CEREBRAL ELECTRICAL ACTIVITY INFLUENCES THE EFFECTS OF ETOMIDATE ON CEREBRAL PERFUSION PRESSURE IN TRAUMATIC COMA

R. M. BINGHAM, F. PROCACCIO, P. F. PRIOR AND C. J. HINDS

Prevention of secondary ischaemic insults in patients in traumatic coma is based on minimizing cerebral metabolic demands and maintaining adequate cerebral perfusion by controlling intracranial pressure (ICP) and optimizing systemic arterial pressure (Moss et al., 1983). Methods currently used to control ICP include the administration of osmotically active agents, diuretics and, less frequently, steroids as well as artificial ventilation. Many centres have also used continuous infusions of i.v. anaesthetic agents, supplemented if necessary, by bolus doses to decrease acute increases in ICP or to prevent increases in ICP in response to stimulating procedures (Moss, Gibson and McDowall, 1980; Prior et al., 1983). Unfortunately, these agents can also depress the cardiovascular system (Traeger et al., 1983) and, consequently, the net effect on cerebral perfusion pressure (CPP) is variable and depends on the relative magnitude of the alterations in ICP and mean arterial pressure (MAP). Thus although the administration of bolus doses of i.v. anaesthetic agents to patients with intracranial hypertension can decrease ICP, on occasions potentially dangerous decreases in CPP can occur (Prior et al., 1983). Clearly, therefore, it would be advantageous to be able to predict in an individual patient the probable effects of such therapy on ICP, MAP and CPP.

Since the reduction of ICP produced by these agents is related to a decrease in cerebral blood

SUMMARY

The effects of 124 boluses of etomidate 0.2 mg kg⁻¹ i.v. on intracranial pressure (ICP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) were studied in eight patients with severe head injury (Glasgow coma score < 8). The data were divided into two groups based on the minimum voltage of the cerebral function monitor (CFM) recording before the bolus. In group A this was less than 5 µV (representing profound cortical electrical depression), while in group B the minimum voltage was greater than 5 µV. The mean decrease in ICP following etomidate was significantly greater in group B (mean ± SEM: −8.6 ± 0.7 mm Hg) than in group A (−3.8 ± 0.6 mm Hg) (P < 0.0001). The decrease in arterial pressure was similar in both groups. Consequently, there was a small mean increase in CPP in group B (2.2 ± 0.9 mm Hg), whereas in group A CPP decreased (−4.7 ± 1.5 mm Hg) (P < 0.001). There was a strong correlation between the decreases in ICP and MAP in group A (r = 0.70, P < 0.01), but not in group B (r = 0.05). Thus, when cortical electrical activity was already maximally suppressed, further administration of an i.v. anaesthetic agent produced only relatively small decreases in ICP, largely as a passive response to decreases in MAP. CPP was therefore usually reduced. Conversely, in the absence of such depression larger decreases in ICP, unrelated to hypotension, occurred and these were usually associated with increases in CPP. However, even under these circumstances, potentially dangerous decreases in CPP may be seen.
flow (CBF), which is, in turn, a response to a reduction in cerebral metabolic requirements (cerebral metabolic rate for oxygen, CMRO₂) (Pickerodt et al., 1972; Sari et al., 1976; Renou et al., 1978), the effect is likely to be least when neuronal metabolism is already significantly depressed. We have investigated the relationship between cerebral metabolic rate, as reflected by cortical electrical activity (Paulson and Sharbrough, 1974) monitored using the cerebral function monitor (CFM) and the changes in ICP, MAP and CPP occurring in response to the i.v. administration of bolus doses of etomidate.

PATIENTS AND METHODS

Patients

Eight consecutive patients (two female) admitted to the Intensive Care Unit with severe head injury (Glasgow Coma Score < 8) were studied. Their ages ranged from 3 to 37 yr. Evacuation of an intracranial haematoma was performed in three patients (one intracerebral, one extradural, one subdural). Four had diffuse swelling and the remaining patient had, predominantly, oedema of the left hemisphere.

Monitoring

Indwelling Teflon cannulae in a radial artery and in the right internal jugular vein were used to permit the continuous monitoring of arterial and central venous pressures (CVP), respectively (Bell & Howell type 4/327/1 pressure transducers).

A pre-calibrated subdural pressure transducer (Gaeltec Ltd) was used for the continuous measurement of ICP, and the electroencephalograph (EEG) was recorded continuously using a Cerebral Function Monitor (Par Medex Ltd). Three scalp needle electrodes were used in standardized left and right parietal positions with a mid-frontal “guard” electrode to help rejection of interference. All monitoring equipment was calibrated at least twice a day, and more frequently if necessary.

