THE EFFECT OF METHOXYFLURANE ON CEREBROSPINAL FLUID PRESSURE IN PATIENTS WITH AND WITHOUT INTRACRANIAL SPACE-OCCUPYING LESIONS

BY

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SUMMARY

The effect of methoxyflurane 0.5 per cent and 1.5 per cent on cerebrospinal fluid (c.s.f.) pressure has been studied in patients with normal c.s.f. pathways and in patients with intracranial space-occupying lesions. In patients with normal c.s.f. pathways, methoxyflurane 0.5 per cent produced variable responses, causing small increases in c.s.f. pressure in some and small decreases in others. On the other hand, methoxyflurane 1.5 per cent caused significant increases in c.s.f. pressure in all patients, increases that were not associated with any alteration in either carbon dioxide tension or central venous pressure. In those patients studied with intracranial space-occupying lesions, both 0.5 per cent and 1.5 per cent methoxyflurane produced increases in c.s.f. pressure which were markedly greater than those found in the patients without space-occupying lesions. The mean rise in c.s.f. pressure was dependent on the concentration of the drug administered, being small with 0.5 per cent methoxyflurane, but much greater with the higher concentration. A possible hazard in such patients is that the administration of methoxyflurane may lead to gradients of intracranial pressure, thus aggravating brain shifts and mid-brain distortion and, if the skull is opened, lead to external brain herniation.

The elucidation of the effects of anaesthesia on the cerebrospinal fluid pressure has been the object of many investigations both in man and in animals. Although much discussion has centred around the interwoven aspects of respiratory obstruction, respiratory acidosis and hypoxia, little attention has been paid to the effects of the anaesthetic agents themselves on c.s.f. pressure. Indeed a search of the literature shows that until recently it was generally believed that anaesthetic agents per se did not directly affect the c.s.f. pressure, although several workers excluded ether from this generalization (Lundberg, Kjallquist and Bein, 1959).

Recently, however, it has been shown that in man both halothane and trichloroethylene can produce significant increases in c.s.f. pressure in the absence of associated changes in either central venous pressure or carbon dioxide tension (McDowall, Barker and Jennett, 1966). In addition, the increase in c.s.f. pressure produced by both halothane and trichloroethylene has been demonstrated to be greatly augmented in patients with intracranial space-occupying lesions (Jennett et al., 1969).

In the past, methoxyflurane* has been extensively studied both from the cardiovascular (Bagwell and Woods, 1962; Walker, Eggers and Allen, 1962; Brassard et al., 1963; Payne, 1963; Black, 1967) and from the respiratory (Black and McKane, 1965; Tomlin, 1963, 1965) aspects. However, at the present time there remains very little information as to the effect of this drug on cerebral haemodynamics and c.s.f. mechanics. This present study has thus been undertaken both to augment the pharmacology of methoxyflurane and to determine whether or not it has

* Methoxyflurane: Penthrane, Abbott Laboratories.
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any advantages over halothane or trichloroethylene in patients with space-occupying lesions.

METHODS
In this assessment of the effects of methoxyflurane on the c.s.f. pressure, two separate groups of patients have been studied:
(a) patients with normal c.s.f. pathways;
(b) patients with intracranial space-occupying lesions.
Each group has been further subdivided so that some patients received 0.5 per cent methoxyflurane and the others 1.5 per cent.

Patients with normal c.s.f. pathways.
The initial studies were carried out on patients undergoing operative treatment for prolapsed intervertebral disc lesions, it being assumed that these otherwise healthy patients would have normal c.s.f. pathways. In each case studied, the informed consent of the patient was obtained. In all, 15 patients (10 male and 5 female) with normal c.s.f. pathways were investigated. The average age of these patients was 34 years (range 19-56 years). Methoxyflurane 0.5 per cent was given to 10 of these patients, and methoxyflurane 1.5 per cent to the remainder.

As the detailed methodology of each investigation closely followed that previously described (McDowall, Barker and Jennett, 1966), only the salient features are summarized in this paper.

