COMPARISON OF ETOMIDATE AND ALTHESIN IN THE REDUCTION OF INCREASED INTRACRANIAL PRESSURE AFTER HEAD INJURY

N. M. DEARDEN AND D. G. McDOWALL

The measurement of intracranial pressure (ICP) following severe head injury has led to the use of aggressive intensive care management regimens in attempts to decrease the mortality associated with severe post-traumatic intracranial hypertension. Reports during the early 1970s suggested that use of barbiturates to control ICP might improve mortality without increasing morbidity in patients with post-traumatic diffuse brain swelling (Shapiro et al., 1974). However, the tendency for barbiturates to cause hypotension (Schulte am Esch, Pfeifer and Thiemig, 1978) and to prolong recovery following cessation of the drug has led to the investigation and use of shorter-acting anaesthetic agents to control the increases in ICP (Vesari et al., 1980; Prior et al., 1983).

Althesin has been shown to decrease cerebral oxygen consumption, cerebral blood flow (CBF) and ICP in man (Turner et al., 1973; Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978). During the past 5 years it has been used increasingly in Leeds as a first-line agent in the control of increased ICP following severe head injury (Moss et al., 1983), because of its advantage over the barbiturates of rapid elimination (Simpson, 1978). Etomidate has also been in use in several centres for the treatment of severe intracranial hypertension, so that a study of its efficacy is important, especially when its place in intensive care is under critical review for other reasons. A comparative trial of the influence of i.v. infusions of etomidate and Althesin on the control of ICP after severe head injury has been undertaken, and is reported in this communication.

SUMMARY

The increasing use of shorter-acting hypnotic agents to control intracranial pressure (ICP) following severe head injury has prompted a prospective double-blind controlled trial comparing the efficacy of etomidate and Althesin, given by i.v. infusion. Over the dose ranges used, the two drugs appeared equipotent in decreasing ICP whilst preserving cerebral perfusion pressure. However, in two patients (one in each group) ICP did not respond to hypnotic infusion, a feature noted in other studies to occur in a minority of patients. With the cessation of Althesin manufacture and the discussion about the use of etomidate infusions, it is timely to document the effectiveness of etomidate in decreasing ICP.

MATERIALS AND METHODS

Head-injured patients older than 14 years of age undergoing intensive care management with full neuromuscular blockade were admitted to the study if a sustained unstimulated increase in mean ICP above 20 mm Hg was recorded for more than 10 min. The 10 patients in this study had suffered severe head injury as indicated by low Glasgow coma scores and increases in ICP (table I). Surface subarachnoid pressure was recorded using the Leeds bolt (Coroneos et al., 1973). Treatment was instituted by commencing an i.v. infusion of either etomidate (five patients) or Althesin (five patients), chosen on a random basis, at a pre-determined rate based on estimated body weight, to a central vein (CV) using an infusion pump. Any patients receiving other drugs known to influence ICP during the infusion period of 70 min were excluded from the study, and no other drugs were given via the CV line during the study. The study comprised one infusion of either etomidate or Althesin in each of 10 patients.
TABLE I. Clinical details, initial ICP and outcome in 10 patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>Althesin</th>
<th>Etomidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>4M:1F</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Mean</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>27.0</td>
<td>15-44</td>
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</table>

<table>
<thead>
<tr>
<th>Glasgow Coma Score</th>
<th>Mean</th>
<th>SEM ±</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>5</td>
<td>2.4</td>
<td>3-7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain swelling</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Intracerebral haematoma</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subdural haematoma</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial ICP (mm Hg)</th>
<th>Mean</th>
<th>SEM ±</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23.0</td>
<td>2.4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome after 1 year:</th>
<th>Dead/Vegetative</th>
<th>Severely disabled</th>
<th>Moderately disabled/ good recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

The infusate was dispensed by the Pharmacy, in containers with concealed labels to prevent identification by the medical staff, as undiluted Althesin or etomidate in a concentration of 6 mg ml⁻¹ in 5% dextrose. The infusion rates are shown in table II.