A continuous record of CVP, MAP, ICP and cerebral electrical activity was obtained on a Devices M19 4-channel chart recorder.

Treatment

All patients received intermittent positive pressure ventilation to maintain $P_{A\text{CO}_2}$ between 3.4 and 4.7 kPa. Inspired oxygen concentration was adjusted to maintain arterial oxygen saturation greater than 90%.

Patients were sedated with a continuous infusion of etomidate (initially 5 $\mu$g kg$^{-1}$ min$^{-1}$ i.v.) and intermittent opiates (usually phenoperidine 1-2 mg i.v.). Pancuronium 2-4 mg i.v. was administered if necessary to prevent the patient resisting the ventilator.

If the ICP increased to more than 20 mm Hg, further etomidate was administered, either as a bolus (0.2 mg kg$^{-1}$) or by increasing the rate of the infusion (up to 25 $\mu$g kg$^{-1}$ min$^{-1}$). Mannitol (0.3 g kg$^{-1}$) was also used to control ICP. However, if on any occasion the ICP failed to decrease following mannitol, its use was discontinued and frusemide 20 mg i.v. followed by acetazolamide 250 mg i.v. 6-hourly was substituted. All but one patient received a dose of mannitol at some stage during their treatment, although only four required additional administrations.

Fluid intake was restricted to 5% dextrose 1 ml kg$^{-1}$ h$^{-1}$. Colloidal solutions (Haemaccel or plasma protein fraction) were administered as required to maintain circulating volume.

Prophylactic anti-convulsant therapy (phenobarbitone 60 mg i.m. 8-hourly in adults) was given to all patients (supplemented with diazepam and phenytoin if seizures occurred).

Essential stimulating procedures (physiotherapy, tracheal suction) were preceded by the administration of a bolus of etomidate 0.2 mg kg$^{-1}$ to attenuate the associated increase in ICP.

All events, drug administrations and procedures were noted on the four-channel chart recording, which was continued for the duration of ICP monitoring (up to 7 days).

The effects of bolus doses of etomidate were measured by retrospective analysis of the chart records by one author (R.B.). Random and independent checks of consistency were made by another (F.P.). Analysis was restricted to the 124 occasions on which the bolus of etomidate was not accompanied by the administration of any other drug(s), and during which no stimulating procedure had occurred.

The data were divided into two groups on the basis of the minimum voltage of the CFM trace immediately preceding the bolus. Either (group A; $n = 29$ observations obtained in five patients) this was depressed to 5 $\mu$V or less (representing marked reduction in cortical electrical activity) or (group B; $n = 95$ observations obtained from eight
ETOMIDATE AND THE CFM IN TRAUMATIC COMA

patients) CFM minimum voltage was greater than 5 μV. This value was chosen to discriminate between the two groups as it represents a profound decrease in cerebral electrical activity, which has been shown by previous work to correspond to a “burst suppression” pattern on the conventional EEG (Prior, Maynard and Brierley, 1978).

The measurements made and the derivation of the calculated values are shown in the appendix. The Pearson product–moment correlation and the two-sample t test were used for statistical analyses.

RESULTS

Baseline values of ICP did not differ significantly between the two groups (table I). Although the pre-bolus MAP was slightly lower in group A (mean ± SEM: 73.9 ± 3.1 mm Hg) than that in group B (81.5 ± 1.6 mm Hg) (P = 0.04) (table I), there was no significant difference in the decrease in MAP following etomidate in the two groups (group A: −8.4 ± 1.9 mm Hg; group B: −6.4 ± 0.7 mm Hg) (table II). The administration of etomidate decreased ICP on 90% of occasions in group A and 97% in group B. However, the magnitude of the decrease was significantly greater in group B (−8.6 ± 0.7 mm Hg) than in group A (−3.8 ± 0.6 mm Hg) (P < 0.0001) (table II, fig. 1).

Since the mean decrease in MAP was similar in both groups, the larger reduction in ICP in group B resulted in a small mean increase in CPP (2.2 ± 0.9 mm Hg) whereas, in group A, the boluses of etomidate produced a mean decrease in CPP (−4.7 ± 1.5 mm Hg) (table II, fig. 1). These differences in CPP following the boluses were significant (P < 0.001).

Although mean CPP increased in group B, the effects of individual boluses were variable (table III). In this group CPP decreased following 38% of the etomidate boluses, and remained unchanged in 3%. In group A CPP usually decreased (69% of occasions), although on 14% of occasions it remained unchanged (table III).

