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In Reply:—Although we appreciate the report by Donahue and Dineen of an apparent emergence reaction to oral ketamine, we do not agree with the conclusion they draw from this experience. However, their letter raises important points that need further clarification.

First, it is not at all clear that the larger oral dose of ketamine required for effective sedation may predispose to the occurrence of emergence delirium. As was pointed out in our article,[1] orally administered ketamine is only 16% bioavailable, as opposed to 93% bioavailable when administered intravenously or intramuscularly.[2] This renders the 6-mg/kg oral dose roughly equivalent to a 1-mg/kg dose administered intramuscularly. It also has been stated that the incidence of adverse reactions to ketamine is proportional both to the dose given and to the rapidity of the administration.[3] It therefore stands to reason that emergence phenomena should be more frequent with the intramuscular and intravenous administration of bioequivalent doses, because the peak ketamine levels achieved are higher, and these peaks are reached much more quickly.[2]

Subsequent to our study, we have used oral ketamine frequently for short procedures without adverse effects. Perhaps the reaction reported by Donahue and Dineen was related to the fact that the child was allowed to become extremely agitated before premedication was considered. As we stated in our study, much larger controlled trials will probably be needed to determine accurately the relative frequency of side effects caused by different premedication regimens.

Another important point that needs to be emphasized is that all premedications will have side effects. They have been observed following opioids and benzodiazepines as well as ketamine. It is also clear that choosing not to premedicate a child also can have "side effects," since unpremedicated children have been shown to experience postoperative nightmares and behavioral regression.[4] One cannot make valid recommendations about the relative merits of any premedication or anesthetic regimen based on one clinical experience.

In sum, when considering preanesthetic medication for an infant or child, one must weigh the relative benefits of using the premedication against the risk of its known and potential side effects. One must also consider the possibility of a traumatic induction of anesthesia in an unpremedicated child. Further research needs to be done to evaluate the myriad premedication alternatives available to the anesthesiologist.

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Spinal Toxicity after Repeated Intrathecal Sufentanil Administrations in Sheep

To the Editor:—Rawal *et al.*[1] reported recently that repeated administrations of large intrathecal doses of sufentanil in sheep are associated with severe behavioral and histologic spinal cord changes that may reflect a neurotoxic potential in humans. As a result, the authors expressed concern and argued for additional safety data. We therefore believe it necessary to summarize the various experimental and clinical evidence confirming the safety of adequately dosed spinal sufentanil.

Table 1 summarizes the available animal toxicity data gathered after intrathecal administration in rats[2] and cats[2] and epidural administration in dogs[3] and guinea pigs.* In these studies, histologic spinal cord changes, *i.e.*, inflammatory responses to the presence of the tubing, were observed without evidence of any abnormal tissue reaction related to sufentanil. The latter was given at several times its maximally effective dose for several days. Furthermore, in patients—as correctly reported by the authors[1]—doses as high as 600–800 μg/day were administered epidurally for periods of weeks to control cancer pain. Despite the presence of very high concentrations of sufentanil in the white and gray matter of the spinal cord around the site of the catheter tip, no evidence of histopathologic changes was noted.[4]

Different variables may account for the discrepancy observed between the study performed by Rawal *et al.*[1] and the above-mentioned reports. The diluent volume in relation to the available cerebrospinal fluid was much higher in the study by Rawal *et al.* than in the other trials. The same is true for the frequency of the injections. Both the relatively large volumes and high frequency may have contributed to

* Edwards WT, DeGirolami U: Histopathologic changes in the epidural space of the guinea pig during long-term narcotic infusion. A report to Janssen Pharmaceutica, August 1986