs. While the reasons for these changes are not clear, it has been suggested that morphine alters adrenal medullary release mechanisms and, to a lesser extent, stimulates catecholamine release from sympathetic nerve endings. Other possibilities include reflex responses to increased carbon dioxide or hypotension (secondary to morphine-induced ventilatory depression and/or vasodilatation). Increases in plasma catecholamine concentrations appear to be responsible for the positive inotropic effect of morphine in dogs, since they are blocked by beta-adrenergic blocking drugs or previous surgical adrenalectomy.

Morphine also can increase concentrations of catecholamines in both blood and urine in humans. Secretion of catecholamines in humans may be related to inadequate analgesia (anesthesia) but may be also dependent on the functional state of the sympathetic nervous system and the plasma concentration of morphine, e.g., patients with hypertension and other evidence of increased sympathetic activity and patients with low morphine blood levels have higher urine norepinephrine excretion rates than similar normotensive patients or those with high morphine blood levels. There is also evidence that the change in plasma norepinephrine concentration with induction of anesthesia with morphine is related to the preinduction plasma norepinephrine concentration; patients with low preoperative plasma norepinephrine concentrations experience a small rise in these amines, whereas patients with higher preoperative plasma norepinephrine concentrations experience no change or decreases in these concentrations after anesthetic induction.

Although morphine is known to stimulate ADH secretion in dogs and rats, it does not appear to do so in the absence of surgical stimulus in humans. Plasma ADH rises significantly during morphine (1 mg/kg) plus nitrous oxide anesthesia in humans during surgery before cardiopulmonary bypass and increases further during bypass. Plasma renin activity also increases markedly in patients anesthetized with morphine (1–3 mg/kg) and nitrous oxide during cardiac surgery. Increases in plasma renin are frequently but not always correlated with simultaneous increases in mean arterial pressure in these patients.

FENTANYL

Fentanyl and some of its newer congeners seem to be even more effective than morphine in modifying hormonal responses to surgery. In a study of healthy women undergoing prolonged gynecologic surgery, anesthesia with nitrous oxide supplemented with fentanyl (50 μg/kg) was compared with halothane and nitrous oxide. Fentanyl abolished the hyperglycemic response to surgery and reduced plasma cortisol and growth hormone responses when compared with halothane. Similar results also have been reported with large doses of fentanyl in patients undergoing gastric surgery.

The catecholamine response to induction of anesthesia with fentanyl infusion in patients about to undergo coronary artery surgery has been investigated recently. Plasma norepinephrine levels were significantly elevated after fentanyl, 15 μg/kg, had been administered (probably secondarily to inadequate analgesia), remained elevated after 30 μg/kg, but returned to control values after 50 μg/kg. No significant changes occurred in plasma epinephrine or dopamine. Other investigations have found that fentanyl in doses of 50 μg/kg or greater prevents increases in plasma catecholamine concentrations during cardiac surgery, although marked increases may occur during cardiopulmonary bypass. The hormonal changes associated with fentanyl (60 μg/kg) anesthesia during cardiac surgery are summarized in figure 3. Marked increases in catecholamine concentrations measured during cardiopulmonary bypass that are not blocked by maintaining plasma concentrations close to prebypass levels or increasing these concentrations above prebypass levels (Stanley TH, unpublished data) are presumably a response to the significant abnormal physiologic state during this period, i.e., hemodilution, hypothermia, and nonpulsatile flow. Indeed, there is some evidence that vasopressin and catecholamine response to cardiopulmonary bypass can be attenuated significantly by the use of pulsatile flow, although this has not been confirmed by all investigators.

Anesthesia with fentanyl (60–100 μg/kg) prevents rises in plasma ADH, renin, and aldosterone in the period before cardiopulmonary bypass. This is in contrast to the significant increases of these hormones observed in similar patients anesthetized with morphine. However, during bypass plasma ADH rises significantly in spite of high doses (100 μg/kg) of fentanyl. High-dose fentanyl anesthesia usually prevents increases in blood glucose, plasma cortisol, and growth hormone concentrations in most patients throughout open heart operations. However, this reduction in the stress response is not found consistently in all patients, especially during and after cardiopulmonary bypass and in the postoperative period, even when fentanyl administration is continued for 12–18 h after surgery.

In summary, fentanyl appears to be somewhat more effective than morphine in reducing the endocrine and
metabolic responses to surgery. Although this may be due to pharmacologic differences between the drugs, it also may be the result of differences in potency (as sufentanil, which is five to 10 times as potent as fentanyl, appears more effective as an inhibitor of stress hormonal responses than the latter\textsuperscript{105}), increased dosage,\textsuperscript{66,68,102,108} anesthetic technique,\textsuperscript{65,66} or increased speed of onset of action (as has been suggested with alfentanil in clinical studies and carfentanil in investigations with wild animals).\textsuperscript{108,109} The effects of other opioids on the stress response to surgery have received little attention. Papaveretum (extract of opium) is significantly less effective than fentanyl in attenuating the changes associated with cardiac surgery.\textsuperscript{108} However, the new narcotics, alfentanil and sufentanil, seem to be more effective than fentanyl in cardiac and noncardiac operations,\textsuperscript{107,110} although only a few carefully controlled clinical studies have been completed.\textsuperscript{110}

The mechanism by which large doses of opioids inhibit the stress response to surgical trauma is unknown. However, whatever the mechanism, it probably involves pituitary release of ACTH and perhaps other stress hormonal precursors because ACTH secretion is reduced by high doses of opioids. It is interesting that decreases in plasma human growth hormone concentrations produced by morphine (4 mg/kg) are totally reversible after ACTH administration.\textsuperscript{85} It is known that the endogenous opioid-like peptides play an important regulatory role in the secretion of several pituitary hormones,\textsuperscript{111} possibly via alteration in the release of neurotransmitters (e.g., dopamine) that regulate secretion of pituitary hormone-releasing or release-inhibiting factors.\textsuperscript{112,113} Perhaps exogenous opiates have similar inhibiting or stimulating actions.

