Intracranial Pressure Increases during Alfentanil-induced Rigidity

James L. Benthuysen, M.D.,* Nguyen D. Kien, Ph.D.,† Darcy D. Quam, M.S.‡

Intracranial pressure (ICP) was measured during alfentanil-induced rigidity in rats. Ten rats had arterial, central venous (CVP), and subdural cannulae inserted under halothane anesthesia. The animals were mechanically ventilated to achieve normocarbia (PCO₂ = 42 ± 1 mmHg, mean ± SE). Following instrumentation, halothane was discontinued and alfentanil (125 μg/kg) administered iv during emergence from halothane anesthesia. In the five rats that developed somatic rigidity, ICP and CVP increased significantly above baseline (ICP 7.5 ± 1.0 mmHg, ACVP 5.9 ± 1.3 mmHg). These variables returned to baseline when rigidity was abolished with meperidine. In five rats that did not become rigid, ICP and CVP did not change following alfentanil. These observations suggest that rigidity should be prevented when alfentanil, and, presumably, other opiates, are used in the anesthetic management of patients with ICP problems. (Key words: Analgesics, narcotics: alfentanil. Complications: increased intracranial pressure; rigidity.)

In patients with intracranial pathology, control of intracranial pressure (ICP) is important, in part, for optimal maintenance of cerebral perfusion. Patients with decreased intracranial compliance and elevated ICP are often administered potent opiates during induction of anesthesia, to decrease ICP and to attenuate the adverse cardiovascular reflexes associated with anesthetic induction and tracheal intubation. A side effect of these agents when used in large doses is muscle rigidity. While clinically insignificant changes in cardiac output and mean arterial pressure (MAP) occur during alfentanil rigidity, pronounced increases in central venous pressure (CVP) have been described. Because changes in CVP can directly influence ICP, it is important to clarify the effect narcotic-induced rigidity might have on ICP.

Alfentanil, a short-acting synthetic opiate with one-fourth the analgesic potency of fentanyl, in anesthetic doses can produce intense rigidity in both humans and rats. Alfentanil was used in this study to examine the relationship between rigidity and the associated changes in CVP and ICP in instrumented rats.

Materials and Methods

This study was performed within guidelines approved by the UC Davis Animal Research Committee.

Ten male Sprague-Dawley rats weighing 544 ± 36 g were fed and watered ad lib until the day of study. Each animal was anesthetized with 1.5% inspired halothane in oxygen. Tracheal intubation with a 14-gauge teflon cannula (Jelco®) was performed under direct vision. This cannula size allowed for a slight leak of respiratory gases. Ventilation was controlled with a rodent respirator (Harvard Bioscience Model 680, Dover, MA).

PE-90 polyethylene tubing (Innaramedic®) was surgically inserted into the femoral artery and vein for measurement of mean arterial (MAP) and central venous (CVP) pressures. ICP was measured from the cisterna magna by means of a percutaneously inserted 24-gauge blunt needle introduced through the foramen magnum. Placement of the ICP cannula was confirmed by the return of clear cerebral spinal fluid, the presence of an IGP waveform, and parallel changes in both CVP and ICP with gentle manual thoracic compression. MAP, CVP, and ICP were measured with Statham transducers that were calibrated with a mercury column and placed at a mid-thoracic level. The respective waveforms were recorded continuously on paper.

Intermittent positive pressure ventilation was adjusted by increasing the respiratory rate (50–100/min) while maintaining low tidal volumes (0.5–2.0 ml). A blood gas measurement just before alfentanil administration (pH 7.38 ± 0.02, PaCO₂ 42 ± 1 mmHg, PaO₂ 267 ± 24 mmHg) was used to confirm normocarbia. Equal volumes of 0.9% saline were used to replace the 0.5-cc aliquots of blood used for these determinations.