Intravenous induction of anaesthesia using only a sleep dose of thiopentone sodium was followed by endotracheal intubation under suxamethonium paralysis. Controlled ventilation with nitrous oxide and oxygen was instituted and adjusted to maintain normocapnia. The initial minute volume required to produce normocapnia was calculated using the Nunn blood-gas predictor (Nunn, 1962). Arterial carbon dioxide tension was assessed by continuous measurement of end-tidal \( P_{CO_2} \) and by intermittent measurement of blood \( P_{CO_2} \) by the technique of Siggaard-Andersen and associates (1960). By reference to these measurements, ventilation was adjusted to hold \( P_{CO_2} \) within the normocapnic range, throughout the period of duty. Muscular relaxation was maintained by tubocurarine chloride.

Lumbar puncture was performed in the lateral recumbent position and the needle was connected by a saline-filled tube to a low-pressure Statham transducer, from which, after suitable amplification, the c.s.f. pressure was continuously displayed on an ultra-violet recorder. Once steady control measurements of c.s.f. pressure had been obtained, methoxyflurane in a concentration of either 0.5 per cent or 1.5 per cent was added to the inspired gas mixture from a calibrated vaporizer.* The effect of this volatile anaesthetic agent on the c.s.f. pressure was then followed for 10 minutes, at which point the methoxyflurane was discontinued and any further alterations in c.s.f. pressure monitored over the next 10 minutes.

Patients with intracranial space-occupying lesions.
This group comprised 9 patients, all of whom presented with signs and symptoms of increased intracranial pressure, and who on subsequent investigation were shown to have intracranial space-occupying lesions. The average age of the patients in this group (6 males and 3 females) was 50.8 years (range 38-65 years). Of these 9 patients, 4 were given methoxyflurane 0.5 per cent and 5 methoxyflurane 1.5 per cent.

Anaesthesia in these patients followed a pattern similar to that already described for the patients with normal c.s.f. pathways. However, once the patient had been anaesthetized, he was transferred to the operating theatre and positioned in the usual way for craniotomy but with the table horizontal. The head was draped, and the first of the burr holes required for the subsequent surgical exposure was made. Through this, a metal brain cannula was inserted into the lateral ventricle and connected, as described previously, to the ultra-violet recorder. No further surgery was undertaken until all measurements of the c.s.f. pressure had been completed. Thus, prior to completion of the pressure measurements, there was no significant decompression of the skull.

The stability of the intracranial pressure was verified for a few minutes before methoxyflurane, in a concentration of either 0.5 per cent or 1.5 per cent, was administered from a calibrated vaporizer. In most instances, methoxyflurane was administered for 10 minutes and then discontinued—the resulting intracranial pressure changes being fol-

* Pentec; Cyprane Ltd.
allowed continuously for 15–20 minutes in all. If
the c.s.f. pressure rose very abruptly, the agent
was discontinued before the end of the 10 minutes.

In addition to the measurement of $P_{\text{CO}_2}$ in
both groups of patients arterial and central venous
pressures were also monitored. Arterial blood
pressure was measured either by upper arm
sphygmonanometry (patients with normal c.s.f.
pathways) or by direct intra-arterial recording
(patients with space-occupying lesions). In 18
patients, central venous pressure was measured
from the superior vena cava via a catheter inserted
percutaneously in the antecubital fossa. Finally,
oesophageal temperature was measured in all
patients, and this allowed temperature correction
of the blood-gas results, using the Severinghaus
blood-gas calculator (Severinghaus, 1966).

RESULTS

In the tabulation of the results of these studies
and in the discussion which follows, values for
c.s.f. pressure are presented as values of mean
c.s.f. pressure; i.e., diastolic pressure + $\frac{1}{3}$ pulse
pressure, and in order to obtain comparable
results, systolic and diastolic pressure readings
were always taken at the end-expiratory level. In
the patients with normal c.s.f. pathways systolic
blood pressure was recorded. In patients with
space-occupying lesions, however, mean arterial
blood pressure was taken (i.e. diastolic blood
pressure + $\frac{1}{3}$ pulse pressure), since it is mean
pressure that determines the adequacy or other-
wise of tissue perfusion. Cerebral perfusion pres-
sure (mm Hg) was calculated as mean arterial
blood pressure (mm Hg)−mean c.s.f. pressure
(mm Hg).