Thus, techniques of opioid analgesia, particularly techniques of high-dose fentanyl anesthesia, diminish the hormonal stress response to surgery. This metabolic response is appropriate when "fight or flight" is required, for it insures an increase in metabolism and energy availability necessary for the increased work associated with these states. However, such responses may be totally inappropriate in patients undergoing some forms of cardiovascular surgery, e.g., patients with ischemic coronary artery disease undergoing coronary artery bypass grafting. Increases in plasma catecholamine concentrations in these patients will lead to increased myocardial work and may further compromise an already damaged myocardium. Elevated plasma levels of the stress hormones in the period after surgery increase protein catabolism and may delay recovery. If these metabolic responses are modified, then morbidity and mortality should be reduced. However, there is as yet no evidence to support this theoretic benefit. "Stress-free anesthesia" is at best an attractive biochemical concept. Whether it is of clinical benefit is uncertain. Certainly, any reduction in the metabolic responses to anesthesia and surgery is short lived,\textsuperscript{99,101,106} and with morphine, at least, there is no improvement in postoperative nitrogen balance.\textsuperscript{84} Whether the same is true following high doses of fentanyl or the newer synthetic opioids remains to be documented.

**Disadvantages of Opioids in Anesthesia**

**CARDIOVASCULAR**

**Effect on Heart Rate**

The intravenous injection of fentanyl produces bradycardia in humans,\textsuperscript{58,59,73,114–116} and animals.\textsuperscript{46,56,57} In this respect fentanyl is similar to other opiates with the exception of meperidine, which often causes tachycardia.\textsuperscript{47,48,116} The latter may be related to the structural similarity between meperidine and atropine but also may be reflexly induced secondary to hypotension.
Tachycardia also occasionally occurs during induction of anesthesia with morphine, usually accompanied by facial and upper torso flushing. This may be related to histamine release.\textsuperscript{117}

Fentanyl-induced bradycardia is more marked in anesthetized than conscious dogs or human subjects.\textsuperscript{57,114} When used for induction there is a higher incidence of bradycardia when patients or dogs breathe pure oxygen than when nitrous oxide is used with oxygen.\textsuperscript{57,118} This may be due to the increase in sympathetic nervous system activity associated with nitrous oxide anesthesia.\textsuperscript{119,120} Second and subsequent doses of fentanyl cause less bradycardia than initial doses.\textsuperscript{57,121} Infusion experiments in dogs have shown that most of the decrease in heart rate occurs with the first 50 μg/kg of fentanyl.\textsuperscript{57} Administration of additional drug (up to 2 mg/kg) is required to duplicate the initial percentage decrease in heart rate in dogs.\textsuperscript{121} The degree of bradycardia after infusion of opioids may, to some extent, be dose related,\textsuperscript{109,121,122} although an equally important factor is the speed of injection. While a well-controlled experimental investigation has not been published, clinical experience in humans\textsuperscript{58,66} and animal studies with numerous species\textsuperscript{55,57,109,123,124} suggest that bradycardia can be minimized by slow administration of potent opioids. Premedication with atropine can minimize bradycardia induced by morphine, fentanyl, or other highly potent opioids but does not always eliminate it.\textsuperscript{55,57,62,66,105,121} Atropine is also usually effective in treating opioid-induced bradycardia, but anecdotal reports suggest on occasion even large doses (1–2 mg) are ineffective.\textsuperscript{66} Prior administration of small to moderate doses of intravenous pancuronium (0.5–2.0 mg) before induction of anesthesia with fentanyl or other potent narcotics attenuates bradycardia and reduces the incidence and magnitude of muscle rigidity.\textsuperscript{62,66,67,107,108,125}

The mechanism of fentanyl-induced bradycardia is not understood completely, although there is experimental evidence that it is caused by stimulation of the central vagal nucleus.\textsuperscript{122} It is blocked almost totally by bilateral vagotomy\textsuperscript{122} or pharmacologic vagal block with atropine.\textsuperscript{57} Blockade of sympathetic chronotropic action also may play a minor role.\textsuperscript{122} Similar mechanisms have been proposed for morphine.\textsuperscript{126,127} Morphine also is thought to have a direct effect on the sinoatrial node\textsuperscript{128–130} and to depress atrioventricular conduction.\textsuperscript{131} It is likely that fentanyl has a similar action. The latter properties may play a role in the antiarrhythmic actions of morphine\textsuperscript{129–131} and fentanyl.\textsuperscript{55,56}


\textbf{Influence on Blood Pressure}

Hypotension: Anesthesia with morphine occasionally may be associated with hypotenion,\textsuperscript{40,132} which may be severe. In one report involving patients undergoing cardiac valvular surgery, there was a 10% incidence of hypotension (systolic blood pressure below 70 mmHg).\textsuperscript{132} One patient in this series sustained a myocardial infarction as a result of morphine-induced hypotension. However, the incidence of severe hypotension in this study was similar in patients anesthetized with morphine or halothane. The mechanism(s) of hypotension after morphine are unclear and are probably multifactorial. The rate of administration and the underlying pathology of the patient may be important. In the abovementioned series involving patients with mitral and/or aortic valve disease, the minimum rate of administration of morphine was 5 mg/min.\textsuperscript{41} In patients with coronary artery disease, hypotension occurs when morphine is infused at 10 mg/min\textsuperscript{41} but not when the infusion rate is limited to 5 mg/min.\textsuperscript{133}

Hypotension after morphine does not appear to be associated with significant myocardial depression, although in healthy volunteers morphine (2 mg/kg) does cause a prolongation of the prejection period, an estimate of isovolumetric cardiac contractility.\textsuperscript{134} Even small doses of morphine (10 mg iv) can cause hypotension.\textsuperscript{135} Hypotension after larger doses of morphine, 1 mg/kg in dogs, may be related to changes in the distribution of regional blod flow.\textsuperscript{136} However, a more important cause is probably a decrease in systemic vascular resistance secondary to significant increases in plasma histamine concentrations.\textsuperscript{117,137–142} The recent development of a sensitive and accurate assay for histamine, together with the development of specific histamine receptor antagonists, has enabled a reappraisal of the role of histamine in the cardiovascular changes resulting from morphine anesthesia.\textsuperscript{117,142} Morphine (1 mg/kg) produces marked increases in plasma histamine and cardiac index and decreases in blood pressure and vascular resistance (figs. 4 and 5). Similar cardiovascular changes occur when patients are pretreated with diphenhydramine (a histamine H\textsubscript{1} antagonist) or cimetidine (a histamine H\textsubscript{2} antagonist) before morphine. However, in patients pretreated with both H\textsubscript{1} and H\textsubscript{2} antagonists, the cardiovascular responses to morphine are attenuated significantly, despite comparable increases in plasma histamine concentrations.\textsuperscript{142} These data strongly suggest that many of the hemodynamic effects of morphine can be attributed to histamine release and indicate possible means of preventing these changes. Hypotension rarely occurs with high-dose fentanyl anesthesia, possibly because, unlike morphine, fentanyl does not cause histamine release (figs. 4 and 5).
Hypertension: The most common cardiovascular disturbance during high-dose fentanyl anesthesia for cardiac surgery is hypertension during or after sternotomy. The reported evidence of hypertension with fentanyl based anesthesia varies widely. Stanley et al. reported no change in cardiovascular variables following surgical stimulation. Other investigators have reported incidences of hypertension specifically related to sternotomy from 45 to 100% in patients given fentanyl 50–100 μg/kg. The reason for this variability between institutions is not clear. Possible

