pre-treatment with antihistamines. A more direct approach to the problem is simply to use drugs like fentanyl that do not release histamine.

We administered sufentanil in a dose and at an infusion rate representative of those being evaluated in cardiac surgery and found no evidence of histamine release. That is not to say we found no cardiovascular effects. Both fentanyl and sufentanil lowered systemic pressure and peripheral vascular tone. Both drugs presumably reduce central sympathetic tone, and may share morphine's peripheral effects on capacitance and resistance vessels.

In summary, sufentanil produces rapid loss of consciousness, moderate decreases in systemic pressure and peripheral resistance, and no histamine release. In these respects it is clinically indistinguishable from fentanyl.

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Intracranial Pressure, Mean Arterial Pressure, and Heart Rate Following Midazolam or Thiopental in Humans with Brain Tumors

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Midazolam maleate is a water-soluble benzodiazepine that recently has been recommended as an effective intravenous agent for induction of anesthesia. Midazolam has a short onset and duration of action, is nonirritating to veins, relieves anxiety, produces antegrade amnesia, and is a mild respiratory depressant.

No significant cardiovascular differences have been demonstrated between midazolam (0.25 mg/kg) and thiopental (4 mg/kg) when either drug is intravenously administered to healthy surgical patients for induction of anesthesia, and midazolam has minimal cardiovascular effects even when administered to patients with ischemic heart disease who are undergoing coronary artery bypass surgery.

Midazolam (0.2 mg/kg) decreases cerebral blood flow (CBF) by 35% in humans and 55% in dogs and produces dose-related decreases in cerebral metabolic rate of oxygen (CMRO\textsubscript{2}) in dogs to a maximum of 55% after 10 mg/kg. Thiopental in equivalent doses has similar effects on CBF and CMRO\textsubscript{2}.

The effect of midazolam and thiopental on intracranial pressure (ICP), mean arterial pressure (MAP), and heart
rate (HR) during anesthetic induction and endotracheal intubation were studied in patients who were undergoing craniotomy for tumor excision.

**MATERIALS AND METHODS**

Seventeen unpremedicated patients about to undergo elective craniotomy for brain tumor resection were studied after obtaining informed consent with the approval of the hospital's Human Research Committee. Exclusion criteria included significant cardiovascular, respiratory, hepatic, or renal disease; an ICP of 20 mmHg or greater; a functioning ventriculo-peritoneal shunt; pregnancy; allergy to the study drugs; or receipt of drugs other than steroids on the day of surgery.

Prior to induction, a radial artery catheter and peripheral vein catheters were inserted to measure MAP, sample arterial blood gases, and administer drugs and fluids. Cardiac rate and rhythm were monitored continuously with an electrocardiogram. After infiltration of a local anesthetic (2% lidocaine with epinephrine 1:200,000), an intracranial subarachnoid screw was placed and coupled by a fluid connection to an appropriate transducer with a zero reference level at the level of the foramen of Munro.

Patients were assigned to two groups, and drugs were given in a double-blind manner. Group M received midazolam for induction and Group T received thiopental. Induction of anesthesia was considered successful when there was no response to verbal commands, a loss of eyelid reflex, and a loss of voluntary movement in response to placement of a face mask. A dose of 0.25 mg/kg midazolam or 4 mg/kg of thiopental was given initially, followed by 25% incremental doses every 2 min until induction criteria were met. All drug doses were given over 30-s intervals. After induction, pancuronium bromide (0.1 mg/kg) was given and intubation was performed when response from a blockade monitor was abolished.