Patients with normal c.s.f. pathways.

Effect of methoxyflurane 0.5 per cent. In the 10
patients given methoxyflurane 0.5 per cent, the
mean initial c.s.f. pressure (± SD), i.e. the pres-
sure under nitrous oxide-oxygen anaesthesia alone,
was 111 ± 75 mm H$_2$O. After 10 minutes of
methoxyflurane inhalation, varied changes in pres-
sure were seen in the individual patients (fig. 1); in 5 patients the c.s.f. pressure fell, while in the
others it increased. The range of change in pressure
was from −33 mm H$_2$O to +32 mm H$_2$O (fig. 1), and the mean c.s.f. pressure at the 10th
minute of methoxyflurane administration at 109 ±
77 mm H$_2$O was virtually unchanged from the
initial value (0.90 > P > 0.80).

In this group of patients methoxyflurane 0.5 per
cent produced a significant fall in systolic arterial
blood pressure from a mean control value of
115 ± 10 mm Hg to a final value of 95 ± 9 mm Hg
(P < 0.001). There was also a significant, though
small, fall in carbon dioxide tension, the $P_{\text{CO}_2}$ fall-
ing from an initial value of 40.1 ± 3.0 mm Hg to
37.6 ± 2.6 mm Hg (0.05 > P > 0.025). As can be
seen from table I(A) there was no significant
change in central venous pressure during the
administration of the anaesthetic agent.

Effect of methoxyflurane 1.5 per cent. Under
nitrous oxide-oxygen anaesthesia the mean c.s.f.
pressure in this series of patients was 117 ± 60 mm
H$_2$O, a value essentially similar to that obtained
in the previous 10 patients (cf. table I(A)). How-
ever, following administration of 1.5 per cent
methoxyflurane, the c.s.f. pressure rose by a mean
value of 57 ± 20 mm H$_2$O to a final mean of
174 ± 92 mm H$_2$O on discontinuing drug adminis-
tration. This change in pressure is statistically
significant (P < 0.005). As can be seen from figure
1, each of the 5 patients investigated showed a
similar response. Figure 2 shows the effect of
methoxyflurane 1.5 per cent on one of the patients
in this group. Both systolic and diastolic c.s.f.
pressure are shown against time, and it can be seen
that there was a steady and progressive increase
in pressure during the administration of the drug.
TABLE I(A)
The effect of 10 minutes administration of 0.5 per cent methoxyflurane on c.s.f. pressure, systolic arterial blood pressure and central venous pressure in 10 patients with normal c.s.f. pathways.

<table>
<thead>
<tr>
<th></th>
<th>C.s.f. pressure (mm H₂O)</th>
<th>Systolic arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H₂O)</th>
<th>PaCO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O+O₂</td>
<td>111±75</td>
<td>115±10</td>
<td>1.2±1.5</td>
<td>40.1±3.0</td>
</tr>
<tr>
<td>N₂O+O₂+10 min</td>
<td>109±77</td>
<td>95±9.0**</td>
<td>1.3±0.9</td>
<td>37.6±2.6</td>
</tr>
<tr>
<td>0.5% methoxyflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values for PaCO₂ measured prior to and after methoxyflurane administration are also shown. Statistically significant difference: * P<0.05; † P<0.01; ‡ P<0.001.

TABLE I(B)
The effect of 10 minutes administration of 1.5 per cent methoxyflurane on c.s.f. pressure, systolic arterial blood pressure and central venous pressure in 5 patients with normal c.s.f. pathways.