Morphine causes a significant reduction in venous and arterial tone in both animals and humans and a decrease in venous return to the heart, which may contribute to hypotension. Arterial dilation occurs sooner and is of shorter duration than venodilation. The degree of venodilation is dose related and causes a significant increase in the amount of blood and/or crystalloid fluid required to maintain adequate ventricular filling pressures (Table 2). Greene and co-workers have shown that morphine reduces venous return to the heart in the dog by causing hepatic sequestration of plasma, however, there is no evidence that this mechanism is of any significance in humans. Others have suggested that venous vasodilation after large doses of morphine is the primary cause for decreased venous return. This is not caused by the preservatives present in the commercial preparations of the drug or opiate receptor stimulation but may be related to a reflex mechanism(s). Vasodilation after morphine also may be due to a direct effect of morphine, as well as histamine, on vascular smooth muscle.

![Graphs and charts](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931417/)
factors may be the rate of administration and/or the dose of fentanyl; the dose, time of administration, and kind of muscle relaxant used for endotracheal intubation and maintenance of relaxation; the degree of beta-adrenergic and/or calcium channel blockade present at the time of surgery; ventricular function; patient habits; and numerous other factors.\textsuperscript{66,70,147-151} In an investigation comparing fentanyl requirements in patients undergoing coronary artery surgery in Salt Lake City and Leiden (The Netherlands), it was found that poststernotomy hypertension occurred in only 10\% of patients in Salt Lake City with fentanyl (75 \text{ mg/k}}) but was present in 80\% of Dutch patients in spite of 121 \text{ mg/k}} of fentanyl.\textsuperscript{148} Higher doses of fentanyl (130–140 \text{ mg/k}}) reduced this incidence of hypertension in Dutch patients. A recent study suggests that these differences in fentanyl requirements between populations may be related to different patient habits.\textsuperscript{149} The data indicate that a history of smoking plus alcohol and caffeine consumption increase fentanyl requirements for anesthesia. Although it appears that satisfactory control of hemodynamics can be achieved by increasing the dose of fentanyl,\textsuperscript{70,148} it is questionable whether the use of such extremely high doses are necessary or even desirable, considering associated problems and the availability of alternative techniques. Doses of fentanyl of 140 \text{ mg/k}} are likely to result in prolonged respiratory depression in the postoperative period.\textsuperscript{148} Satisfactory blood pressure control can be achieved with fentanyl 50–120 \text{ mg/k} plus vasodilator therapy.\textsuperscript{57,69,70,101,148} However, with lower doses of fentanyl (50 \text{ mg/k}) and no supplements there may be an increased risk of intraoperative awareness, which has never been reported with doses over 120 \text{ mg/k} but has occasionally been reported with lower doses.\textsuperscript{152-154}

It is the current practice of some authorities to limit the total amount of fentanyl to 100 \text{ mg/k}. When hemodynamic control is not achieved with this dose, vasodilator therapy is begun with sodium nitroprusside. Other clinicians would supplement with a potent inhalational agent and/or an intravenous sedative/hypnotic\textsuperscript{150,152} to control episodes of hypertension. Mixing opioids with inhalation agents has been shown to decrease stroke volume, cardiac output and mean arterial blood pressure, and increase ventricular filling pressure.\textsuperscript{29,156} On the other hand, some investigators have shown it is possible to employ fentanyl and potent inhalation agents (enflurane or halothane) without decreasing myocardial contractility or blood pressure, cardiac output, and stroke volume.\textsuperscript{70,156,157} Furthermore, there is evidence some inhalation agents (halothane or isoflurane) may be protective to the myocardium during periods of ischemia.\textsuperscript{158,159} Nonetheless, the effects of the addition of inhalation agents during large doses of fentanyl or other opioids on the myocardial oxygen supply/demand ratio in patients with coronary artery disease is uncertain.

Hypertension during cardiovascular surgery was also a problem in patients anesthetized with morphine.\textsuperscript{40,43,45,60,132} Arens et al.\textsuperscript{45} reported a 36\% incidence of hypertension—defined as a rise in systolic blood pressure to over 200 mmHg or an increase of 60 mmHg above preoperative pressure—in patients undergoing coronary artery surgery with 2 mg/kg of morphine. Hypertension during morphine anesthesia has been attributed to light or inadequate anesthesia,\textsuperscript{40,66} reflex mechanisms,\textsuperscript{10,66} and stimulation of the renin-angiotensin mechanism.\textsuperscript{97} These explanations, with the exception of inadequate anesthesia,\textsuperscript{148} do not appear to be valid in the case of fentanyl, and to date the mechanism responsible for the phenomenon is unknown, although various explanations have been suggested.\textsuperscript{98,67}

\textbf{Respiratory Depression}

Fentanyl, in common with all other pure agonist opioids, produces dose-related respiratory depression.\textsuperscript{160-165} Both the responsiveness to carbon dioxide (fig. 6) and respiratory rhythmicity and reflexes are affected by opioids.\textsuperscript{141,161-165} Maximum respiratory depression with most of the narcotics occurs within 5 min after intravenous injection, however, some depression may persist for much longer periods. Even with small doses of fentanyl (2–9 \text{ mg/kg}), minute ventilation in response to increases in \text{PaCO}_{2} may be depressed 2–4 h after administration.\textsuperscript{160,161,165} (Fig. 7). This is in contrast to the much shorter duration of analgesia with this dose of fentanyl.\textsuperscript{29,164} Shorter duration of analgesia relative to respiratory depression may be a reflection of the sensitivity of current methods to measure these variables. The important point is that substantial blood levels of