The dose regimen was based on the literature available for the two agents when used to produce anaesthesia, sedation and reduction of ICP, and our own previous experiences with the two agents in an ICP reducing role (Ramsay et al., 1974; Savege et al., 1975; Kay, 1976; Popescu, 1976; Sari et al., 1976; Jago and Restall, 1977; Van Hamme, Ghoneim and Ambre, 1978; Sear and Prys-Roberts, 1979; Zattoni et al., 1980; Boys et al., 1981; Ransom, 1981; de Ruiter et al., 1981).

Based on the pharmacokinetic studies of Sear and Prys-Roberts (1979) in the case of Althesin, the above regimen should provide steady-state plasma concentrations at 30, 50 and 70 min. Furthermore, analysis of Ransom's paper (1981) would suggest that a steady-state plasma concentration of etomidate might be reached at 30 min, although the more recent work of Hebron and co-workers (1983) would refute this.

During the 70-min study period the following measurements were made: arterial pressure (AP) either directly from the radial artery or indirectly (Automatic BP Monitor, Electrical Medical Equipment, Brighton) to provide both systolic and diastolic pressures at 5-min intervals. Mean arterial pressure was calculated later as diastolic + 1/3 (systolic – diastolic pressure). Good correlation between "Dinamap" and direct arterial pressure readings has been confirmed by Hutton, Dye and Prys-Roberts (1984). ICP was displayed throughout the study on a chart recorder and measurements of mean ICP, taken as the mid-point of the trace width, were made at 5-min intervals. The validity of the ICP measurements was verified using an infusion test (Dearden, McDowall and Gibson, 1984). Blood-gas tensions were obtained at the beginning of the infusion and are given in table III.

Central and peripheral temperatures and central venous pressure (CVP) were measured at the start and end of each infusion. Crystalloid maintenance fluids were administered at a rate equal to the urine output for the previous hour plus 30 ml, to a maximum of 150 ml h⁻¹. CVP measured at mid-axillary level was maintained between +3 and +10 cm H₂O (on IPPV) using colloid, when necessary.

Pupillary reactions were recorded at the start of the study and at 10, 30, 50 and 70 min. Monitoring of cerebral function (CFM) was undertaken in all patients (although two traces in each group were of poor quality).

Differences between the groups were tested by unpaired Student's t test, with values of P less than 0.05 being considered significant. In all figures n = 5 except where stated.

TABLE II. Infusion rates of Althesin and etomidate

<table>
<thead>
<tr>
<th>Time</th>
<th>Infusion rate</th>
<th>Equivalent to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Althesin</td>
<td>Etomidate</td>
</tr>
<tr>
<td>0-10 min</td>
<td>0.5 ml kg⁻¹ h⁻¹</td>
<td>0.5 ml kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>10-30 min</td>
<td>0.2 ml kg⁻¹ h⁻¹</td>
<td>0.2 ml kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>30-50 min</td>
<td>0.3 ml kg⁻¹ h⁻¹</td>
<td>0.3 ml kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>50-70 min</td>
<td>0.4 ml kg⁻¹ h⁻¹</td>
<td>0.4 ml kg⁻¹ h⁻¹</td>
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</tbody>
</table>

TABLE III. Blood-gas tensions (mean ± SEM) at the start of hypnotic infusion

<table>
<thead>
<tr>
<th></th>
<th>Althesin</th>
<th>Etomidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂(kPa)</td>
<td>3.7±0.29</td>
<td>3.9±0.41</td>
</tr>
<tr>
<td>PaO₂(kPa)</td>
<td>17.9±1.7</td>
<td>18.6±1.4</td>
</tr>
</tbody>
</table>

RESULTS

Intracranial pressure

ICP decreased progressively during the infusion in four out of five patients in each group. Seventy five per cent of the mean decrease in ICP occurred during the first 10 min of the Althesin infusion,
while only 54% of the total mean decrease in ICP occurred during this period with etomidate. There was a significant percentage reduction in ICP in the etomidate group at 10 and 30 min, and in the Althesin group at 30, 50 and 70 min (fig. 1). Using absolute mean values, the decrease in ICP reached statistical significance at all times only when the data from the etomidate and Althesin groups were combined.

If the two non-responder patients, one in each drug group, are excluded, there was a significant correlation between initial mean ICP and the absolute reduction in ICP at 30, 50 and 70 min for both drugs (fig. 2). Variations in the amplitude of the ICP with pulse pressure and artificial respiration were reduced equally by the two drugs, and in proportion to the change in mean ICP (fig. 3).

