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High-Dose Epidural Morphine in a Terminally Ill Patient

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Intrathecal and epidural opiates have been used successfully in the treatment of pain in patients with terminal cancer.[1-6] We report a case in which a patient who had required large doses of systemic narcotics subsequently received epidural morphine, initially in small doses, and eventually in massive doses administered by constant infusion pump.

REPORT OF A CASE

A 46-year-old woman presented with severe left hip pain, secondary to metastatic cervical cancer, for which she had undergone pelvic exenteration and received radiation and chemotherapy. Daily analgesic therapy consisted of 90 mg methadone, po, 240–280 mg morhine, iv, administered by constant infusion, and morphine elixir, po, as tolerated. Persistent nausea and vomiting almost precluded oral intake. Several antiemetic regimens had been tried unsuccessfully and the patient was receiving 3.5 mg droperidol every two hours. She was somnolent and in considerable pain, particularly when moved.

A epidural catheter was introduced at the L 3–4 interspace and 2.5 mg morphine sulfate‡ in 10 ml of sterile water was injected. Within one hour the patient was pain-free and could be moved from her bed for the first time in several days. Other narcotic therapy was discontinued and droperidol dosage was decreased to 1.25 mg every 4 hours. Analgesia was maintained over the next four days by further epidural injections of morphine at the patient's request or whenever pain was experienced. The dose had to be increased from 2.5–15 mg to sustain analgesia and after day 5, even the latter dose resulted in only a few hours of analgesia (fig. 1). The possibility that the catheter had become displaced prompted us to replace it at a higher interspace, but this did not lead to prolongation of analgesia. To avoid the need for multiple reinjections, a continuous epidural infusion of morphine was commenced, initially at a rate of 1.5 mg/hr and later, 7–10 mg/hr, in order to maintain analgesia. Tachyphylaxis apparently had developed, so that on day 7 an alcohol spinal block was performed, and the epidural catheter was removed. Inadequate analgesia resulted and systemic narcotic therapy was reinstituted. When receiving the highest epidural morphine dose the patient had remained moderately alert, comfortable, and able to converse with her family. However, when the same dose of systemic morphine was substituted, she became increasingly somnolent and again complained of severe pain on movement. Nausea and vomiting also became much more severe with systemic morphine administration, and the droperidol dose was increased, causing further somnolence and dysphoria. At no time did the patient exhibit any signs of narcotic withdrawal. Respiratory rate varied between 16 and 24 breaths/min, even with the highest epidural morphine dosage. The patient did not complain of itching. The presence of urinary retention could not be assessed as the patient had an ileal conduit.

DISCUSSION

This case is of interest for several reasons. First, in spite of an abrupt decrease in total morphine dosage from 330 mg/24 hr to 5 mg/24 hr after epidural morphine was started, no significant signs or symptoms of opiate withdrawal syndrome occurred in this patient. This is in contrast to the report of Tung *et al.*,[5] who noted fever, agitation, vomiting, tachypnea, disorientation, hypertension, and tachycardia under similar circumstances. The reason for this difference in response is not immediately apparent. However, there is wide variation among addicts in sensitivity to narcotic withdrawal and our observation may simply reflect individual differences. A second point of interest relates to the large dose of epidural morphine which our patient received without exhibiting any evidence of respiratory depression. Late respiratory depression has been reported following epidural narcotic administration[7,8] which may result from high morphine levels adjacent to the respiratory center.[9] Although tolerance to morphine might explain why respiratory depression did not occur, that explanation is not consistent with the observation that the patient became more sedated when the same morphine dose that had been administered through the epidural catheter was administered intravenously. This suggests that epidural administration of morphine results in lower concentrations of opiate in the respiratory center than does administration of a similar dose parenterally. Although central nervous system levels would be expected to be higher when the drug is infused epidurally, cephalad spread of morphine to the brain from the spinal cord seems to be limited. The pharmacokinetics of epidurally and intrathecally administered narcotics remain poorly defined, but analgesia in the former circumstance appears to be due to passage of the narcotic across the dura, where it acts on opiate receptors in the spinal cord. Yaksh and Reddy[10] recently refer to unpublished data which confirm that cisternal opiate levels in monkeys are much lower following administration of an intrathecal dose than following a comparable intravenous dose of morphine.