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Pathology & Anesthetic & Intravenous & Postoperative \\
\hline
Aortic valve & Morphine & 2,822* & 1,091* \\
& disease & Halothane & 998 & 767 \\
Coronary artery & Morphine & 2,763* & 1,418* \\
& disease & Halothane & 1,726 & 708 \\
\hline
\end{tabular}
\caption{Blood Requirements during Operation and for the First Postoperative Day in 61 Patients Anesthetized with Morphine (1–4 mg/k) plus Oxygen or Halothane (0.1–1.5%) plus 30% Nitrous Oxide and Oxygen and Undergoing Aortic Valve Replacement or Coronary Artery Bypass Operation}
\end{table}
fentanyl persist for many hours. With the higher doses of fentanyl that are used in cardiac surgery, respiratory depression can persist for many hours, and patients may have to be ventilated for 12–18 h after induction of anesthesia. However, some patients can tolerate extubation within 4 h of the end of operation with minimal or no elevation in $P_aCO_2$. When moderate (20–50 μg/kg) or larger doses of fentanyl are used during major noncardiac surgery, facilities should exist for postoperative mechanical ventilation, if necessary.

Delayed respiratory depression occurring after a period of adequate spontaneous ventilation has been reported following small doses of fentanyl. This may be due to varying or decreased stimulation in the postoperative period. Another explanation may be the occurrence of secondary increases in plasma fentanyl concentrations during the elimination phase of metabolic processing, possibly caused by enterorehepatic recirculation, which has been described by some, but not other, investigators.

Reversal of Respiratory Depression

Opioid-induced respiratory depression can be reversed by opioid antagonists, e.g., naloxone. However, recurrence of respiratory depression may occur if the antagonist is shorter acting than the agonist. The analgesic effects also will be reversed by the antagonist.

Extreme caution must be exercised when naloxone is given to reverse the depressant effects of opioids, particularly when these have been administered in high doses. There have been several reports of intense pressor responses occurring when this drug has been used to reverse morphine in animals and humans. Similar responses also have been reported following naloxone administration during enflurane anesthesia. Flacke et al. reported hypertension with severe pulmonary edema and multiple premature atrial contractions immediately after naloxone 0.4 mg iv. Although these cardiovascular responses to naloxone may be explained partly by reversal of analgesia, this cannot be the complete explanation. In one experiment, dogs anesthetized with halothane and nitrous oxide not undergoing surgery were given morphine 2 mg/kg. When naloxone (15 μg/kg) was given 45 min later, tachycardia, hypertension, and 60% increases in coronary artery blood flow and myocardial oxygen consumption occurred. The enflurane-anesthetized patients reported by Azar et al. also were pain free after naloxone was administered. These authors suggest that naloxone causes release of catecholamines when administered after opioids. Whatever the explanation, these effects potentially are extremely dangerous, especially in patients with coronary artery disease. Therefore, we strongly recommend that opioid antagonists be used with caution (increments of 50–100 μg when using naloxone) or not at all to reverse the respiratory effects of high doses of opioids in patients with cardiovascular disease. We are less strongly opposed to the use of opioid antagonists when cardiovascular disease is not present. Indeed,
there may be a place for administration of naloxone to enable neurologic assessment, e.g., after neurosurgery with large doses of opioids when brain damage is suspected and neurologic assessment may dictate treatment. However, the risk of severe hypertension must be balanced against the advantages of rapid recovery when naloxone is used after large doses of any opioid in all patients.

**MUSCLE RIGIDITY**

Problems with muscular rigidity associated with the use of opioids during anesthesia first were reported by Hamilton and Cullen in 1953 but did not gain wide spread attention among anesthesiologists until the introduction of neuroleptanalgesia. Corssen et al. reported an 80% incidence of some rigidity in patients receiving droperidol and fentanyl. Grell, Koons, and Denson found that single intravenous doses of fentanyl (0.5–0.8 mg) consistently produced chest wall rigidity within 60–90 s of administration.

Opioid-induced rigidity is characterized by increased muscle tone progressing to severe stiffness, particularly in the thoracic and abdominal muscles. If it occurs, rigidity usually begins just as the patient is losing consciousness, however, it can be present and felt by conscious patients. Rigidity of the thoracic muscles, so-called “wooden chest,” can cause severe difficulties with ventilation in the nonparalyzed anesthetized patient. While a well-controlled study evaluating numerous rates of infusion of fentanyl or any other opioid on the incidence of chest wall (truncal) rigidity has not been performed, analysis of numerous studies suggests that rapid or bolus injection increases the severity.

Rigidity is also more common in older patients (>60 years) when dosage is high or when nitrous oxide is used together with narcotic analgesic compounds. The exact mechanism by which opioids cause muscle rigidity is not clearly understood but probably is related to the catatonic state that all of them can induce. Muscle rigidity is not due to a direct action on muscle fibers, since it can be decreased or prevented by pretreatment or concomitant use of neuromuscular blocking drugs. Interestingly, small doses of diazepam (0.1 mg/kg) potentiate the effects of small (pretreatment) doses of pancuronium (0.022 mg/kg) as an inhibitor of opioid-induced chest wall rigidity. A recent study demonstrated that equipotent doses of metocurine were more effective than pancuronium in both attenuating and abating rigidity, suggesting that neuromuscular blocking agents acting on prejunctional receptors should be more effective at minimizing rigidity than those acting on postjunctional receptors. Chest wall rigidity also has been reported after emergence (during recovery from) anesthesia but is likely a rare occurrence. Opioid-induced muscle rigidity is not associated with increases in creatinine phosphokinase, suggesting that little or no muscle damage occurs during this period. Opioids do not have significant effects on nerve conduction and result in only minimal depression of monosynaptic spinal reflexes associated with muscle stretch receptors. Most evidence suggests rigidity is the result of stimulation at a single central nervous system site, possibly the caudate nucleus and is related to enhanced dopamine biosynthesis. Morphine-induced catatonia in rats has been ascribed to activation of extensor alpha motor neurons.