After halothane was discontinued, the instrumented, unrestrained animals were closely observed during emergence, while intubated and ventilated with 100% oxygen. The first movement during emergence (head, extremities, or tail) was used as an indication for the administration of alfentanil 125 μg/kg iv. Pilot data had indicated that this dose of alfentanil would reproducibly induce rigidity in the unanesthetized rat.† The

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† J. L. Benthuyyen, unpublished results.
TABLE 1. Alfentanil-induced Hemodynamic and ICP Changes in Rigid and Non-rigid Rats (All Volumes are in mmHg—Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Post-alfentanil</th>
<th>Change from Control (Δ)</th>
<th>Post-metocurine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1—Rats with rigidity following alfentanil (N = 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>7 ± 1.1</td>
<td>14.5 ± 1.4*</td>
<td>7.5 ± 1.0†</td>
<td>7.1 ± 1.0‡</td>
</tr>
<tr>
<td>CVP</td>
<td>2.4 ± 0.4</td>
<td>8.3 ± 1.3*</td>
<td>5.9 ± 1.3†</td>
<td>2.6 ± 0.3‡</td>
</tr>
<tr>
<td>MAP</td>
<td>103 ± 8.3</td>
<td>79 ± 9.3*</td>
<td>-24 ± 2.0†</td>
<td>79 ± 9.3‡</td>
</tr>
<tr>
<td><strong>Group 2—Rats without rigidity following alfentanil (N = 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>7.4 ± 1.0</td>
<td>6.2 ± 1.6‡</td>
<td>-1.2 ± 0.5†</td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>2.3 ± 0.2</td>
<td>2.1 ± 0.3‡</td>
<td>-0.2 ± 0.16†</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>101 ± 9</td>
<td>64 ± 10*</td>
<td>-37 ± 5†</td>
<td></td>
</tr>
</tbody>
</table>

Control values are stable baseline measurement just prior to alfentanil. The values recorded following alfentanil (post-alfentanil groups 1 and 2) and metocurine (post-metocurine: group 1) were measured at the point of greatest ICP change.

Alfentanil was administered in 1.0–1.3 ml 0.9% saline over 15 s. A similar volume of saline alone had no effect on MAP, CVP, or ICP in these relatively large rats.

Rigidity was considered present when the rats displayed stiffly extended hind limbs and tails, as described by Browne et al. The rigid animals were monitored until a maximal response in ICP was obtained. At this time, metocurine 0.5 mg/kg iv was given, and the respective variables were again measured when the animals became flaccid.

MAP, CVP, and ICP and the changes (Δ) in these variables with respect to baseline are expressed as mean ± standard error.

Following alfentanil, all values were measured at the point of maximal ICP change. Paired Student’s t tests was used to assess the significance of these changes with respect to control, with P < 0.05 taken as significant. Because some rats subsequently did not develop rigidity, ANOVA was used to assess differences between rigid and non-rigid animals.

**Results**

When alfentanil was administered during emergence from halothane, rigidity occurred in five of ten animals. These animals had rigid extension of the hind limbs with the tail elevated off the table surface. The five non-rigid animals had flaccid extremities and tails. Metocurine was not given to this group of rats.

Hemodynamic and ICP changes recorded from these animals are presented in table 1. Baseline data for the rigid and non-rigid groups of rats were not different prior to alfentanil administration. When alfentanil was administered, ICP increased significantly in the rigid rats. This change in ICP (Δ) was also significant between groups. The maximal change in ICP occurred within 12.0 ± 1.5 s of alfentanil administration. Similarly, CVP increased in rigid animals over the same time course. Subsequent metocurine administration rapidly eliminated rigidity within 10 s, and, at this time, both ICP and CVP returned to baseline (table 1). When rigidity did not occur following alfentanil, there was no significant change in CVP or ICP with respect to control.

MAP decreased following the administration of alfentanil in both rigid and non-rigid rats. While there was no post-alfentanil difference in absolute MAP between these groups (79 ± 9 mmHg vs. 64 ± 10 mmHg), the change in MAP with respect to baseline (Δ) following alfentanil was significantly greater in the non-rigid versus the rigid group. When metocurine was administered to the rigid group, no further change in MAP occurred (table 1).