<table>
<thead>
<tr>
<th></th>
<th>C.s.f. pressure (mm H₂O)</th>
<th>Systolic arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H₂O)</th>
<th>PaCO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O+O₂</td>
<td>117±60</td>
<td>105±10</td>
<td>1.9±2.9</td>
<td>43.2±2.0</td>
</tr>
<tr>
<td>N₂O+O₂+10 min</td>
<td>174±92†</td>
<td>84±5†</td>
<td>0.55±1.6</td>
<td>42.0±2.4</td>
</tr>
<tr>
<td>1.5% methoxyflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conversely, once methoxyflurane was discontinued, there was a steady fall in pressure to its initial value.

Once again there was a significant fall in systolic arterial blood pressure from an initial value of 105±10 mm Hg to 84±5 mm Hg at the end of methoxyflurane administration (P<0.005). As can be seen from table I(B), there was no significant difference in central venous pressure or carbon dioxide tension measured before, as compared with after, methoxyflurane administration.

**Patients with intracranial space-occupying lesions.**

**Effect of methoxyflurane 0.5 per cent.** In each of the 4 patients with space-occupying lesions to whom methoxyflurane 0.5 per cent was given, there was a rise in c.s.f. pressure. From a mean initial pressure under nitrous oxide-oxygen of 148±25 mm H₂O, the pressure rose by 71±27 mm H₂O during the administration of the drug to a mean value of 219±39 mm H₂O—a significant pressure increase (0.02>P>0.01) (table II(A)).

As can be seen from table II(A), mean arterial blood pressure fell significantly during the administration of 0.5 per cent methoxyflurane (0.05>P>0.025), while both central venous pres-
TABLE II(A)
The effect of 10 minutes administration of 0.5 per cent methoxyflurane on c.s.f. pressure, mean arterial blood pressure and central venous pressure in 4 patients with space-occupying lesions.

<table>
<thead>
<tr>
<th></th>
<th>C.s.f. pressure (mm H$_2$O)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H$_2$O)</th>
<th>Pa$_{CO_2}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N$_2$O + O$_2$</td>
<td>148 ± 25</td>
<td>97 ± 22</td>
<td>4.3 ± 0.11</td>
<td>34.2 ± 2.6</td>
</tr>
<tr>
<td>N$_2$O + O$_2$ + 10 min 0.5% methoxyflurane</td>
<td>219 ± 39*</td>
<td>78 ± 14*</td>
<td>4.5 ± 0.5</td>
<td>34.8 ± 3.9</td>
</tr>
</tbody>
</table>

TABLE II(B)
The effect of 10 minutes administration of 1.5 per cent methoxyflurane on c.s.f. pressure, mean arterial blood pressure and central venous pressure in 5 patients with space-occupying lesions.

<table>
<thead>
<tr>
<th></th>
<th>C.s.f. pressure (mm H$_2$O)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H$_2$O)</th>
<th>Pa$_{CO_2}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N$_2$O + O$_2$</td>
<td>171 ± 84</td>
<td>101 ± 22</td>
<td>7.0 ± 4.1</td>
<td>33.6 ± 3.9</td>
</tr>
<tr>
<td>N$_2$O + O$_2$ + 10 min 1.5% methoxyflurane</td>
<td>561 ± 186‡</td>
<td>73 ± 22†</td>
<td>8.25 ± 4.5</td>
<td>32.6 ± 4.8</td>
</tr>
</tbody>
</table>

Values for Pa$_{CO_2}$ measured prior to and after methoxyflurane administration are also shown. Statistically significant difference: * P<0.05; † P<0.01; ‡ P<0.001.

sure and carbon dioxide tension showed no significant change. In these patients, calculation of cerebral perfusion pressure from arterial and c.s.f. pressures (as described earlier) showed that there was a significant fall in this parameter due to the administration of methoxyflurane 0.5 per cent. The cerebral perfusion pressure fell from 86 ± 20 mm Hg under nitrous oxide-oxygen alone, to 59 ± 14 mm Hg under nitrous oxide, oxygen and methoxyflurane 0.5 per cent (0.02>P>0.01). The changes produced in the individual patients are shown in table III(A).