**AWARENESS**

In addition to the cardiovascular, respiratory, and neuromuscular problems mentioned above, one of the most serious drawbacks of morphine and other types of opioid anesthesia is a high incidence of inadequate anesthesia. Inadequate anesthesia is defined as signs and symptoms (sweating, pupillary dilation, wrinkling of the forehead, opening of eyes) of incomplete anesthesia and, most important, awareness or incomplete amnesia during anesthesia and/or operation. Some clinicians consider the above signs and symptoms of inadequate anesthesia unreliable. However, in our experience these signs appear to be quite reliable, especially if they are observed repeatedly in the same patient. In addition, we talk softly to patients during surgery in an attempt to elicit changes in these signs and symptoms. Recent work in wild animals suggests that suppression of the ability to hear requires larger doses of opioids than suppression of pain, tactile sensation, or motor function.

The relationship of narcotic analgesia dosage, central nervous system opiate receptor occupancy, and ablation of consciousness and awareness is unknown in humans. However, in a recent study, Stanley and colleagues demonstrated that increasing doses of lofenatran, an extremely potent (5,000 × morphine) long-acting narcotic analgesic, produce increasing analgesia, then anesthesia and eventually complete opiate receptor occupancy in rats. Analgesia occurred with doses of lofenatran that resulted in levels of central nervous system (CNS)-opiate-receptor binding too low to be measured and anesthesia with doses of lofenatran that produced occupancy of 25% of the available opiate receptors in the brain and spinal cord. Eight times the anesthetic dose was needed to saturate virtually all available CNS opiate receptors. While it is difficult to apply these findings in rats to humans, the results suggest a critical dosage is necessary to saturate a certain percentage of CNS opiate receptors and that once this percentage, or more, of the
receptors are occupied, anesthesia will be present. The critical dosage and receptor binding seem to vary somewhat in specific individuals; however, with 25–30% or more of CNS opiate receptors bound with lofentanil, all rats always were anesthetized.

The incidence of awareness during morphine anesthesia cannot be assessed from the literature, as reports of awareness and inadequate anesthesia are mainly anecdotal. However, awareness seems to occur more commonly in patients undergoing coronary artery surgery, especially in patients who do not have a history of congestive heart failure. In the relatively healthy patient, much larger doses of morphine are required to abolish awareness and to produce adequate surgical anesthesia. Doses of up to 11 mg/kg of morphine have been required in certain populations. Wong et al. found that morphine (2 mg/kg) given to healthy, unpremedicated volunteers did not reliably produce amnesia or unconsciousness, which was achieved only by the addition of 70% nitrous oxide.

One factor that may contribute to awareness immediately after induction of anesthesia with morphine is the prolonged induction time required when the alkaloid is used alone. This probably is related to morphine's low lipid solubility. Although the technique can be modified by preceding morphine with a barbiturate, this usually is associated with cardiovascular depression.

Awareness and inadequate anesthesia has been less of a problem when high doses of fentanyl are used. Even a small dose of fentanyl (5–10 µg/kg) can affect patient awareness. However, patient requirements for fentanyl vary greatly, and probably for all opioids, vary a great deal, and signs and symptoms suggesting that depth of anesthesia is marginal and additional opioid is needed may be subtle. When drugs with amnesic properties such as diazepam or scopolamine are omitted, 50% of patients become amnesic to visual stimuli following a dose of 6–7 µg/kg of fentanyl. To date, there are only a few reports in the literature of awareness occurring during operations with high-dose fentanyl anesthesia. In one report, awareness occurred during the second, but not the first, of two fentanyl anesthetics that were 6 days apart. The total doses of fentanyl were similar in both cases (75.8 µg/kg and 72 µg/kg), although diazepam was given during the first and not during the second anesthetic. Another report concerned a 41-year-old woman undergoing an elective mitral valve replacement who was given a total dose of fentanyl of 90 µg/kg. She was aware of sounds and conversation during the period of sternotomy. There is as yet insufficient data to accurately assess the incidence of awareness during fentanyl anesthesia or to draw comparisons between comparable anesthetic doses of morphine.

Supplements

A variety of supplementary drugs have been used in combination with the opioids in an effort to reduce the incidence of awareness, to control hypertension, and, by decreasing and/or limiting the total dose of opioid required, to attenuate the extent of postoperative respiratory depression. Unfortunately, with few exceptions, the use of supplements during high-dose opioid anesthesia results in some loss of cardiovascular stability. The most common supplement used with intravenous opioids is nitrous oxide. Nitrous oxide alone has minimal effects on cardiovascular dynamics, although it does depress myocardial contractile force in dogs. On the other hand, its use in combination with opioids is associated with significant myocardial depression, increases in systemic vascular resistance, and decreases in cardiac output (fig. 8) and blood pressure. This has been a consistent finding in humans and animals with all opioids studied, including morphine, imipramine, and fentanyl. The reason(s) that nitrous oxide should have such cardiovascular depressant effects in the presence of opioids is unknown. Interestingly, cardiovascular depression with N₂O and opioid mixtures appears not to be related to the plasma concentration of the opioid.

In a similar manner, diazepam, which by itself has little cardiovascular effects, decreases myocardial contractility in combination with fentanyl in isolated heart muscle experiments and causes significant depression of arterial blood pressure and cardiac output when given to patients who have received fentanyl (fig. 2) or morphine. Similar interactions also probably will occur with other combinations of opioids and benzodiazepines. Of other intravenous supplements that have been studied, it appears that only scopolamine and droperidol do not produce significant myocardial depression and changes in cardiovascular dynamics when combined with opioids, although droperidol may cause decreases in systemic vascular resistance and arterial blood pressure. The addition of low to moderate concentrations of halothane after large doses of morphine also produces marked cardiovascular depression in patients with coronary artery disease.

Techniques of High-dose Opioid Anesthesia

MORPHINE

In order to minimize the risk of hypotension during induction of anesthesia, morphine often is administered slowly over a minimum of 10–15 min. This is accomplished most easily with the use of a 0.1% solution of morphine in either dextrose (5%) or dextrose–saline at a rate of 5–10 mg/min, with the patient breathing
FIG. 8. Mean values ± SE for mean arterial blood pressure (MAP), heart rate (HR), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and central venous pressure (CVP) when 60% nitrous oxide was added for 10 min and then discontinued and measurements repeated for 10 additional minutes. After this, the incision of the skin was made, and measurements were repeated 2 min later. The 0 (control) values are those obtained 30 min after the start of the morphine infusion. Reprinted from Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine–nitrous oxide in valvular heart disease and coronary artery disease. ANESTHESIOLOGY 38:45–52, 1973, with permission of the publisher.

