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# Naloxone-associated morbidity and mortality

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Naloxone (Narcan) is generally considered to be a narcotic antagonist devoid of pharmacologic activity except for its reversal of opioid (narcotic) effects. Case reports indicate that naloxone in its role of narcotic antagonist may induce hypertension, pulmonary edema, atrial and ventricular arrhythmias, or cardiac arrest in certain patients, particularly those with pre-existing cardiac abnormalities. These adverse effects of naloxone may be due to extreme sympathetic nervous system activity resulting from the reversal of narcotic analgesia, an effect of the drug on peripheral or central opioid receptors or a drug interaction with other anesthetic agents. Any patient given naloxone, particularly in the presence of surgical pain, should be closely monitored for adverse cardiovascular effects.

It is generally accepted that the narcotic antagonist, naloxone (Narcan), is devoid of any therapeutic or toxic effects except in the diagnosis and treatment of the signs and symptoms of opioid (narcotic) overdose and detection of narcotic dependence (the pupillary naloxone test). According to *Facts and Comparisons* (April, 1981): "... in the absence of narcotics or agonistic effects of other narcotic antagonists, naloxone exhibits essentially no pharmacologic activity." The only contraindication to naloxone is allergy, and the drug must be used with extreme caution in opioid-dependent persons and in pregnant women.

Over the past several years, however, a number of reports associating acute hypertension, pulmonary edema, and cardiac arrhythmias with naloxone employed for opioid antagonism have appeared. In two of the reported cases the patients died.

## REVIEW OF THE LITERATURE

In 1974, Tanaka<sup>1</sup> reported severe hypertension (blood pressure of 340/150) and atrial tachycardia in a 51-year-old man with a previous history of mild hypertension, hyperlipidemia, and mild diabetes mellitus who was given naloxone (0.4 mg.) to antagonize the respiratory depressant effects of

morphine-nitrous oxide anesthesia. Also in 1974 Michaelis and associates<sup>2</sup> reported two cases in which patients undergoing open heart surgery for a prosthetic tricuspid valve and aortic graft experienced ventricular fibrillation or tachycardia immediately after intravenous administration of naloxone (0.1 to 0.4 mg.) to reverse morphine anesthesia. Both patients had also received diazepam and nitrous oxide, and one patient had received additional thiopental, halothane, and succinylcholine. In 1977 a 70-year-old man with precordial pain and congestive heart failure, undergoing coronary bypass surgery with the anesthetic combination of morphine, diazepam, prednisolone, and pancuronium, was given intravenous naloxone (0.4 mg.) and immediately developed a blood pressure of 170/100 with concomitant pulmonary edema and left ventricular failure.<sup>3</sup> In 1979 a 73-year-old man with sick sinus syndrome received an epicardial pacemaker under fentanyl, thiopental, succinylcholine, nitrous oxide, and enflurane anesthesia.<sup>4</sup> Postanesthetic respiratory depression was treated with intravenous naloxone (0.4 mg.); subsequently, the blood pressure rose to 270/140 and was associated with numerous atrial premature contractions (APC's). In 1980 Andree<sup>5</sup> reported the deaths of two healthy female patients after administration of naloxone to reverse narcotic respiratory depression. One patient received meperidine, hydroxyzine, atropine, thiopental, succinylcholine, and nitrous oxide and suffered cardiac arrest immediately after intravenous administration

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of naloxone (0.4 mg.). The ventricular fibrillation was unresponsive to defibrillation, epinephrine, and closed-chest cardiac massage. The second patient received diazepam, meperidine, thiopental, succinylcholine, topical lidocaine, halothane, enflurane, nitrous oxide, and curare and experienced respiratory and cardiac arrest after intravenous administration of naloxone (0.2 mg.). Normal sinus rhythm and respiratory rate were eventually restored, but the patient never recovered consciousness and died on the eighth postoperative day.

## DISCUSSION

These reports are most disconcerting to all who have previously considered naloxone to be an innocuous drug except to the opioid addict. Yet a most basic principle of pharmacology dictates that no drug has a single action. It would now appear that naloxone has serious adverse cardiovascular effects in certain patients.