The maximum increase in CPP was only 6 mm Hg in group A (this was secondary to an increase in MAP of 5 mm Hg rather than a reduction in ICP), whereas in group B an increase in CPP of greater than 6 mm Hg occurred following 30% of the administrations of etomidate,
TABLE III. Effects of individual boluses of etomidate 0.2 mg kg\(^{-1}\) on CPP in groups A (CFM < 5 \(\mu\)V) and B (CFM > 5 \(\mu\)V).

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(CFM &lt; 5 (\mu)V)</td>
<td>(CFM &gt; 5 (\mu)V)</td>
</tr>
<tr>
<td>Decrease in CPP</td>
<td>20 (69%)</td>
<td>36 (37%)</td>
</tr>
<tr>
<td>CPP unchanged</td>
<td>4 (14%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Increase in CPP</td>
<td>5 (17%)</td>
<td>56 (59%)</td>
</tr>
</tbody>
</table>

the maximum increase being 21 mm Hg. The maximum decrease in CPP was similar in both groups (group A = -28 mm Hg, group B = -25 mm Hg).

There was a strong positive correlation between the decrease in ICP and the decrease in MAP in group A (\(r = 0.70; P < 0.01\)), whereas there was no such correlation in group B (\(r = 0.05\); ns) (fig. 2).

Finally, when both groups were combined, there was a positive correlation between the value of the baseline of the CFM trace before the bolus and the subsequent change in CPP (\(r = 0.304; P < 0.001\)), a relationship which was absent when groups A and B were analysed separately.

**DISCUSSION**

The extent and direction of the change in CPP following the bolus administration of an i.v. anaesthetic agent to a patient with intracranial hypertension will depend on the relative magnitude of the alterations in MAP and ICP.

The change in arterial pressure will be influenced by the anaesthetic agent used (etomidate, for example, causes little cardiovascular depression (Gooding and Corssen, 1977)) and the state of the cardiovascular system before the bolus is administered. In particular, a compensated reduction in circulating volume may be unmasked by i.v. anaesthetics, leading to marked hypotension (Traeger et al., 1983).

The decrease in ICP following the administration of these agents is secondary to a reduction in cerebral blood flow (CBF) and intracranial blood volume (IBV) (Pickerodt et al., 1972; Turner et al., 1973). Thus, the magnitude of the pressure change will depend on the extent of the volume change as well as the intracranial compliance.

Two mechanisms may account for the decrease in CBF and IBV following the administration of an i.v. anaesthetic agent. First, because auto-regulation of CBF is often impaired in traumatic coma (Overgaard and Tweed, 1974), decreases in MAP will be associated with passive reductions in CBF. Second, the cerebral metabolic depression produced by these agents will result in a secondary reduction in CBF. Thus, once cerebral metabolism is substantially depressed, further administration of an i.v. anaesthetic agent is unlikely to decrease ICP significantly, except as a passive response to the decreases in MAP. Under these circumstances CPP is unlikely to increase and will often decrease.

In 1974, Michenfelder demonstrated that, in dogs, a continuous high-dose infusion of thiopentone produced a progressive decrease in CMRO\(_4\) until cortical electrical activity had been

**FIG. 2.** Scatter diagram of change in ICP against change in MAP following bolus doses of etomidate 0.2 mg kg\(^{-1}\) in groups A (CFM < 5 \(\mu\)V) and B (CFM > 5 \(\mu\)V). There is a significant correlation between these two variables in group A (\(r = 0.70; P < 0.01\)), but none in group B (\(r = 0.05\); ns).
ETomidate and the CFM in Traumatic Coma

abolished. Thereafter, additional, larger doses of thiopentone produced no further reduction in CMRO₂ (Michenfelder, 1974). Kassell and his colleagues performed similar work in canine models, but also measured CBF. They found that neither CMRO₂ nor CBF could be decreased further once sufficient anaesthetic had been given to produce burst suppression of between 30 and 60 s duration on the EEG (Kassell et al., 1980). Thus the degree of suppression of cortical electrical activity indicates the extent of cerebral metabolic depression and it is unlikely that the administration of i.v. anaesthetic agents in the presence of such electrical depression would result in useful reductions in ICP (decreases in ICP unrelated to reductions in MAP, and therefore associated with increases in CPP). The results of this study support this contention.

We have used the CFM rather than the conventional EEG because it is better suited to continuous monitoring in the intensive care unit, interpretation is relatively simple and it is particularly valuable for the detection of cerebral ischaemia (Matoušek et al., 1984). Previous work has shown that when the minimum voltage of the CFM decreases to less than 5 μV there is profound cerebral electrical depression, often equivalent to a "burst suppression" pattern on the conventional EEG (Prior, Maynard and Brierley, 1978). Before analysis of the data, we selected this voltage to discriminate between the two groups. During the period of sedation we were unable to exclude the possibility that, in some instances, this depression might have been a result of cerebral damage rather than the administration of anaesthetic agents.