100% oxygen or oxygen plus N₂O until a satisfactory level of anesthesia occurs.58,40–45 The incidence of hypotension during induction also may be minimized by concurrent administration of a rapid infusion of intravenous fluids42,66 by placing the patient in a slight Trendelenberg position42,66 and/or by pretreatment with histamine (H₁ and H₂) receptor blockers.142

Induction of anesthesia usually requires 1–3 mg/kg of morphine,58,40–45 depending on the patient’s clinical condition, but may require larger amounts, especially in patients with reasonable cardiac reserve.42 Since significant respiratory depression will occur before loss of consciousness in most patients, ventilatory assistance and then controlled ventilation usually is required. Often sedative/hypnotic compounds are added before or during administration of morphine to reduce opioid dosage and insuring amnesia.40,198 Once unconsciousness has been achieved, a muscle relaxant is given, the trachea is intubated, and ventilation continued with either oxygen, an air–oxygen mixture, or nitrous oxide in oxygen.58,41 Careful observation of the patient’s response to laryngoscopy and intubation can provide useful information as to the adequacy of anesthesia. Increases in blood pressure and heart rate, muscle or eyelid movement, and furrowing of the forehead all suggest an inadequate depth of anesthesia and are indications for additional morphine and/or intravenous or inhalation anesthetic supplementation before surgery commences.66,150 Likewise, reactions to surgical stimuli usually can be treated by similar therapies or, if the patient is considered to be adequately anesthetized, with an intravenous (nitroglycerin or sodium nitroprusside) or inhalation (low concentrations of enfurane or isoflurane) vasodilator.306

Similar induction techniques have been used by many clinicians and investigators to obtain anesthesia with fentanyl.58–65,182,184,188 Induction of anesthesia via slow infusion of fentanyl, in contrast to infusion of morphine, usually is begun after a small dose of a nondepolarizing muscle relaxant (pancuronium, 1–1.5 mg, d-tubocurarine, 3–4.5 mg, or metocurine, 1.0–3.5 mg) to minimize or prevent muscle rigidity. Infusion rates of fentanyl generally have ranged from 200–400 µg/min,58,182,188,189 but the rationale for and techniques of preoperative patient preparation, premedication, anesthetic supplementation during induction and maintenance periods, determination of unconsciousness (anesthesia), muscle relaxants and doses used for endotracheal intubation, and the remainder of the operation and total doses of fentanyl have varied enormously.58,50,65,66,148,184,188,189,204,207–210 Many of these differences may be attributed to the question (debate) whether fentanyl should be considered an anesthetic.207–210 Similar questions
were raised more than a decade ago, when high doses
of morphine were popular. Unfortunately, these ques-
tions are, as yet, incompletely answered, and it is likely
that the debate and enormous variety of methods of
using fentanyl for complete anesthesia or as an analgesic
supplement will continue.

Some clinicians felt it is quicker, easier, and more
rational to infuse a single large, precalculated bolus dose
of fentanyl (50–100 \(\mu g/kg\)), usually with a large bolus
dose of pancuronium (0.1–0.12 mg/kg, to minimize
fentanyl-induced bradycardia) for both induction and
maintenance of anesthesia.\textsuperscript{67–71,74,102–154} Following
this, ventilation is controlled, the trachea intubated,
and, within moments, the patient is ready for surgical
preparation. Variations on the “bolus” technique are as
numerous as the slower “infusion” approach of using
fentanyl, undoubtedly for the same reasons.

The New Opioids

**AGONIST OPIOIDS**

Two new synthetic fentanyl derivatives now are under-
going clinical investigation as anesthetics and analgesic
supplements. They may prove to have certain advantages
over the currently available compounds in some situations.

**SUFTANIL**

Sufentanil is an N-4 substituted derivative of fentanyl
(fig. 9). Its chemistry first was described in 1976.\textsuperscript{212}
Animal experiments have shown it to be extremely
potent; in the tail-withdrawal reflex of rats, it is 4,521,
times as potent as morphine.\textsuperscript{213} It is also very safe; the
LD\textsubscript{50} /ED\textsubscript{50} ratio in rats is 25,111 (morphine = 69 and
fentanyl = 277).\textsuperscript{214} Dogs have survived doses of 5 mg/
kg intravenously without respiratory assistance and with
complete recovery after 24 h. Infusions of very high
doses of sufentanil (40 \(\mu g/kg/min\)) in atropinized, me-
chanically ventilated dogs produce very little change in
cardiovascular dynamics.\textsuperscript{55} In Sprague–Dawley rats su-
fentanil is capable of decreasing the MAC of halothane
by more than 90% at an infusion rate of 1
\(\mu g \cdot kg^{-1} \cdot min^{-1}\).\textsuperscript{28} These data may indicate an important
difference between sufentanil and fentanyl, as the latter
is only capable of reducing the MAC of enfurane a
maximum of 65% after a loading dose of 270 \(\mu g/kg\)
followed by an infusion of 3.2 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) in dogs.\textsuperscript{214}
However, the validity of comparing these studies (in
different species with different inhalation agents) may
be debatable. Furthermore, the significance of MAC
reduction of inhalation agents by opioids in animals
other than subhuman primates and humans is open to
question because of the marked differences (decrease)
in sensitivity of dogs, rats, and virtually all other mammals
to most, if not all, narcotic analgesics when compared
with humans.\textsuperscript{38,56,59,109,123,124,197,214,215}

Clinical experience in humans using sufentanil alone
and in supplemented balanced anesthesia suggests that
sufentanil is five to 10 times as potent as fentanyl and
that doses up to 10 \(\mu g/kg\) produce little change in
cardiovascular dynamics.\textsuperscript{215–217} In a study comparing
the effects of sufentanil \((0.7 \mu g/kg)\) with fentanyl \((7 \mu g/kg)\) on general and coronary hemodynamics, no
differences could be detected between the two drugs.\textsuperscript{218}
No differences in cardiovascular or hormonal effects
could be detected between sufentanil \(2 \mu g/kg\) or fentanyl
\(20 \mu g/kg\) as an anesthetic supplement during hysterecto-
my.\textsuperscript{219} On the other hand, Van de Walle and collegues\textsuperscript{210}
compared sufentanil \((0.8 \mu g \cdot kg^{-1} \cdot h^{-1})\) with
fentanyl \((7.15 \mu g \cdot kg^{-1} \cdot h^{-1})\) as anesthetic supplements
and found that sufentanil provided greater cardiovascular
stability. A recent study by Flacke et al.\textsuperscript{211} confirmed
these findings in a double-blind evaluation of meperidine,
morphine, fentanyl, and sufentanil employed in a nitrous
oxide–narcotic technique for general or orthopedic
operations.
The pharmacokinetics of sufentanil have been studied in surgical patients. They are essentially similar to those described for fentanyl, except that the terminal elimination half-life ($T_{1/2\beta}$) is shorter (149 min) compared with the values reported for fentanyl, which vary between 219 min and 495 min. This difference should result in a shorter duration of action for sufentanil, particularly where high doses or repeated doses are being used. However, studies comparing anesthetic doses of sufentanil with comparable doses of fentanyl in patients undergoing coronary artery surgery have not demonstrated any clinically significant differences in recovery from anesthesia or time to extubation.