Effect of methoxyflurane 1.5 per cent. In each patient studied in this group, there was a marked and striking increase in c.s.f. pressure during the period of methoxyflurane administration—an increase that was, in each case, greater than that found in the 5 similar patients without space-occupying lesions given the same concentration of methoxyflurane (fig. 3). From an initial value of 171 ± 84 mm H$_2$O, the pressure rose by 390 ± 135 mm H$_2$O to a value of 561 ± 186 mm H$_2$O after 10 minutes administration—a significant rise in pressure (P<0.001) (table IIb).

Associated with the rise in c.s.f. pressure there was, in addition, a significant fall in mean arterial blood pressure, from an initial value of 101 ± 22 mm Hg to 73 ± 22 mm Hg (0.01>P>0.005). The cerebral perfusion pressure, since it is affected both by the rise in c.s.f. pressure and the fall in mean arterial blood pressure, also showed a significant fall, from an initial value of 88 ± 20 mm Hg to 32 ± 15 mm Hg, after 10 minutes administr-
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**TABLE III(A)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>N₂O + O₂</th>
<th>N₂O + O₂ + 10 min 0.5% methoxyflurane</th>
<th>Change in perfusion pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>64</td>
<td>43</td>
<td>-21</td>
</tr>
<tr>
<td>145</td>
<td>113</td>
<td>73</td>
<td>-40</td>
</tr>
<tr>
<td>147</td>
<td>83</td>
<td>54</td>
<td>-29</td>
</tr>
<tr>
<td>148</td>
<td>84</td>
<td>68</td>
<td>-16</td>
</tr>
<tr>
<td>Mean</td>
<td>86</td>
<td>59</td>
<td>-27</td>
</tr>
<tr>
<td>SD</td>
<td>±20</td>
<td>±14</td>
<td>±11</td>
</tr>
</tbody>
</table>

P<0.02.

**TABLE III(B)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>N₂O + O₂</th>
<th>N₂O + O₂ + 10 min 1.5% methoxyflurane</th>
<th>Change in perfusion pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>82</td>
<td>20</td>
<td>-60</td>
</tr>
<tr>
<td>109</td>
<td>111</td>
<td>39</td>
<td>-72</td>
</tr>
<tr>
<td>112</td>
<td>62</td>
<td>18</td>
<td>-44</td>
</tr>
<tr>
<td>114</td>
<td>83</td>
<td>30</td>
<td>-53</td>
</tr>
<tr>
<td>119</td>
<td>104</td>
<td>54</td>
<td>-50</td>
</tr>
<tr>
<td>Mean</td>
<td>88</td>
<td>32</td>
<td>-56</td>
</tr>
<tr>
<td>SD</td>
<td>±20</td>
<td>±15</td>
<td>±11</td>
</tr>
</tbody>
</table>

P<0.001

Discussion

**Patients with normal c.s.f. pathways.**

These results show that in normocapnic patients with normal c.s.f. pathways, methoxyflurane 1.5 per cent will increase the c.s.f. pressure by a significant degree, and that this increase in pressure is quantitatively similar to that found in earlier studies of the effect of halothane 0.5 per cent and trichloroethylene 0.9 per cent (McDowall, Barker and Jennett, 1966). With methoxyflurane 1.5 per cent, the average increase in c.s.f. pressure was 57±20 mm H₂O, and this compares with 63±31 mm H₂O for halothane 0.5 per cent and 105±46 mm H₂O for trichloroethylene 0.9 per cent. As occurred with halothane, this increase in c.s.f. pressure with methoxyflurane occurred despite quite marked degrees of arterial hypotension induced by the drug.

It is interesting to note that despite the high blood solubility of methoxyflurane, its effect on c.s.f. pressure was evident within the first minute of administration in 4 of the 5 cases studied. This feature is confirmed by the increase per minute in mean c.s.f. pressure which is evident from the 1st to the 10th minutes (fig. 4). Indeed, as can be seen from figure 4, the fall in pressure after discontinuing administration of the agent was similarly rapid and progressive. In this respect, the pattern of c.s.f. pressure change was similar to that found previously with halothane (McDowall, Barker and Jennett, 1966). In the absence of any change in central venous pressure, the increased c.s.f. pressure is most probably due to increased cerebral blood flow and cerebral blood...
intracranial blood volume. Consequently, it would appear that the intracranial blood volume is greater with methoxyflurane at a blood pressure of 84 mm Hg, than it is under nitrous oxide-oxygen anaesthesia with a blood pressure of 105 mm Hg.