In the presence of such cerebral electrical depression, the administration of etomidate did produce a small mean decrease in ICP (−3.8 mm Hg), but this was significantly less than that occurring when the CFM was not depressed (−8.6 mm Hg). Since, in addition, MAP often decreased, CPP was usually decreased (in 69% of instances). Furthermore, although CPP increased on 17% of occasions in group A, the magnitude of the increases was usually small (<2 mm Hg). In only one instance did CPP increase by more than this, and on this occasion a 6-mm Hg increase was principally mediated by an unexplained 5-mm Hg increase in MAP. Finally, the strong correlation between the changes in MAP and ICP in this group suggests that any reduction in ICP which did occur was a passive response to the decrease in MAP.

However, when cerebral electrical activity was not depressed, boluses of etomidate produced larger decreases in ICP (mean −8.6 mm Hg) so that, although a similar degree of hypotension occurred, CPP increased in more than one-half (59%) of instances and overall by a mean of +2.2 mm Hg. In these circumstances, 30% of the boluses produced increases in CPP greater than 6 mm Hg (the maximum increase in group A). Furthermore, in this group there was no correlation between the changes in MAP and ICP; this suggests that hypotension was not the sole mechanism responsible for the decrease in ICP. Although CBF was not measured in this study, it is probable that, when the CFM was not suppressed, the decreases in ICP were largely in response to a reduction in CBF caused by depression of cerebral metabolic rate.

The positive correlation (in the combined data) between the value of the baseline of the CFM and the subsequent change in CPP provides further support for the hypothesis that the effect of the boluses of etomidate on CPP is influenced by the preceding cerebral electrical activity.

In conclusion, the CFM would seem to be a clinically useful guide to the administration of etomidate (and probably other anaesthetic agents (Procaccio, personal communication)), to patients in traumatic coma with intracranial hypertension. In our patients, administration of etomidate in the presence of a minimum CFM voltage of less than 5 μV produced relatively small reductions in ICP and no useful increase in CPP; indeed CPP was usually reduced. Under these circumstances, further administration of i.v. anaesthetic agents is unlikely to be of benefit and should probably be avoided. In the absence of such depression, CPP increased following more than one-half the boluses. However, marked hypotension sometimes resulted in potentially damaging decreases in CPP, even in this group. We would recommend that i.v. boluses of anaesthetic agents should be administered to patients in traumatic coma only when the CFM voltage is greater than 5 μV, the cardiovascular system is stable and the circulating volume adequate. Furthermore, since a positive correlation between the initial ICP and the extent of the subsequent decrease has been demonstrated previously (Turner et al., 1973; Prior et al., 1983), such treatment should be restricted to those with significant intracranial hypertension (for example, >25 mm Hg).
## APPENDIX

MEASUREMENTS TAKEN FROM CHART RECORDS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate infusion rate</td>
<td>μg kg⁻¹ min⁻¹</td>
</tr>
<tr>
<td>Etomidate dose</td>
<td>mg</td>
</tr>
<tr>
<td>Procedure or stimulus (if any associated with bolus)</td>
<td>—</td>
</tr>
<tr>
<td>Systolic and diastolic arterial pressures before bolus; steady state</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Systolic and diastolic ICP before bolus; steady state</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Maximum and minimum CFM before bolus; steady state</td>
<td>μV</td>
</tr>
<tr>
<td>Systolic and diastolic arterial pressures after bolus; maximum change</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Systolic and diastolic ICP after bolus; maximum change</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Maximum and minimum CFM after bolus; maximum change</td>
<td>mms</td>
</tr>
</tbody>
</table>

### Derivation of calculated values

- Mean ICP (ICP) = \( \frac{\text{Systolic ICP} - \text{Diastolic ICP}}{2} \)
- Mean arterial pressure (MAP) = \( \text{Diastolic AP} + \frac{\text{pulse pressure}}{3} \)
- CPP = MAP - ICP
- Change in ICP (ICP) = ICP after bolus - ICP before bolus
- Change in CPP (CPP) = CPP after bolus - CPP before bolus
- Central venous pressure (measured at mid-axillary line) was never sufficiently increased in these patients (all of whom were nursed in a 45° semi-reclining posture) to influence CPP and was therefore not included in the calculation.

### ACKNOWLEDGEMENTS

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### REFERENCES