Arterial pressure

The baseline values of arterial pressure were slightly higher in the etomidate group, but the difference was not significant. No difference in the state of hydration of the two groups was apparent from analyses of temperature, fluid balance and CVP. Both systolic and mean arterial pressures decreased during the infusion. Mean arterial pressure decreased by 11% with Althesin and by 9.5% with etomidate during the first 10 min, the decreases
reaching statistical significance in the etomidate group at 10 and 50 min for systolic and at 50 min for mean arterial pressure. At no time was the decrease in systolic or mean pressure significant in the Althesin group. Combination of the etomidate and Althesin data results in a significant decrease in both mean and systolic arterial pressures at all times. There was statistically no difference in the decrease in arterial pressure between the two groups (fig. 4).

There was no correlation between change in mean arterial pressure and in mean ICP with drug administration, except in one patient in each group. In general arterial pressure decreased more than ICP, but the lack of correlation in most patients might indicate that other factors are important in the reduction of the ICP.

Cerebral perfusion pressure

Cerebral perfusion pressure (CPP) (mean AP – mean ICP) decreased to less than 60 mm Hg in one patient in the etomidate group (at 50 min in patient No. 5, whose ICP did not respond to the infusion) and in two patients in the Althesin group (at 30, 50 and 70 min in patient No. 4 and at 50 min in patient No. 5, whose ICP was also non-responsive). On the other hand, in one patient in the Althesin group, an initially low CPP of 45 mm Hg increased to 81 mm Hg at 10 min. Although mean CPP appears reduced at all times in both groups, the differences did not reach statistical significance even when data from both groups were combined. Furthermore, there were no statistically significant differences between CPP of the groups at any time (fig. 5).

Heart rate

The heart rate (HR) was slightly faster in the Althesin group at the start of the study, but the difference was not significant. HR increased by 9.5% with etomidate and by 14% with Althesin during the first 10 min of the infusion. Increases in HR in both groups appear dose-related and reach statistical significance at 10, 30 and 70 min in the etomidate group, and at 10, 50 and 70 min in the Althesin group (fig. 6). Although increases in HR are consistently higher in the Althesin group, no statistically significant difference in heart rate was reached at any time between the two groups.

Temperature

There was no change in rectal temperature during the study.

Pupils

Although there was a tendency for pupillary reactions to become sluggish during the infusion, no consistent change was noted in pupillary size, and no obvious differences emerged between the two agents.
Cerebral function monitoring

There were inadequate data to compare the two agents, but both infusions appeared to depress the lower border of the cerebral function monitor (CFM) trace with time. These observations are consistent with the reports of Prior, Maynard and Brierey (1978) and Frank and colleagues (1982) for Althesin, and Doenicke and co-workers (1982) for etomidate.

DISCUSSION

The introduction of infusions of hypnotic drugs in the treatment of post-traumatic increases in ICP in an effort to minimize secondary brain damage, has led to a search for agents with a shorter duration of action and fewer side effects than the barbiturates. It is well established that Althesin and etomidate decrease ICP (Pickerodt et al., 1972; Takahashi et al., 1973; Turner et al., 1973; Schulte am Esch, Pfeifer and Thiemig, 1978; Moss et al., 1979; Zattoni et al., 1980; Prior et al., 1983). The mechanism is probably via a reduction in cerebral metabolism and thus CBF (Pickerodt et al., 1972; Van Aken and Rolly, 1976; Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978; Renou et al., 1978). The fact that the decrease in ICP correlated poorly with the change in arterial pressure in this study would be consistent with this hypothesis.

Althesin has, however, several disadvantages, including the relatively high incidence of allergic reactions (Beamish and Brown, 1981; Clarke, 1982) and the potential hazards of larger doses of the solubilizing agent Cremophor EL (Knell, Turner and Chambers, 1983; Lawler, McHutchon and Bamber, 1983). Furthermore, during continuous infusion anaesthesia, Althesin appears to induce a more marked derangement of hepatic enzyme activity than do either etomidate or thiopentone (Blunnie et al., 1981). These problems have led to the discontinuance of the manufacture of Althesin. This study was conducted before the decision to cease manufacture, but we believe that Althesin provides a well-accepted standard with which to compare the action of other agents. In contrast, etomidate is reported to provide greater cardiovascular stability than Althesin (Popescu, 1976) and does not release histamine (Doenicke et al., 1973). It is a potent anticonvulsant, and has been shown to undergo rapid elimination (Kay, 1976). In addition, the solubilization of 125 mg of the drug in 1 ml of alcohol avoids the administration of Cremophor.

