Alleviation of Prolonged Postoperative Central Nervous System Depression after Treatment with Naloxone

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Residual narcosis following anesthesia using nitrous oxide–narcotic–relaxant is a known complication and, when caused by an overdose of narcotic, is usually readily reversed by a narcotic antagonist. Such residual narcosis, even when it is not reversed with a narcotic antagonist, resolves in several hours, the time course usually being proportional to the rate of elimination of the drug. We report here two cases of inexplicably prolonged recovery from nitrous oxide–morphine–d-tubocurarine anesthesia lasting several days, which was repeatedly, but only transiently, reversed by naloxone.

REPORT OF TWO CASES

Patient 1. A previously healthy 57-year-old white man with a 20-year history of hypertension was admitted to the hospital with a tentative diagnosis of subarachnoid hemorrhage. Pertinent physical findings included blood pressure 150/100 mm Hg, pulse rate 130/min, and temperature 39.5°C. Meningismus was present. Positive neurologic findings included gait preference to the right.

Shortly after admission the patient had a right focal motor seizure. A computerized axial tomography scan later that day revealed a suprasellar mass with probable hemorrhage. An arteriogram revealed a suprasellar mass with elevation of the anterior cerebral arteries. The patient was thought to have pituitary apoplexy.

Over the ensuing two days the moderate lethargy present on admission lessened, and a bitemporal hemianopia developed. The patient's medical condition was stable, and he was able to undergo evacuation of a hemorrhagic pituitary tumor through a right frontal craniotomy. Anesthesia was induced with thiopental and succinylcholine and maintained with nitrous oxide–morphine–d-tubocurarine. Anesthesia and operation were uneventful except for a transient episode of hypotension during induction. Total dose of morphine used during the six-hour procedure was 28 mg. Postoperatively the patient was still comatose eight hours later with no new localized neurologic findings. Ventilation was assisted. At this time the patient responded to balloon injections of naloxone, 0.2–0.4 mg iv, with increasing blood pressure and agitation, which lasted 10–20 minutes. Twenty-four hours postoperatively the patient remained comatose, unresponsive to painful stimuli. At this time another dose of naloxone, 0.4 mg, was given iv. Within minutes the patient's mental status improved; he not only became responsive to painful stimuli, but was able to follow simple commands. This effect wore off after 15–30 minutes and the patient relapsed into coma. The serum morphine concentration at this time was 5–6 ng/ml, measured by radioimmunoassay. With repeated doses of naloxone, the patient's neurologic status gradually improved during the second postoperative day. His subsequent course was one of gradual improvement and increasing visual acuity. After four weeks of radiotherapy, repeat computerized axial tomography scan revealed no evidence of suprasellar mass.

Patient 2. A 53-year-old white man was admitted to the hospital for an elective left carotid endarterectomy. He had had recurrent episodes of amaurosis fugax in the left eye for two years prior to admission, and two months prior to admission had had a transient paresis of his right arm, which recovered except for a persistent weakness of the hand. Past medical history was significant for hypertension. Arteriogram revealed a plaque at the origin of the left internal carotid artery.

General physical examination on admission was unremarkable. Neurologic examination revealed decreased memory. Motor examination showed slight weakness of the right upper extremity. The EKG showed sinus bradycardia and left axis deviation. Serum cholesterol was 330 mg/dl. Results of other routine laboratory tests were normal.

Anesthesia was induced with thiopental, followed by succinylcholine to facilitate intubation. Anesthesia was maintained with nitrous oxide–morphine (35 mg)–d-tubocurarine (60 mg) for the 3½-hour procedure. A complete occlusion of the left internal carotid artery was opened. At the end of the uneventful operation, neuromuscular blockade was reversed with atropine, 1.0 mg, and neostigmine, 2.5 mg, iv. Naloxone, 0.4 mg, was given iv. This was followed shortly by another 1.0 mg atropine and 2.5 mg neostigmine and 0.2 mg naloxone, with only minimal improvement in the level of consciousness. Two and a half hours postoperatively the patient remained unresponsive to command and to painful stimuli. The pupils were equal and reactive to light, with conjugate gaze. Following iv injection of 1.2 mg naloxone, the respiratory rate increased and the patient responded appropriately to noxious stimuli.

