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 rats,3-6 has not been reported to occur in man. We describe below a case in which the patient experienced a dramatic stimulating 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 penicillin, 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 scopolamine, 0.5 mg, i.m. 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 external stimulus, the patient abruptly opened his eyes, shook his head once, briefly closed his eyes and then again, as though startled, opened his eyes, flexed his arms, attempted to sit up, and exclaimed clearly and loudly “I am burning all over.” Diazepam, 20 mg, in four equal doses, and morphine, 1 mg/kg, were administered iv over the next 10 minutes, and satisfactory surgical anesthesia was obtained. During this hyperexcitable episode systemic arterial pressure increased from 140/65 to 175/90 mm Hg, pulmonary arterial pressure increased from 24/14 to 30/22 mm Hg, and heart rate increased from 88 to 90 beats/min. These variables returned to preoperative levels when surgical anesthesia was obtained. The operative procedure and postoperative course were uneventful, and the patient was discharged on the ninth postoperative day. Morphine sulfate was avoided as a postoperative analgesic.

Subsequent in-depth interview of the patient and his wife revealed that at the age of 22 years, he had received morphine im as premedication for tonsillectomy, and while being taken to the operating room had become combative and uncontrollable, recalling “I broke the straps on the bed. It (morphine) gave me super-strength.” On another occasion, he had received morphine for anesthesia following a myocardial infarction, and shortly thereafter had again become combative, pulling out his intravenous catheters and hallucinating. Family history revealed that a daughter had had a similar reaction following a preoperative injection of “pain killer.” Additionally, a granddaughter by the patient’s son and a deceased sister were “allergic” to morphine, but characterization of these reactions was not possible.

DISCUSSION

The rage or “manic” phenomenon found in cats following morphine administration1,2 and the hyperexcitability and explosive motor behavior found in rats following intracerebral or periaqueductal gray-matter morphine administration3-5 have been well documented. The mechanism by which these hyper-arousal states occur is uncertain. However, they may in part be mediated by the release of CNS catecholamines.6-8 Among morphine’s many effects on neurotransmitters are increased synthesis and turnover of the CNS catecholamines, dopamine and norepinephrine.6-9 There is evidence that the rage
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.10,11

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, \( \beta \)-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.12 Electrical stimulation of the amygdaloid region of man, the cat, and the monkey elicits behaviors of alert attention, rage and aggression.13–15 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 \( \beta \)-endorphin and not blocked by specific opioid antagonists such as naloxone. Indeed, Jacquet et al.9 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 \( \beta \)-endorphin, 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,9 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.9 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

5. Jacquet YF, Lajtha A: Morphine action at central nervous system sites in the rat, analgesia or hyperalgesia depending on site and dose. Science 182:490–492, 1973