Morphine-induced Hyperexcitability in Man

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Paradoxical rage or manic or hyperexcitable behavior following the administration of morphine, documented in cats1,2 and rats3-5 has not been reported to occur in man. We describe below a case in which the patient experienced a dramatic stimulatory effect following intravenous administration of morphine during the induction of anesthesia.

REPORT OF A CASE

A 70-year-old, 72-kg man was scheduled for coronary artery bypass grafting for unstable angina. Past medical history included two myocardial infarctions, controlled hypertension, and "allergic" reactions to pentazocine, which resulted in nausea, and to morphine, which was characterized as "it makes me wild." No cardiopulmonary difficulty was associated with these reactions. Medications were nitroglycerin, digoxin, indomethacin, propranolol, hydralazine, hydrochlorothiazide, and orally administered potassium. Preoperative laboratory data were normal.

The day of operation, the patient was premedicated an hour prior to arrival in the operating room with diazepam, 10 mg, p.o., and prochlorperazine, 10 mg, and scopalamine, 0.5 mg, im. Upon arrival in the operating room, he was sedated, yet responsive to commands. After transfer to the operating table, the patient dozed off to sleep, breathing oxygen, 5 l/min, through a disposable plastic mask.

While the patient slept quietly, routine monitors, intravenous catheters, and pulmonary vascular and systemic arterial pressure lines were secured, without any discernible discomfort to him. The induction of anesthesia was formally begun with the patient unstimulated and sleeping, by administering morphine sulfate, 5 mg/ min, iv. After 2 minutes (10 mg morphine), and without any ex-

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response precipitated by morphine in the cat is mediated via central dopaminergic pathways. Thus, when cats are pretreated with a CNS catecholamine depletor (i.e., reserpine or tetrabenazine), or a CNS dopamine receptor blocker (haloperidol or chlorpromazine), morphine does not elicit the rage response. Similarly, jumping behavior in the rat and mouse, a behavior appearing very similar to morphine-induced hyper-excitability, has been shown, at least in part, to be due to increased dopaminergic activity.

It is possible that endogenous opiate receptors are also important in the etiology of the above-mentioned hyperexcitable behavior. The greatest concentrations of naloxone-blockable, β-endorphine-sensitive opiate receptors in man and other animals have been found in the limbic system, amygdaloid complex, hypothalamus, head of the caudate nucleus, periventricular and periaqueductal gray matter, and to a lesser extent, in the frontal cortex. Electrical stimulation of the amygdaloid region of man, the cat, and the monkey elicits behaviors of alert attention, rage and aggression. Therefore, it is at least possible that in cats and rats, morphine effects CNS stimulation via opiate receptors, which in turn stimulate dopaminergic or other arousal-inducing pathways.

Alternatively, morphine may have a direct impact upon receptors not responsive to endogenous ligands such as β-endorphine and not blocked by specific opioid antagonists such as naloxone. Indeed, Jacquet et al. presented evidence that the hyperexcitability and explosive motor behavior seen in rats following intracerebral or periaqueductal morphine administration is due to stimulation of a class of arousal-inducing receptors not stimulated by β-endorphine, not blocked by naloxone, and not stereospecific for morphine.

In man, morphine does not usually cause disinhibition and hyperstimulation. However, it is possible that man has the potential for experiencing behaviors that parallel the hyper-excitability seen in cats and rats. Possibly, as has been postulated to occur in rats, morphine can alter inhibitory and excitatory effects that are in dynamic balance. Thus, man may normally have the potential for hyperexcitability, which is, however, suppressed by the concurrent effects of morphine on behaviorally inhibiting receptors and related neuronal circuits. However, it is possible that, in some individuals, this inhibition may be altered or absent due to a genetic or other mechanism, leading to a net hyperexcitability. In support of this possibility, Jacquet et al. have presented evidence that the hyperresponsiveness of rats following localized periaqueductal administration of morphine is due to a deficit in the stimulation of behaviorally-inhibiting opiate receptors.

The case reported here is important for two reasons. First, it documents the occurrence of a stimulatory effect of morphine in man, and, although the mechanism underlying this phenomenon is speculative, its occurrence may serve as a link, relating animal data to human physiology. Second, and of more practical importance, the description of morphine-induced hyperactivity in man alerts physicians to a new, possibly adverse reaction to morphine.

References

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