Because very large doses of sufentanil produce minimal hemodynamic changes in dogs, sufentanil has been suggested as an alternative opioid anesthetic to fentanyl. Some studies now have been carried out evaluating this agent as a complete anesthetic. Sufentanil 15 μg/kg, with air/O2 as an anesthetic for cardiac surgery, produced no significant changes in cardiovascular dynamics. There was also a lesser incidence of hypertension related to sternotomy (10% of patients required vasodilator therapy) using sufentanil 15 μg/kg than fentanyl 70 μg/kg (50% required vasodilators). In a study comparing fentanyl (mean total dose 122 μg/kg), with sufentanil (mean total dose 12.9 μg/kg) a similar reduction in intraoperative hypertension was found with the newer opioid. In addition, speed of induction was faster with sufentanil. In contrast, Fossum et al., in a double-blind comparison with fentanyl, found that sufentanil did not provide better "hemodynamic stability" in patients undergoing coronary artery surgery. Despite the use of as much as 30 μg/kg of sufentanil (equivalent to between 150–300 μg/kg of fentanyl), most patients receiving both opioids had hypertensive responses to sternotomy and/or aortic manipulation requiring supplemental inhalation anesthesia or vasodilator therapy.

The electroencephalographic responses to sufentanil anesthesia consist of high-voltage slow delta waves and are indistinguishable from those described for fentanyl. This is in keeping with the similar pharmacologic profiles of the two compounds. There is as yet little information available as to the hormonal and substrate responses to sufentanil anesthesia, but it appears that sufentanil blocks some hormonal "stress" responses (e.g., antidiuretic hormone) during cardiac surgery, including cardiopulmonary bypass. During cardiopulmonary bypass, however, large increases in plasma catecholamine concentrations occur similar to those described during fentanyl anesthesia.

Investigations of the peripheral circulation and central hemodynamics following sufentanil and morphine anesthesia in dogs have shown that peripheral infusion was better maintained with sufentanil and unaltered by beta blockade. In addition, central hemodynamics were more stable following sufentanil than morphine. Thus, sufentanil has certain advantages over morphine, but no comparisons were made with fentanyl in these studies.

**ALFENTANIL**

Alfentanil is a less potent, shorter-acting drug than fentanyl. Its chemical structure is shown in figure 9. In the tail-withdrawl test in rats, it is approximately one-fourth to one-third as potent as fentanyl and has one-third the duration or action, with a safety ratio (LD$_{50}$/ED$_{10}$) of 1,080. Hemodynamic studies in ventilated dogs show that the acute toxicity of alfentanil is between that of morphine and fentanyl and that myocardial function and cardiovascular dynamics remain little changed at low doses (160 μg/kg). At doses of 5 mg/kg, alfentanil results in transient cardiac stimulation (increases in left ventricular contractility, aortic blood flow velocity, and acceleration). At this dose (5 mg/kg), peripheral and pulmonary vascular resistances also were increased, as was heart rate and cardiac output. DeBrujin and colleagues also found evidence of transient increases in myocardial contractility in dogs, but at lower doses of alfentanil (200 μg/kg). The pharmacokinetics of alfentanil have been studied in doses of 50 and 125 μg/kg in surgical patients. Plasma concentrations declined triexponentially with a shorter elimination half-life than that of related compounds ($T_{1/2\beta} = 87$ min). The rapid elimination and short duration of the clinical action of alfentanil suggest that it would be suitable for repeated administration or administration by continuous infusion.

The respiratory effects of alfentanil have been compared with fentanyl in rabbits. Alfentanil has an earlier peak effect and shorter duration of action than fentanyl, but otherwise the respiratory effects of the two drugs are similar. In human volunteers, small doses of alfentanil (1.6–6.4 μg/kg) produced transient depression of ventilation, with no change in mean ventilatory response to carbon dioxide demonstrable 30 min after injection.

Small doses of alfentanil (0.8–1.0 mg) have been used for anesthetic supplementation for minor surgery in spontaneously breathing patients and (0.05 mg/kg) during balanced anesthesia for laparoscopic surgery. Anesthesia was described as adequate (no movement or evidence of awareness); heart rate and arterial blood pressure remained unchanged; and recovery was fast, but there was a high incidence of side effects: movement, apnea, difficulty in assisting ventilation, and nausea and vomiting in the patients having minor surgery.

Alfentanil has been compared with fentanyl in patients...
undergoing short outpatient procedures with \( \text{N}_2\text{O} \). The authors found that alfentanil was superior to fentanyl (with respect to speed of postoperative recovery), whether administered via bolus or continuous infusion technique, and continuous infusion of alfentanil resulted in the fastest postoperative recovery. In patients undergoing longer operations (1.5–2.5 h) with \( \text{N}_2\text{O} \)-alfentanil or \( \text{N}_2\text{O} \)-fentanyl anesthesia in which both opioids were given in small equianalgesic bolus injections throughout operation, recovery was significantly slower in patients getting alfentanil. These data suggest that frequent bolus administration of alfentanil for longer operations may result in accumulation of the drug. Furthermore, they raise a question of whether the compound has advantages over fentanyl for other than short operations. A study comparing fentanyl and alfentanil administered as a continuous infusion for longer operations might be valuable in settling this question. However, Shafer and co-workers suggest that determining ideal infusion rates for alfentanil may not be easy, since clearance of the drug may vary as much as five-fold, depending on the site of the operation and perhaps other factors as well.