In this study both agents appeared to decrease ICP to the same degree. The failure to reach statistical significance at certain times probably reflects the small sample size and the fact that one patient in each group failed to respond to the treatment. In a series of 48 patients (unpublished data) treated in Leeds with Althesin infusions for increases in ICP after severe head injury, seven were unresponsive. Prior and colleagues (1983) reported that two out of 10 patients failed to respond to an etomidate infusion of up to 25 µg kg⁻¹ min⁻¹. Both unresponsive patients in their series and in this study had subdural haematomas with associated cerebral oedema.

The shape of the intracranial compliance curve might lead one to anticipate that the decrease in ICP should relate to the initial ICP, and this proved to be the case in this study, as in other previous reports with etomidate (Moss et al., 1979; Prior et al., 1983) and Althesin (Turner et al., 1973).

Preservation of CPP as demonstrated for both agents is in accord with previous results: Sari and colleagues (1976) using Althesin 0.1-mg kg⁻¹ bolus followed by 0.3-ml kg⁻¹ h⁻¹ infusion; Moss and colleagues (1979) using etomidate 0.3-ml kg⁻¹ boluses;
ever, Popescu (1976), in a comparative study of 0.07 ml kg\(^{-1}\) and etomidate 0.15 mg kg\(^{-1}\). How-

Lamalle (1976) reported increases in heart rate of 30% and 11% 2 min after bolus doses of Althesin 0.07 ml kg\(^{-1}\) and etomidate 0.15 mg kg\(^{-1}\). How-

ever, Popescu (1976), in a comparative study of etomidate 0.19 mg kg\(^{-1}\) and Althesin 0.523 ml kg\(^{-1}\) given as boluses, reported a 2.75% reduction in HR with etomidate and a 21% increase in HR with Althesin.

**CONCLUSIONS**

In conclusions, this prospective, randomized, double-blind trial has demonstrated that both etomidate and Althesin infusions decrease ICP follow-

ing severe head injury to a similar degree. Both agents reduce systolic and mean arterial pressures in normovolaemic patients, but CPP is little changed. HR increases significantly with both agents—appar-

ently in relation to dose.

It appears that etomidate provides an effective alternative to Althesin in the treatment of increases in ICP following severe head injury at an initial infu-

sion rate of 50 μg kg\(^{-1}\) min\(^{-1}\) for 10 min (to provide a loading dose) and then of 20–40 μg kg\(^{-1}\) min\(^{-1}\). If ICP is not controlled with this dose range, an alternative or additional agent should probably be used.

In Britain, the continuing use of infusions of etomidate in intensive care is under review at the time of writing, following the reports of Allolio and colleagues (1983), Fellows, Byrne and Allison (1983), Fellows and colleagues (1983), Ledingham and Watt (1983), and Sebel, Verghese and Makin (1983) on the effects of the drug on adrenocortical secretion. However, the drug does have certain advan-

tages in that it is associated with cardiovascular sta-

bility and possesses anticonvulsant activity. In addi-

tion, as demonstrated here, etomidate decreases ICP as effectively as does Althesin. Since the study was completed, the manufacture of Althesin has been discontinued because of concern about anaphylactoid reactions. None-the-less, withdrawal is so recent that the drug provides a useful and familiar yardstick of comparison in respect of controlling ICP following head injury (Mcllhany et al., 1983; Moss et al., 1983). Certainly, an hypnotic drug to control ICP is needed—other than the barbiturates, which are associated with circulatory depression and delayed excretion (Krier et al., 1984; Miller et al., 1984). If the problems of adrenocortical suppression can be resolved, perhaps through the use of steroid supplements (Reis Miranda and Stoutenbeek, 1983), then etomidate may have a role in the management of severe head injury.

**REFERENCES**


