Are Barbiturates Hyperalgesic?

To the Editor.—Thirty years ago a leading article pointed out that for barbiturate hyperalgesia to have clinical relevance it must be shown to have a demonstrable effect on postoperative pain. A recent editorial on the subject appeared after we had commenced a study to examine this issue by measuring pain scores and morphine use in patient-controlled analgesia after gynecologic surgery. We had been influenced by the Joint Colleges Working Party on Pain After Surgery, exhorting us to find ways to reduce postoperative pain and also by the ready availability of propofol as a comparison.

We entered 130 patients into a prospective randomized trial, and 117 completed records were available for analysis. All patients were undergoing either total or subtotal abdominal hysterectomy by a standard lower abdominal incision and received either thiopental (5 mg·kg⁻¹) or propofol (2.5 mg·kg⁻¹) as the induction agent. The anesthetic technique included fentanyl 0.2–0.3 mg, droperidol 1.25

mg if indicated, enflurane as the inhalational agent, and a nondepolarizing muscle relaxant; neither nonsteroidal antiinflammatory drugs nor local anesthetics were permitted.

Pain, scored by nursing staff on a four-point scale after patient questioning (1 = no pain; 2 = mild pain; 3 = moderate pain; and 4 = severe pain), and patient-controlled morphine use without continuous infusion were recorded over the 48-h postoperative period. The pain scores on a ranked ordinal nonparametric scale were compared by using the chi-squared test of association for the intervals 0–4, 4–12, 12–24, and 24–48 h, and morphine use was compared by using Student's t test for the difference between the means of two samples.

The results are shown in table 1. For all periods except 0–4 h there was no difference between the thiopental or propofol groups. For the 0–4-h interval, patients in the thiopental group reported significantly more moderate and less mild pain compared with those in the propofol group. A lower morphine use in the thiopental group approached statistical significance.

These results suggest that barbiturate hyperalgesia, if present, occurs only in the early postoperative period after a single dose at induction, when the possibility of residual barbiturate sedation re-

Table 1. Morphine Use and Pain Scores

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Thiopental</th>
<th>Propofol</th>
<th>Standard Error of Mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(h)</td>
<td>(mean [range])</td>
<td>(mean [range])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td>0–4</td>
<td>19.00 (6–36)</td>
<td>22.00 (7–42)</td>
<td>1.330</td>
<td>0.05 &gt; P &gt; 0.025</td>
</tr>
<tr>
<td></td>
<td>4–12</td>
<td>18.00 (4–43)</td>
<td>18.00 (1–47)</td>
<td>1.812</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>12–24</td>
<td>24.00 (2–58)</td>
<td>25.00 (3–58)</td>
<td>2.520</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>24–48</td>
<td>22.50 (0–82)</td>
<td>25.00 (0–82)</td>
<td>2.884</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>83.00 (12–161)</td>
<td>86.00 (39–151)</td>
<td>6.169</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Pain Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (%) for each score</td>
<td>0–4</td>
<td>35.5</td>
<td>41.5</td>
<td>18.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>4–12</td>
<td>55.5</td>
<td>36.5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>12–24</td>
<td>42</td>
<td>52</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>24–48</td>
<td>57</td>
<td>39.5</td>
<td>3.5</td>
<td>0</td>
</tr>
</tbody>
</table>

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CORRESPONDENCE

Reducing patient-controlled demands for analgesia cannot be discounted. Further studies, we believe, should concentrate on this period and perhaps in addition measure serum drug concentrations in an attempt to achieve a correlation and produce a definitive answer. In the meantime, our study suggests barbiturate hyperalgesia to have little clinical relevance.

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References


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Difficulties Encountered in a Comparative Study of Orally Administered Midazolam and Ketamine

To the Editor:—In children, psychological preparation along with effective premedication may help alleviate psychobehavioral sequelae resulting from the surgical experience. Many premedications administered via various routes exist. Of these, the oral route appears the simplest and least traumatic in children for whom there is no intravenous access. Recent studies have established the efficacy of and have suggested dosing for oral midazolam and oral ketamine in children.1,2 We planned a randomized, prospective, double-blind study to determine if one presented a significant benefit when compared with the other. The study was aborted after undesirable side effects attributable to ketamine were consistently noted.

Our children were between the ages of 3 and 6 yr; five were boys, and one was a girl. All were ASA physical status I scheduled for herniorrhaphy or circumcision. No child had a history of psychiatric disorders. Four children received 6 mg/kg oral ketamine, and two children received 0.75 mg/kg oral midazolam in 0.2 ml/kg sweetened fruit-flavored drink. Monitoring included noninvasive blood pressure, pulse oximetry, continuous electrocardiogram, and respiratory rate.

After peak premedicant effect had been attained, the children were taken to the operating room, and inhalation induction was accomplished with 70% nitrous oxide in oxygen, with halothane in 0.2% increments after each four breaths to 1.5% and then 0.5% increments after each four breaths to 3%.

Of the four children premedicated with ketamine, significantly increased secretions during induction leading to desaturation (oxygen saturation by pulse oximetry < 95%) developed in three, who required pharyngeal suctioning, positive-pressure ventilation, and (in two) a small dose of succinylcholine to relieve laryngospasm. All children recovered with no further difficulties. In the fourth child, an acute hallucinatory experience developed approximately 10–15 min after premedication so severe as to require intramuscular midazolam. He had neither recall nor nightmares immediately postoperatively and at follow-up 1 week later.

Oral ketamine at this dose was used by several attending anesthesiologists before the study. One other child had a dyshoric experience treated with rapid uncomplicated inhalation induction, and several reported secretion and airway difficulties similar to those reported above. In addition, in several children an adequate level of sedation was not achieved with 6 mg/kg oral ketamine.

Although ketamine is known to have these side effects,3,4 in previous pediatric studies3,4 with oral premedication they have not been reported. Finally, we realize that the appearance of children premedicated with ketamine was obviously different from those medicated with midazolam, such that a blind study was impossible.

As a result of the issues raised in terms of safety and study logistics, we discontinued the study. The search for an ideal pediatric premedicant continues.

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