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Narcotic "Anesthesia" in the Eighties

WHILE OPIATES were given small scale trials as primary anesthetics as long ago as the beginning of this century, large scale application for this purpose awaited the late nineteen sixties.[1] One decade ago, we summarized some insights concerning narcotic "anesthesia", along with attributes, reservations, and shortcomings.[2] In the intervening period, an enormous amount of experience and knowledge has been gained, but the area is neither stagnant nor clear, as exemplified by the articles on high-dose fentanyl "anesthesia" by Sebel *et al.*[3] and Waller *et al.*[4] in this issue of ANESTHESIOLOGY, and numerous other recent articles and abstracts.

Perhaps every anesthetist has in mind a different set of attributes which would compose an ideal anesthetic drug. Certainly such a list would include lack of permanent organ toxicity, hemodynamic stability, a single dose regimen, reliable analgesia and amnesia, smooth conduct into the postoperative period, and lack of adverse interaction with other drugs. It has also recently been proposed that favorably influencing the metabolic stress response may be desirable.[5] Muscle relaxation, formerly a prerequisite, may now be relegated to a supplementary role.

Intravenous morphine, 1–3 mg/kg, was first employed in patients with severe valvular heart disease because it provided hemodynamic stability and allowed retention of an endotracheal tube into the postoperative period, in addition to virtually always producing profound analgesia. Incomplete amnesia, with awareness and subsequent psychic disturbances, was sometimes noted. Cardiovascular depression with addition of nitrous oxide,* hypotension associated with induction, and hypertension and tachycardia in response to surgical stimulation were also observed. Morphine "anesthesia" appeared to be less satisfactory in patients with ischemic heart disease than in those with valvular heart disease.[2] Thus, it became clear that although this was a very useful technique, the anesthetist's Nirvana had not yet been attained.

Matters might well have remained in this state were it not for the observations of Stanley *et al.* that doses of morphine greater than 3 mg/kg, though associated with an excessive requirement for blood, were capable of attenuating both hemodynamic and catecholamine response to surgical stimulation,[6] and George *et al.* who demonstrated that cortisol and growth hormone liberation also were blocked.[7] Experimental work led to a proposal that fentanyl might be more suitable than morphine as a primary anesthetic drug,[8] since even in doses comparable to 7–10 mg/kg of morphine, fentanyl did not incur the excessive volume requirement. Other work indicated that both in patients with valvular and ischemic heart disease, 75 μg/kg fentanyl was associated with maintenance of circulatory homeostasis despite anesthetic and surgical stimulation, attenuation of stress hormone response, a low incidence of chest wall rigidity, and resumption of respiratory adequacy in a similar time frame.[9,10] These observations have not been universally confirmed. For example, the two articles in this issue present a totally different picture of the hemodynamic consequences of similar doses of fentanyl. The reasons for the contradictory data are not immediately obvious, particularly with respect to the circulatory response to induction and surgical stimulation, and to chest wall rigidity.

A principle that may prove useful as a frame of reference is that *similarities between opiates are greater than differences.* To expect each new opiate to have dramatically different characteristics has been, and

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* Martin WE, Hornbein TF, Freund FG, et al: Cardiovascular effects of morphine–O_2 and morphine–N_2O in man. Abstracts of Scientific Papers, American Society of Anesthesiologists, 1970, pp. 127–128.

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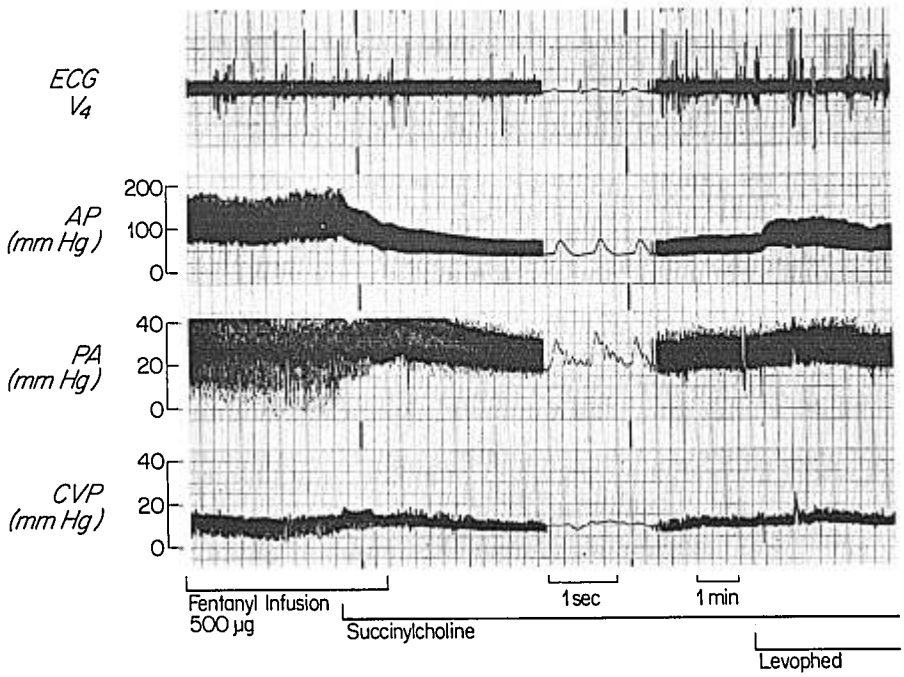