The patient was given five doses of naloxone, 0.4–1.0 mg, iv, at two-hour intervals. His level of consciousness gradually improved during this time to the point where he could follow simple commands. However, nine hours after the last dose of naloxone, he had again progressively lapsed into coma. Repeat angiography showed the left internal carotid artery to be patent. Twenty hours postoperatively, with the patient comatose, a portable ECG showed generalized slowing and asymmetry with lower amplitude on the left side. During the time the EEG was being obtained, the

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respiratory rate was 17/min, and $V_t$ 5.9 l. After obtaining a baseline EEG and these measurements, the patient was given naloxone, 2.0 mg, iv. Almost instantly and for 10 minutes afterward, he became restless and responsive to commands, respiratory rate increased to 20/min, $V_t$ increased to 12.1 l, and the EEG, when the patient was neither being stimulated nor moving, showed a relatively more awake pattern. Representative portions of the EEG record, before and after naloxone administration, are shown in figure 1. Following this, the EEG slowly returned to the previous sleeplike pattern. Several serum samples on the first postoperative day showed free morphine levels ranging from 1 to 15 ng/ml.

The patient's condition gradually improved over the ensuing two weeks, although his course was further complicated by pulmonary embol that necessitated anticoagulation.

**DISCUSSION**

The above two cases are interesting for several reasons. First, each patient received only a modest dose of morphine, one that would not be expected to result in prolonged recovery from anesthesia. Second, the most obvious explanation for such prolonged recovery is that the patients had high serum morphine concentrations resulting from altered metabolism, excretion, or plasma binding. However, we have eliminated this possibility by measuring serum morphine concentrations using a sensitive and specific radioimmunoassay. Berkowitz et al. measured the disposition of morphine in patients and found a mean serum concentration of 20 ng/ml four hours after a parenteral dose of 10 mg/70 kg. These patients showed no obvious sign of residual narcosis. The two patients presented here both had serum morphine concentrations much lower than 20 ng/ml at times when they were unresponsive to noxious stimuli. It would thus appear that the prolonged recoveries reported here were not caused by relative overdoses of morphine, although sequestration of morphine in the brain, which might not be reflected in the measured serum concentrations, cannot be excluded.

The "pure" narcotic antagonists, naloxone and naltrexone, have been shown to antagonize the central nervous system depression caused by a number of drugs structurally unrelated to the narcotics, both in animals and in man. These include diazepam, pentobarbital, and the general anesthetics halothane, enflurane, cyclopropane, and nitrous oxide. In addition, naloxone antagonizes several non-drug-induced states such as the analgesia produced by electrical stimulation of the periaqueductal grey area of the brain in animals and man and by acupuncture. In spite of these interesting findings, naloxone has never been convincingly shown to act as a central nervous system stimulant or analgesic agent. How, then, does one reconcile these seemingly disparate effects of naloxone?

Perhaps the transient improvement seen after naloxone administration in these two patients with central nervous system disease was related to its interaction with the opiate receptor-endorphin system. Mammalian brains are known to contain stereospecific opiate receptors. In addition, brain tissues are also known to contain endorphins, a group of related peptides that have opiate-like effects when administered in vivo and bind to opiate recep-
tors.15,16 These effects are antagonized by naloxone. The physiologic roles of both opiate receptors and endorphins are presently unknown, although a neurotransmitter role has been postulated. If certain drugs, electrical stimulation of brain areas, or even some central nervous system diseases alter the opiate receptor-endorphin system, for example, by increasing endorphin release, then a common mechanism that explains the selective antagonism by naloxone in seemingly unrelated systems exists. The answers to such questions await more detailed knowledge of the function of the opiate receptor-endorphin system.

Any postulated mechanism of arousal caused by naloxone in these two patients remains speculative. However, since the administration of even very large (12–24 mg) doses of naloxone is without adverse effect in man, a trial of therapy with this drug in patients who have depressed levels of consciousness from uncertain causes may be warranted, even in the absence of antecedent narcotic administration.

In summary, we have presented two cases of unexplained prolonged recovery from nitrous oxide-morphine-relaxant anesthesia that could be antagonized by naloxone. Measured serum morphine concentrations were very low, suggesting that naloxone was antagonizing something other than the action of exogenously administered narcotic.

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REFERENCES