Alfentanil (35–150 \( \mu \text{g} / \text{kg} \)) also has been investigated as an anesthetic induction agent in patients with and without significant cardiac disease. Induction time was fast, 45–140 s, and cardiovascular variables, including heart rate, systemic and pulmonary arterial blood pressures, and cardiac output, minimally changed throughout the induction sequence, even after endotracheal intubation. In addition, when anesthetic induction was followed by halothane (0.2–1.0%) and nitrous oxide (60%), all patients were extubated on the operating room table and were responding to verbal command upon entrance to the recovery room. No patient demonstrated evidence of postoperative respiratory depression at any time in the postoperative recovery period. The only problem noted in this study was a high incidence of chest wall rigidity. Similar findings, little change in heart rate, and blood pressure and a rapid recovery following anesthetic induction and endotracheal intubation have been reported by Black et al. However, Moldenhauer et al. found that alfentanil sometimes result in significant hypotension when used as an induction agent with succinylcholine in ASA class II–IV patients. It appears more experience is necessary before the value, if any, of alfentanil as an induction agent is established.

Alfentanil also has been compared with fentanyl for the treatment of postoperative pain using an on-demand analgesia computer. Both drugs produced good pain relief. The mean rate of infusion of fentanyl was 0.88 \( \mu \text{g} / \text{min} \) and of alfentanil 8.1 \( \mu \text{g} / \text{min} \), a ratio of 1:9.2, which correlates well with the estimated ratios of potency (3:1) and duration of action (3:1).

Alfentanil–oxygen anesthesia has been evaluated for patients undergoing coronary artery surgery. Frequent bolus doses were used to keep the patients adequately anesthetized during surgery, with a mean total dose requirement of 1.22 mg/kg. This technique resulted in shorter induction and recovery times than with fentanyl. However, a high incidence of hypertension during surgery was observed. It would seem more appropriate to administer alfentanil by continuous infusion as a complete anesthetic. Initial experience using doses of the order of 50 \( \mu \text{g} / \text{kg} \) for induction, then infusing approximately 8 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \) during cardiac surgery has produced encouraging results. In this study, de Lange and de Bruijn showed that alfentanil infused at a continuous but variable rate was far superior to alfentanil given as multiple boluses, in terms of prevention of hemodynamic stimulation (hypertension and tachycardia) or depression (hypotension), and in hastening recovery in patients coronary artery surgery. Indeed, these authors, having experience with multiple high-dose fentanyl and sufentanil techniques as well as extensive clinical experience with alfentanil for all types of cardiac surgery, feel that alfentanil given via a continuous but variable infusion is the ideal opioid anesthetic for patients undergoing coronary artery surgery.

Alfentanil is a short-acting opioid analgesic that probably will occupy a unique place as an analgesic supplement for short operative procedures. It is potentially useful as an anesthetic induction agent and for longer operations either as a supplement or as a complete anesthetic if given by continuous intravenous infusion.

**Summary**

In this article, an attempt has been made to review the use of receptor stimulating pure agonist opioids in anesthesia, especially in patients with cardiovascular disease. Particular emphasis has been placed on the use of opioids in high doses to produce anesthesia, techniques that recently have become popular in cardiovascular anesthesia. A major benefit of opioid anesthesia is the cardiovascular stability obtained during induction and throughout operation, even in patients with severely impaired cardiac function. There is a considerable body of evidence to support this claim when fentanyl is used. Anesthetic doses of morphine are associated with a higher incidence of cardiovascular disturbances and other problems, and, therefore, more attention to detail is required in order to achieve adequate anesthesia and hemodynamic stability. Although other opioids have been used as sole or principal agents in anesthesia for cardiovascular surgery, none have gained widespread acceptance. Meperidine, for example, which is widely used in lower (nonanesthetic) doses as a supplement to
nitrous oxide in cardiac and noncardiac surgery, has proved unsuitable because of severe hemodynamic disturbances when high doses are given. However, initial reports concerning two of the newer agonist opioids, sufentanil and alfentanil, suggest that they may prove to be suitable alternatives and perhaps provide advantages over morphine and fentanyl in patients with or without cardiovascular disease.

Although cardiovascular stability usually can be assured in the chronically sick cardiac patient with opioid anesthesia, this is not always so with the healthier patient, particularly those presenting for coronary artery surgery. A frequently occurring problem in these patients is hypertension during or after sternotomy, which can result in myocardial ischemia and infarction. The incidence of severe hypertension (increases in systolic blood pressure greater than 20% of control values) can be reduced drastically by increasing the dose of opioid, e.g., up to 140 μg/kg of fentanyl. However, despite such large doses, some patients will continue to need treatment with vasodilators, inhalation anesthetics, or other supplements at certain periods during cardiovascular operations. The use of very large doses of opioids also will prolong postoperative respiratory depression.

High doses of opioids can reduce or prevent the hormonal and metabolic responses to the stress of surgery. However, even very large doses of fentanyl or its newer analogues do not prevent marked increases in plasma catecholamine concentrations in response to cardiopulmonary bypass. Nor does it appear that the reduction in the hormonal and metabolic stress response is continued during the postoperative period. While it is believed by many that a reduction in hormonal and metabolic responses to surgery is of benefit to the patient, this claim is based largely on theoretic arguments and needs to be documented.

The use of opioids in very high doses is associated with a number of side effects and/or disadvantages. Prolonged respiratory depression is an inevitable consequence of these techniques. However, in many patients recovering from open heart surgery, this may be an advantage, as early postoperative mechanical ventilation is considered desirable. Increased muscle rigidity is a well-recognized side effect of opioids and can be severe when higher doses are infused rapidly intravenously.

The increased interest in opioids in anesthesia has raised numerous questions, only a few of which can be answered at the present time. There is still very limited information as to the neurophysiologic state produced by large doses of opioid angesics. Are these agents really capable of producing an "anesthetic state"? Opioid angesics produce anesthesia with minimal myocardial depression, but are they better than conventional inhalation agents? There is no information comparing morbidity/mortality of opioid with nonopioid anesthesia. However, there has been no proven organ toxicity related to the administration of opioid angesics, and there are no problems of atmosphere pollution and scavenging related to opioid administration. Is suppression of hormonal responses to anesthesia and surgery of any long-lasting clinical benefit to the patient? These, and others, are fundamental questions that remain to be answered.

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