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(Accepted for publication December 15, 1988.)

Anesthesiology
70:719, 1989

A Complication Associated with the Use of Midazolam

To the Editor:—We wish to draw attention to an unusual complication apparently associated with the use of intravenous midazolam. A 27-yr-old oriental female required urgent anesthesia for evacuation of retained products of conception following spontaneous delivery of a nonviable 20-week fetus. Prior to anesthesia, the patient was alert, there was no active bleeding, and cardiovascular signs were stable and within normal limits. A spinal anesthetic was performed at the L3–4 interspace with the patient sitting; lidocaine 50 mg in 8.5% dextrose was administered. Five minutes after placing the patient supine, a T-10 block was documented. Midazolam, 1 mg iv, was administered for sedation, followed 5 min later at the commencement of the procedure by an additional 1 mg. Immediately following the second dose, the patient complained of burning at the site of injection, and within minutes experienced a tonic-clonic seizure lasting 1–2 min. This was managed successfully with ventilation *via* mask with 100% oxygen. The patient regained consciousness shortly after termination of seizure activity, and showed no evidence of cardiovascular, respiratory, or central nervous system abnormality. Her postanesthetic recovery progressed normally and the remainder of her hospital stay was unremarkable. Although there was no history of any neurologic problem, a postoperative neurology consult and electroencephalogram were planned. However, the patient failed to report for follow-up. In view of her prior state of good health, the uncomplicated nature of the anesthetic, and the temporal relationship of the seizure to the administration of midazolam, we believe that this complication may have been drug related. Communication with Roche (the drug manufacturer) revealed that a number of other cases of convulsions associated with the use of midazolam have been reported. It is unclear why midazolam, a drug that might be expected to exhibit anticonvulsant activity, should have this effect. We encourage further reports of similar experiences with this agent.

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(Accepted for publication December 23, 1988.)

Anesthesiology
70:719–720, 1989

A Postoperative Pain Management Service

To the Editor:—We would like to comment on the recent exchange of letters discussing the safety of administering epidural opiates outside the Intensive Care Unit.[1,2]

When we first began using epidural opiates for postoperative analgesia, we too were very concerned about the potential risks of delayed respiratory arrest. Between 1983 and 1986, surgical patients receiving epidural opiates were routinely cared for only in our Intensive Care Units. During that 4-yr period, there was no instance of apnea associated with this therapy. Therefore, as a trial, for 1 yr these patients recovered from surgery on a single selected surgical ward staffed by specially trained nurses. No patient suffered significant delayed respiratory depression, and, therefore, starting in January, 1988, patients receiving epidural opiates have been allowed on all surgical wards at Stanford University Medical Center. During this period, our Acute Pain Service has prospectively followed more than 500 of these patients and have not reported a single episode of apnea. Hypoventilation, as evidenced by carbon dioxide retention, although infrequent, does occur. In our patient population, it is always associated with sedation. Like the Seattle group, we have found that apnea monitors are of little value in detecting gradual development of hypercapnia. Because of their insensitivity and high incidence of false alarms, we have discontinued using apnea monitors for otherwise low-risk patients.

Potential risk factors for delayed respiratory depression must be recognized.[3] In this context, several important points must be emphasized.

First, in our opinion, there is no role for epidural morphine when a catheter has been inserted. The single advantage of morphine over the safer, more lipid soluble opiates is its longer duration of action. However, if intermittent bolus or continuous epidural infusion of drug is offered, agents such as fentanyl or hydromorphone should be used.

Second, another risk factor is the level of administration of opiate (thoracic *vs.* lumbar), because the closer to the brain stem, the greater the chance of respiratory arrest. We have found that lumbar epidural opiates provide excellent analgesia, even for patients undergoing thoracotomy.

Finally, since supplemental parenteral opiates and sedatives increase the risk of respiratory depression, these drugs should be avoided as premedication and during surgery whenever possible.

Dr. Bromage cites a case report to illustrate that all intraspinal opiates are potentially dangerous.[4] Although few would argue this point, it is important to note that his patient received hydromorphone in a moderately large volume of saline given through a catheter inserted at a thoracic level. Furthermore, that patient received diazepam, morphine, and promethazine as premedication. Our clinical experience with over 1200 patients has been that, when those risk factors are minimized or eliminated, the continuous infusion or intermittent administration of hydromorphone through a lumbar epidural catheter has not resulted in a single case of apnea or respiratory arrest.

We agree with Ready and Chadwick[2] that, with appropriate nursing education, standard orders, hospital protocols, and medical supervision by anesthesiologists familiar with the actions and side effects, patients can be safely treated with epidural opiates outside Intensive Care Units on routine postsurgical wards.

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(Accepted for publication December 24, 1988.)

Anesthesiology
70:720, 1989

In Reply:—We are pleased to note that Dr. Brodsky and co-workers have found it safe to administer epidural opiates for postoperative analgesia outside the intensive care environment, and that, as in our experience, they find CO_2 retention in their patients is consistently associated with sedation.

However, we disagree with their statement that epidural morphine has no role when a catheter has been inserted. With appropriate precautions, morphine administered through an epidural catheter can be used safely outside an Intensive Care Unit. It is the most frequently used epidural narcotic in our institution and worldwide. Although it has been well established that the analgesic effect of epidural morphine may last 20–24 h in some patients, its duration of action is dose-related.[1] Our current practice is to administer smaller doses than those that have been used in the past. An indwelling epidural catheter facilitates the use of these smaller and safer doses of epidural morphine which, in some patients, are needed every 6 h to provide satisfactory analgesia.

It has not been established that more lipid-soluble opiates, such as fentanyl or hydromorphone, are safer than morphine for epidural use. We are now aware of unreported cases of severe respiratory depression following epidural fentanyl infusions. As noted by Brodsky and co-workers, epidural hydromorphone has also been reported to cause this complication.[2]

When an epidural catheter is inserted in the thoracic region to facilitate appropriate segmental block with local anesthetic for surgery involving the upper abdomen or thorax, morphine can safely be administered through the same catheter postoperatively. Reduction in morphine dosage in these patients compared with those with lumbar catheters results in effective and safe analgesia.

It should be emphasized that safety using epidural narcotics does not result primarily from selection of drugs with high lipid-solubility, or from restricting their use based on the site of epidural catheter placement. Rather, it results from a thorough understanding of the actions and side effects of the narcotics one chooses to use, and from carefully planned and organized patient care such as we have described.[3] Brodsky and co-workers undoubtedly provide similar care with drugs that work well in their hands. Their excellent record of safety is more likely a consequence of that high quality of patient care rather than the drugs they have chosen to use.

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(Accepted for publication December 24, 1988.)