In Group M, 30% of the induction dose of midazolam was given 2.5 min before intubation; in Group T, thiopental (2.7 mg/kg) was administered 1 min before intubation. Differences in timing were based upon reported differences in onset of peak action** and potency: midazolam being approximately 20 times as potent as thiopental.** Heart rate, MAP, and ICP were monitored continuously. Measurements were taken before, immediately after induction, and 1 min after induction; and they were taken before, immediately after, and 1, 2, and 5 min postintubation. Ventilation was assisted then controlled, giving 100% oxygen, and was maintained. Normocarbia was assured by determination of arterial blood gases at induction and immediately after intubation. Nitrous oxide (N₂O) was not used during the study period. Cerebral perfusion pressure (CPP) was calculated from the formula, CPP = MAP - ICP. Results were analyzed using the Student's t test (paired) to compare values before and after induction and intubation within each group, and a two-way analysis of variance for repeated measures was used to compare the test groups for overall effect. Measures are reported as mean ± SE.

**RESULTS**

Mean age and weight of the nine Group M patients were 49 ± 5 yr and 73 ± 5 kg, respectively, and for the eight Group T patients, 46 ± 4 yr and 65 ± 5 kg, respectively. The required induction dose of midazolam was 0.32 ± 0.024 mg/kg (ED90), and the preintubation dose was 0.1 ± 0.016 mg/kg. Doses of thiopental were 4.7 ± 0.66 mg/kg and 2.7 ± 0.33 mg/kg, respectively. Arterial carbon dioxide tensions were not significantly different before and after induction (37 ± 0.3 and 38 ± 2).

Mean arterial pressure, HR, ICP, and CPP during induction are shown in table 1. Intracranial pressure and HR were unchanged, but MAP and CPP decreased significantly in the thiopental group. Intracranial pressure, CPP, and HR did not decrease in the midazolam group but MAP decreased slightly.

The effects of pretreatment with either midazolam or thiopental immediately before intubation also are shown in the table. Intracranial pressure, CPP, MAP, and HR were increased significantly after intubation in both the M and T groups. Comparing drugs, HR increased in the midazolam group significantly more than in the thiopental group (P < 0.05, t test, not paired).

Two-way analysis of variance for repeated measures did not reveal overall differences between thiopental and midazolam ("F" test not significant).

**DISCUSSION**

In our study, ICP did not decrease when midazolam (0.32 mg/kg) was used for anesthetic induction. Drugs that decrease CBF are assumed to have the potential to decrease ICP, secondary to a decrease in cerebral blood volume (CBV). Midazolam (0.15 mg/kg) has decreased CBF by 35% in awake volunteers and by 11% in patients anesthetized with N₂O/fentanyl, and no change was reported after midazolam during halothane/fentanyl anesthesia. Neither did ICP change significantly after thiopental in our study. Thiopental also decreases CBF and is assumed to decrease CBV and frequently is used to treat intracranial hypertension. Intracranial pressure has been shown to decrease significantly after thiopental only in patients with intracranial hypertension but not in patients with normal ICP. Midazolam also has been reported to decrease ICP significantly in three patients with elevated ICP. These reports are not in disagree-

**Unpublished data—Hoffman-LaRoche, Inc.**
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<tr>
<th>Group</th>
<th>Preinduction</th>
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<tr>
<td>ICP (mmHg)</td>
<td>M</td>
<td>12 ± 1</td>
<td>14 ± 2</td>
<td>15 ± 2</td>
<td>12 ± 1</td>
<td>20 ± 4*</td>
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<td>T</td>
<td>11 ± 1</td>
<td>15 ± 6</td>
<td>15 ± 4</td>
<td>16 ± 3</td>
<td>23 ± 5*</td>
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<tr>
<td>CPP (mmHg)</td>
<td>M</td>
<td>81 ± 4</td>
<td>75 ± 4</td>
<td>72 ± 4</td>
<td>76 ± 5</td>
<td>108 ± 6*</td>
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<td>79 ± 4</td>
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<td>70 ± 4</td>
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<td>106 ± 8*</td>
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<tr>
<td>MAP (mmHg)</td>
<td>M</td>
<td>94 ± 4</td>
<td>89 ± 4†</td>
<td>87 ± 4</td>
<td>88 ± 5</td>
<td>128 ± 7*</td>
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<td>T</td>
<td>91 ± 4</td>
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<td>HR (beats/min)</td>
<td>M</td>
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<td>77 ± 5</td>
<td>85 ± 5</td>
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<td>T</td>
<td>81 ± 4</td>
<td>88 ± 7</td>
<td>94 ± 6</td>
<td>100 ± 7</td>
<td>122 ± 5*</td>
</tr>
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</table>