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‡ Winthrop Laboratories; contains sodium biphosphate, sodium metabisulfate, sodium formaldehyde sulfoxylate, and phenol.

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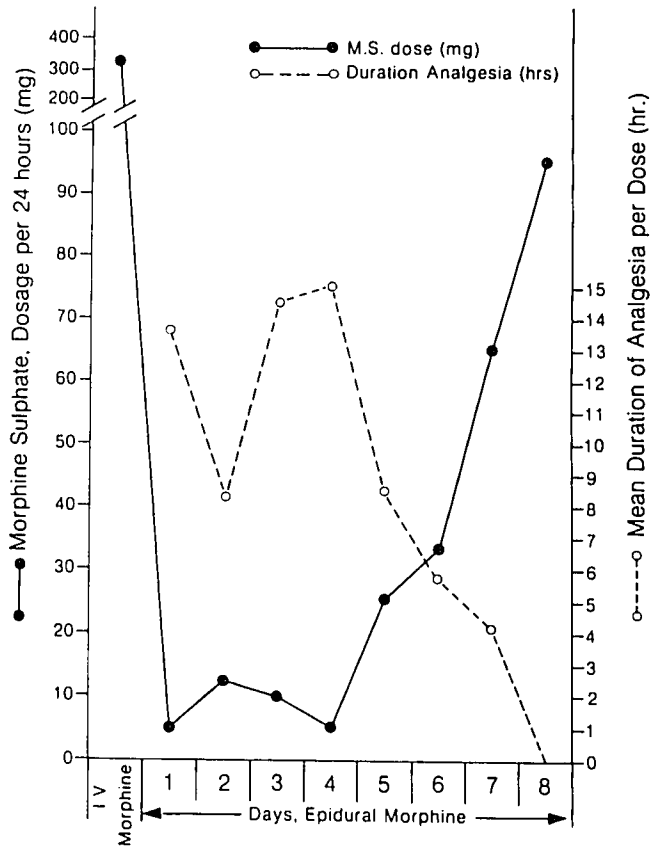

FIG. 1. Dosage of morphine sulfate per 24 hours, and mean duration of analgesia per dose of epidural morphine sulfate.

Binding of the drug at the spinal cord level and slow rostral circulation of cerebrospinal fluid may explain this phenomenon, which should limit respiratory depression with both epidural and intrathecal administration of narcotics.

Finally, the question of tachyphylaxis following epidural morphine administration is of importance if this technique is to be used for chronic pain therapy. Magora *et al.*[4] noted the absence of tachyphylaxis with repeated epidural morphine doses for up to 8 days in chronic pain patients. In contrast, Chayen *et al.*[2] found decreased effectiveness of 2 mg doses of morphine administered via a catheter over a 5-day period. Yaksh and Reddy[10] report tolerance in monkeys to 1.2 mg doses of intrathecal morphine after 5 days, and refer to unpublished data in which tolerance was overcome, at least temporarily, by doubling drug dosage. Our experience supports the latter finding and also demonstrates that tolerance cannot be overcome for more than a short period of time by increasing drug dosage. Of interest, Chayen's group restored analgesic efficacy by administering a single epidural injection of 1 per cent lidocaine whenever tachyphylaxis occurred; adequate analgesia was maintained for three to four weeks until the patient died.[2] We were unaware of his report at the time we cared for our patient or we would have tried to overcome tachyphylaxis in this manner. Yaksh and Reddy[10] were able to overcome tolerance to intrathecal morphine in monkeys, by intrathecal injections of 2 mg clonidine or 60 μg L-baclofen following a 1.2 mg intrathecal dose of morphine. An advantage in using clonidine as opposed to lidocaine or L-baclofen is its absence of sympathetic or motor effects.

The notable absence of somnolence, respiratory depression, or circulatory changes with epidural morphine (combined with periodic restoration of analgesic efficacy with local anesthetic or perhaps clonidine) may facilitate the care of terminally ill patients in pain.

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