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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.3

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.

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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 rats2 and cats3 and epidural administration in dogs4 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 authors1—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

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* 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

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TABLE 1. Comparison of Experimental Conditions in Animal Trials in Which Sufentanil Was Administered Intrathecally or Epidurally.

<table>
<thead>
<tr>
<th>Species</th>
<th>Route of Administration</th>
<th>Mean Dose (μg/kg)</th>
<th>Volume (ml)</th>
<th>Frequency</th>
<th>Spinal Cord Pathology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>Intrathecal</td>
<td>1.5–7.5</td>
<td>4.2–0.8</td>
<td>4X/day for 3 days</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Rat</td>
<td>Intrathecal</td>
<td>0.2–60</td>
<td>0.01</td>
<td>1X</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Cat</td>
<td>Intrathecal</td>
<td>1–100</td>
<td>0.2</td>
<td>1X/day during 5 days</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Dog</td>
<td>Epidural</td>
<td>1.5–10</td>
<td>2.0</td>
<td>1X/day for 15 days</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>Epidural</td>
<td>2,500</td>
<td>0.25</td>
<td>1X/day for 7, 14, 28 days</td>
<td>Yes</td>
<td>*</td>
</tr>
</tbody>
</table>

† Not investigated.

the observed spinal damage—especially so if a hypotonic highly lipophilic substance (sufentanil) is compared to an isotonic hydrophilic control (saline). Moreover, inflammatory changes at the catheter insertion were observed in the saline-injected sheep.1

In addition to these differences in injection techniques, species differences may exist. After an intrathecal injection of local anesthetics, Rosen et al.4 reported neurologic deficits in sheep but not in monkeys. The widespread use of spinally administered local anesthetics in humans is also inconsistent with the reported toxicity in sheep. In conclusion, these data indicate that extrapolations of toxicity data from sheep to humans should be done very cautiously and that clinical and experimental data, in more commonly used laboratory animal species, give no evidence of any drug-related spinal toxicity. Spinal toxicity is even more unlikely to happen with the isosolutive solution of sufentanil, which has recently been made available for spinal and intravenous application.

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In Reply—Van Deun et al. suggest that the neurotoxic changes described by us may be due to large volumes of injectate, species differences, and frequency of injections. For evaluation of the neurotoxic potential of a drug, it is important to investigate histologic and functional changes. The absence of histopathologic changes alone is not sufficient to absolve a drug from possible neurotoxic effects. Conversely, it is possible for behavioral effects not to be observed and toxicity still to be present.1 In our study, there was a general correspondence between the degree of behavior change and the degree of histologic change.

The study mentioned by Van Deun et al., motor dysfunction and catalepsy were noted in all rats receiving 10 or 30 μg intrathecal sufentanil. In fact, a mortality of 20% was noted in rats receiving 10 μg, and a mortality of 60% was noted in rats receiving 30 μg sufentanil intrathecally.2 Similarly, in cats receiving 100 μg intrathecal sufentanil, excitation, labored breathing, and hindlimb motor weakness (lasting 2 h) were noted. Intrathecal administration of 300 μg sufentanil resulted in convulsions and death after 7 h.2

We agree with Van Deun et al. that a large volume of drug can conceivably increase cerebrospinal fluid pressure and cause neurologic deficit. However, we noted a dramatic difference in the behavioral responses between animals receiving large but identical volumes of saline or opioids. When an identical volume of saline was injected intrathecally in animals who had recovered from moderate to severe behavioral effects of sufentanil and butorphanol, no behavioral changes occurred. This suggests that the behavioral and neurologic changes in our study were not due to barotrauma after the administration of large volumes of injectate.

The authors suggest that neurotoxicity may have been related to the frequency of injections. We injected the drugs every 6 h, i.e., four times a day for 4 days, instead of the more usual single daily administration for 1–2 weeks. This was done because of the short duration of action of these drugs and because this closely parallels the use of these opioids in clinical practice. However, this administration schedule was used only in the low-dose sufentanil group. Because of major behavioral changes and prolonged motor weakness of hindlimbs after

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