* Significant change (P < 0.05) as compared with preinduction value.
† Significant change (P < 0.05) as compared with preinduction value.
‡ Significantly larger increase (P < 0.05) than for thiopental group (immediately postinduction compared with any previous measure).

ment with our findings, because in both of our groups, initial ICP was less than 20 mmHg. If pressures had been greater than 20 mmHg, perhaps significant changes in ICP would have occurred following midazolam or thiopental. Further studies will be necessary to test the efficacy of midazolam for treatment of intracranial hypertension.

Mean arterial pressure was reduced significantly by midazolam and thiopental when used for induction. Since ICP was normal and unchanged after both drugs, a change in MAP would have the greater effect on CPP. Midazolam did not decrease MAP enough to significantly reduce CPP but thiopental did. However, even in the thiopental group, CPP was maintained above 50 mmHg, which is considered adequate to maintain CBF. Our MAP and HR results agree with those previously reported.8

Neither midazolam nor thiopental abolished the well-known pressor response to laryngoscopy and intubation in our patients. In both groups, ICP, CPP, MAP, and HR were significantly increased immediately after intubation. Intracranial pressure was approaching control 2 min after intubation in both groups, however, those pretreated with midazolam tended to approach control more rapidly than those pretreated with thiopental, even though the relative preinduction dose of midazolam was less than thiopental (fig. 1). The efficacy of thiopental in preventing an increase in ICP during laryngoscopy and intubation has not been demonstrated. The magnitude of ICP increase in our patients was less than that reported previously by Burney, who showed a significant ICP increase after laryngoscopy and intubation when a hypnotic dose of thiopental was given 3 min before stimulation.19

Without a control, it is not possible to know whether our observed increase in ICP was attenuated by midazolam and/or thiopental. Because both midazolam and thiopental produce dose-related decreases in CBF and CMRO2 and increase cerebral vascular resistance,11,20 larger doses of both drugs might control ICP significantly during laryngoscopy and intubation.

In summary, ICP did not change after anesthetic induction with either thiopental or midazolam, and neither drug abolished the increase in ICP associated with laryngoscopy and intubation. In agreement with Lebowitz et al.,8 no overall differences between midazolam and thiopental were detected during changes in HR and MAP. However, CPP was maintained more effectively during anesthetic induction in our midazolam patients. Midazolam, therefore, may be an alternate drug choice for induction of anesthesia in patients with poor intracranial compliance.
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**Alpha-1-acid Glycoprotein and Beta-endorphin Alterations in Chronic Pain Patients**

**TETSURO FUKUI, M.D.,* STUART R. HAMEROFF, M.D.,† A. JAY GANDOLFI, PH.D.†**

Alpha-1-acid glycoprotein (AG) is an alpha-1 fraction serum protein that binds and reduces bioavailability of various basic drugs.1–5 Unlike other plasma drug binding proteins such as albumin, AG plasma levels are increased in stress responses associated with several clinical situations such as inflammation,6 malignancy,7 rheumatoid arthritis, myocardial infarction, and surgery.8,9 Thus, increased plasma levels of AG may bind and reduce efficacy of basic drugs including analgesics, tricyclic antidepressants, and beta-adrenergic receptor blockers in patients who are stressed.1–4,10–11 Because patients with chronic pain often are stressed and may receive many drugs, we compared AG plasma levels in chronic pain patients to matched control volunteers.

Plasma beta-endorphin (BE) levels decrease in patients with chronic pain,1,2,16 and the role of opioids in chronic pain and stress remains unclear. We measured BE plasma levels in the same samples and investigated correlations between AG, BE, and other patient variables.

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