In contrast to these findings with methoxyflurane 1.5 per cent, methoxyflurane 0.5 per cent produced no consistent or statistically significant change in c.s.f. pressure in these patients. Indeed, in half of the patients studied, a slight fall in pressure was found. The effect of this concentration of methoxyflurane on cerebral blood flow would therefore appear to be small and, in fact, 0.5 per cent methoxyflurane may reduce cerebral blood flow on occasions. Such a reduction in flow with this low concentration of the drug would be in keeping with preliminary measurements of cerebral blood flow in the dog given 0.5 per cent methoxyflurane (McDowall and Harper, 1965). It is possible that a similar biphasic effect on cerebral blood flow occurs with other inhalational anaesthetic agents, for example, cyclopropane (Alexander et al., 1968), and halothane (McDowall, Harper and Jacobson, 1963; McDowall, 1967). Further investigations are required to throw more light on this point, and as regards clinical use during anaesthesia.

Patients with intracranial space-occupying lesions.

Significantly greater increases in c.s.f. pressure were found in this second group of patients when either 0.5 or 1.5 per cent methoxyflurane was administered than occurred in patients with normal c.s.f. pathways.

Following the administration of 0.5 per cent methoxyflurane, the increase in pressure, although significant and occurring in each of the patients studied, was small and was certainly less than the increase produced by halothane 0.5 per cent (Jennett et al., 1969). However, this difference may be partly accounted for by the greater uptake of methoxyflurane 0.5 per cent by the rubber of the anaesthetic system.

The administration of methoxyflurane 1.5 per cent to this group of patients resulted in marked increases in c.s.f. pressure in each case which were significantly greater than those found in patients without space-occupying lesions (fig. 3). This finding accords with our previous experiences with halothane and trichloroethylene. As in patients with normal c.s.f. pathways, there was a rapid increase in pressure within a minute of starting the administration of the agent. The pressure continued to increase throughout the 10 minutes of administration and indeed for a further 2 minutes after discontinuing the drug, before it fell quickly to control values (fig. 5).

It is interesting to note that in these 9 cases, i.e. those with space-occupying lesions, the mean initial c.s.f. pressure (under nitrous oxide-oxygen anaesthesia) was 161 ± 62 mm H₂O. This value, although higher than that found in the patients without space-occupying lesions (113 ± 73 mm H₂O), is not markedly high. It indicates that compensation had occurred to accommodate the intracranial mass without marked change in intracranial pressure. In this situation, the addition of even a modest increase in intracranial blood volume consequent upon the administration of methoxyflurane leads to a magnified pressure rise, presumably because the compensating mechanisms which normally buffer the effect of such
changes in intracranial blood volume on intracranial pressure are already exhausted.

Such changes in intracranial pressure in patients with space-occupying lesions could be of clinical significance if gradients of pressure were to develop between separate intracranial compartments before the skull was opened, since such gradients would produce or aggravate internal brain herniation. Indeed, neurosurgeons are familiar with the sudden deterioration of some critically compressed patients during or following general anaesthesia. Although this has previously been ascribed to faulty anaesthetic technique producing hypoxia and/or hypercarbia, we would suggest that the above mechanism may produce such deterioration even under optimal conditions. Furthermore, on opening the skull, external herniation of the brain may occur, thus seriously restricting surgical access and possibly producing local brain trauma.