FIG. 1. Hemodynamic response of a patient with severe three vessel coronary artery disease to infusion of 500 µg fentanyl over 5 min. Norepinephrine restored arterial blood pressure to acceptable levels. AP, systemic arterial pressure; PA, pulmonary artery pressure; CVP, central venous pressure.

will almost certainly continue to be, unrealistic. Thus, it is not evident why opiate receptor occupancy by any one drug should provide reliable amnesia when a number of other opiates do not. Similarly, since nitrous oxide administered in the presence of morphine causes cardiovascular depression, we should not be surprised when the same proves true of other drugs of this category.

Issues which are of great interest include the EEG response and its relationship to unconsciousness, amnesia, and "anesthesia"; chest wall rigidity; hemodynamic response including that to induction, to anesthetic adjuvants, and to surgical stimulation; metabolic response and histamine release. While other issues are also important, we shall not discuss them here.

Sebel *et al.* showed that the EEG response of premedicated patients to 50–70 µg/kg fentanyl administered over a two minute period along with pancuronium produces predictable EEG changes, which are associated with a lack of response to surgical stimulation for the duration of a cardiac surgical procedure.[3] Lightening of the EEG level was observed in the only patient studied who required supplementation on clinical grounds. This patient was one of ten who received only 30 µg/kg fentanyl. The implication from their data that the EEG level may provide a reliable tool for judging depth of opiate "anesthesia" is an exciting prospect that deserves further study.

Profound analgesia is produced by large intravenous doses of opiates. Amnesia, however, is clearly not reliably provided by morphine or fentanyl. Awareness has been reported following fentanyl, 72 µg/kg and 90 µg/kg, despite premedication with morphine by itself,[11] or morphine plus scopolamine.[12] Whether the ability to administer a relatively higher dose of fentanyl than morphine yields a higher incidence of amnesia remains unanswered. At present it appears prudent to employ drugs other than narcotics to minimize the incidence of awareness.

A high frequency of chest wall rigidity—approaching 100 per cent—may be expected if muscle relaxant administration does not accompany fentanyl.[4,13] A slow rate of administration does not assure avoidance of this annoying and potentially hazardous phenomenon. Though Stanley pretreated his patients with 1 mg of pancuronium to avoid succinylcholine-induced muscle fasciculations, this fact was inadvertently omitted from the description of the method.† This may account for some of the contradictory data and has been a major source of confusion.

Bradycardia has been described for many years as an effect of fentanyl, but has not been prominent in the reports of high-dose administration. Whether this absence reflects pretreatment with, or simultaneous administration of pancuronium, differences in premedication, presence *vs.* absence of beta-adrenergic blockade, or mere under reporting, is not clear. We have observed episodes of severe bradycardia within one minute of starting fentanyl in-

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fusion at a rate of 200 μg/min in beta-blocked, morphine-scopolamine premedicated patients.

Nevertheless, hemodynamic response to induction is most often benign. However, the ideal rate of infusion and total dose are still undefined. Attenuation of the response to noxious anesthetic and surgical stimulation has been less predictable. The reasons for the variability of response are as yet unclear, and desperately need definition. In the series of Waller *et al.*, eight of twelve patients required supplemental anesthesia.[4] A higher dose was required in Leiden than in Salt Lake City,[14] though not by Sebel *et al.* in Amsterdam! Whether an opiate can reliably ablate the hemodynamic response to surgical stimulation at an acceptable cost still requires substantiation.

Anesthetic adjuvants, such as nitrous oxide, change the character of the benign circulatory reponse to fentanyl.[15] This property must be taken into account whenever this regimen is considered.

Attenuation of the metabolic response to trauma appears intuitively to be advantageous.[16] Does high-dose fentanyl merely delay the onset until the postoperative period, or does it avoid it altogether? Will this result in lowered morbidity and mortality? The relevance of this property needs documentation.

A major pharmacologic difference between morphine and fentanyl is that the latter does not appear to release histamine.[17] This may account for a low incidence of induction hypotension and a lesser volume requirement as compared to comparable morphine doses. However, morphine has, in addition, direct and centrally mediated mechanisms for systemic vasodilation.[18] Will the same prove true for fentanyl, and will this be particularly manifest in patients dependent upon sympathetic outflow for circulatory stability (fig. 1)?

Other opiates, both old and new, are under scrutiny as "anesthetics". Hallowell has employed methadone as an alternative to morphine for a decade.‡ Congeners of fentanyl as well as agonist-antagonist opiates are becoming increasingly available. Narcotics constitute a powerful tool in the armamentarium of anesthetistis. Their role may be expected to continue to evolve. Whether they will provide an ideal drug remains a matter of conjecture. If the 1980s yield as much progress as the 1970s, however, the future of narcotic "anesthesia" looks promising indeed.

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