While peak airway pressures were not measured, positive pressure ventilation produced an expected respiratory fluctuation in both CVP and ICP of 1.2 ± 0.1 mmHg. In both rigid and non-rigid groups, there was no change in the magnitude of this respiratory fluctuation following alfentanil administration.

**Discussion**

While potent opioids are clinically effective in establishing a hemodynamically stable anesthetic state, muscle rigidity can occur in a dose-dependent fashion. In this study, ICP and CVP increased rapidly with the onset of alfentanil-induced rigidity and returned to baseline when rigidity was abolished using metocurine. In animals where rigidity did not occur, there was no change in either variable. Like the changes in CVP, the rapid increase in ICP at the onset of rigidity strongly suggests a mechanical etiology.

When studied clinically, increases in CVP were demonstrated in apneic patients during alfentanil-induced rigidity, when changes in airway pressure presumably did not contribute to these observations. Peak airway pressures were not measured in our study; however, there was considerable leakage of inspiratory gases around the tracheal cannulae, and a change in the magnitude of the respiratory fluctuations in CVP or ICP during rigidity did not occur. Taken together, these
observations suggest that increases in airway pressure due to decreased thoracic compliance were, at most, minimal, and that factors relating to ventilation were unimportant in regard to the ICP changes in this study. In a sealed system without the passive leak of respiratory gases, airway pressure would be expected to increase during rigidity, and this might lead to greater changes in ICP.

In the clinical setting, rigidity during anesthetic induction can be associated with hypercarbia due to difficult ventilation by mask, perhaps due to glottic or supraglottic obstruction, since rigid patients with pre-existing tracheostomies are easily ventilated. Furthermore, the rate of rise in CO₂ in apneic patients with prolonged alfentanil rigidity is no greater than in apneic patients receiving thiopental. Because CO₂-induced cerebral vasodilation could exaggerate ICP changes during rigidity, ventilation was established prior to inducing rigidity, and normocarbia was confirmed by arterial blood gas measurements just prior to alfentanil administration. Peak changes in CVP and ICP occurred within 12 ± 1.5 s of the onset of rigidity, and then subsequently returned to baseline following metocurine. The time course of these observations suggests that hypercarbia did not play a role in these changes, and the increases in ICP were probably directly mediated by rigidity.

Because changes in cerebral venous return can adversely influence ICP, the changes in CVP and ICP in our study may be interrelated. Mean CVP and ICP increased by 5.0 ± 1.3 mmHg and 7.5 ± 1.0 mmHg, respectively. It should be pointed out that the relationship between changes in intracranial volume and ICP are nonlinear, and small changes in CVP and, secondarily, in intracranial volume could produce a disproportionate change in ICP depending upon compliance. Therefore, parallel and equal changes in CVP and ICP might not occur.

A weakness of this rat model is that the acutely instrumented rats were studied during emergence from halothane at a time when residual halothane was almost certainly present. Although end-tidal halothane levels were not measured, residual halothane may account for the failure of some animals to exhibit rigidity, as general anesthetics are said to prevent the occurrence of opioid rigidity. Consonant with this hypothesis, the greater decline in ΔMAP in non-rigid rats following alfentanil may have resulted from the interaction of alfentanil with a greater level of halothane than was present in the rigid rats. Finally, residual halothane could have influenced the magnitude of ICP changes reported in the rigid animals.

The reported ICP changes occurred in normal, healthy animals with presumably normal intracranial compliance. This model does not address the influence of rigidity on ICP in the presence of intracranial pathology. However, our data suggest that prevention or early treatment of rigidity related to potent opioids may be clinically important in patients with head injuries or other intracranial lesions. While a controlled clinical study to clarify these observations may be difficult ethically, carefully documented case reports may illuminate the clinical significance of this potential problem.

References