Most of the authors of these case reports attribute the adverse cardiovascular effects of naloxone to a massive endogenous release of catecholamines (epinephrine and norepinephrine) from the adrenal medulla in response to the exacerbation of acute postoperative pain resulting from the abrupt reversal of narcotic analgesia. However, it has been reported<sup>6-8</sup> that naloxone increases pulse rate and left ventricular cardiac work in healthy patients. It is possible that naloxone may displace morphine from central nervous system opioid receptor sites, resulting in a pressor effect from the free narcotic agonist.<sup>9</sup> Other possible explanations for the adverse cardiovascular effects of naloxone may include a previously unknown effect of the drug on peripheral opioid receptors outside the central nervous system or a drug-drug interaction(s) with one or more anesthetic agents.

The majority of these patients had pre-existing heart disease; the young female patients who died did not. It is possible that patients with compromised left ventricular function show adverse effects of pulmonary edema and ventricular fibrillation, while patients with good coronary function respond with atrial fibrillation.<sup>4</sup> It may also be true that these pressor effects of naloxone go undetected in healthy patients, since close cardiovascular monitoring is not routine in such patients.

## SUMMARY AND CONCLUSIONS

It is now apparent that naloxone (Narcan) can no longer be considered an innocuous drug. Several reports have appeared associating adverse cardio-

vascular effects with the use of naloxone as an opioid antagonist. Severe hypertension, cardiac arrhythmias, pulmonary edema, and fatal cardiac arrest have occurred in both healthy and medically compromised patients. These adverse effects may be more severe when naloxone unmasks pain suppressed by morphine and other opioid analgesics and may be dose related.

When naloxone is used to treat narcotic overdose, it would appear prudent to employ as low a dose as possible, monitor the blood pressure for at least 10 minutes after naloxone administration, and have ready access to antihypertensive medication.<sup>4</sup> Nitroprusside would appear to be the safest and most effective agent for the management of hypertensive crisis.<sup>10</sup> This would hold particularly true in patients with pre-existing heart disease and those whose pain is masked by narcotic analgesics. If hypertension should occur, immediate transportation of the patient to a medical facility would appear most advisable.

## REFERENCES

1. Tanaka, G. Y.: Hypertensive Reaction to Naloxone, *J.A.M.A.* **228**: 25-26, 1974.
2. Michaelis, L. L., Hickey, P. R., Clark, T. A., and Dixon, W. M.: Ventricular Irritability Associated With the Use of Naloxone Hydrochloride, *Ann. Thorac. Surg.* **18**: 608-614, 1974.
3. Flacke, J. W., Flacke, W. E., and Williams, G. D.: Acute Pulmonary Edema Following Naloxone Reversal of High-Dose Morphine Anesthesia, *Anesthesiology*. **47**: 376-378, 1977.
4. Azar, I., and Turndorf, H.: Severe Hypertension and Multiple Atrial Premature Contractions Following Naloxone Administration, *Anesth. Analg.* **58**: 524-525, 1979.
5. Andree, R. A.: Sudden Death Following Naloxone Administration, *Anesth. Analg.* **59**: 782-784, 1980.
6. Desmots, J. M., Bohm, G., and Cruderc, E.: Hemodynamic Responses to Low Doses of Naloxone After Narcotic-Nitrous Oxide Anesthesia, *Anesthesiology* **49**: 12-16, 1978.
7. Tigerstedt, I., and Tannisto, T.: Effect of Naloxone Reversal on Carbon Dioxide Output, Oxygen Uptake and Cardiac Index During Recovery From Fentanyl-Supplemented Anesthesia, *Acta Anesthesiol. Scand.* **22**: 158-166, 1978.
8. Huse, K., Hartung, E., and Nadjmabadi, M. H.: The Effects of Naloxone (Narcan) on Circulation and Respiration After Neurolept Anesthesia for Neurosurgical Operations, *Anesthesist* **23**: 493-499, 1974.
9. Freye, E.: Cardiovascular Effects of High Dosage of Fentanyl, Meperidine and Naloxone in Dogs, *Anesth. Analg.* **53**: 40-47, 1974.
10. Cohn, J. N., and Burke, L. P.: Nitroprusside, *Ann. Intern. Med.* **91**: 752, 1979.

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