The simultaneous increase in c.s.f. pressure and fall in arterial blood pressure reduces cerebral perfusion pressure. If one accepts that the normal cerebral perfusion pressure is 80-90 mm Hg (i.e. normal mean arterial blood pressure = 90 mm Hg minus normal mean c.s.f. pressure = 7 mm Hg), then it can be seen from tables III(A) and III(B), that the mean initial perfusion pressures under nitrous oxide-oxygen anaesthesia are within normal limits. However, following the administration of either 0.5 per cent or 1.5 per cent methoxyflurane, perfusion pressure fell by a significant degree. Similar findings have been found following halothane and trichloroethylene administration. Indeed, the fall in perfusion pressure with methoxyflurane 1.5 per cent is the largest produced by any agent so far studied, the mean fall being $56 \pm 11$ mm Hg for 1.5 per cent methoxyflurane as compared with $40 \pm 15$ mm Hg for 1 per cent halothane and $23 \pm 15$ mm Hg with 0.9 per cent trichloroethylene (Jennett et al., 1969). It can also be seen from table III(b) that the final perfusion pressure following methoxyflurane 1.5 per cent administration was only $32 \pm 15$ mm Hg, a value considerably below the level of 40–50 mm Hg given by Zwetnow, Kjallquist and Siesjo (1968) as that at which evidence of cerebral hypoxia appears in animals. Indeed, of the 5 patients given methoxyflurane 1.5 per cent, 3 had cerebral perfusion pressure below 30 mm Hg (table III(b)).

Thus, it would seem that methoxyflurane 1.5 per cent administration during normocapnia, or even slight hypocapnia, can lower the perfusion pressure of the brain to values which have been shown to be partially inadequate in animals. It is worthy of note, however, that in the experimental situation described by Zwetnow, Kjallquist and Siesjo, the perfusion pressure was reduced by the injection of mock c.s.f. solution into the cisterna magna with a resultant increase in c.s.f. pressure and eventually a secondary reduction in cerebral blood flow. In the present studies, on the other hand, the reduction in cerebral perfusion pressure was due to a combination of systemic arterial hypotension and a primary increase in cerebral blood flow. Thus, should the cerebral perfusion pressure be lowered to such an extent that the cerebral blood flow is reduced, the intracranial pressure must of necessity also fall and consequently the perfusion pressure rise. In this way the system is partially autoregulatory. For this reason, reductions in cerebral perfusion pressure produced by the administration of volatile anaesthetic agents may not be of great clinical significance except in those patients with areas of regional ischaemia due to arterial disease. In such patients it is probable that such autoregulation cannot take place and any reduction in perfusion pressure could augment the existing ischaemia.

It has been shown previously that hyperventilation in patients with normal c.s.f. pathways reduces the extent of the c.s.f. pressure rise with volatile anaesthetic drugs (McDowall, Barker and Jennett, 1966). Furthermore, in one case with a cerebral tumour to whom halothane was given, Jennett, McDowall and Barker (1967) showed that the intracranial pressure rise was less at a $P_{C0_2}$ of 19 mm Hg than at one of 34 mm Hg. It was therefore suggested in that paper that hyperventilation would partially protect against such pressure changes, and indeed it may do so in any individual case. Nonetheless, in the present study, the mean $P_{C0_2}$ in patients with space-occupying lesions given methoxyflurane 1.5 per cent was in fact only $33.8$ mm Hg, and so the large increases in intracranial pressure recorded with methoxyflurane occurred despite mild hypocarbia. Furthermore, some of the cases with the lowest values for $P_{C0_2}$ showed the greatest c.s.f. pressure increases. This is, however, not to say that in any individual
patient the extent of the intracranial pressure change is not modified by lowering the P_{CO_2}, but it does seem that the anaesthetist cannot rely on the use of mild hyperventilation to prevent large changes in intracranial pressure. A study of the changes produced on c.s.f. pressure with more extreme hyperventilation is now in progress.

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EFFECT OF METHOXYFLURANE ON CEREBROSPINAL FLUID PRESSURE

Die Wirkung von Methoxyflurane in Konzentrationen von 0,5 Prozent und 1,5 Prozent auf den Zerebrospinalflüssigkeits-Druck ist bei Patienten mit normalen Liquor-Räumen und bei solchen mit raumfordernden intrakraniellen Läsionen untersucht worden. Bei Patienten mit normalen Liquor-Räumen löste eine 0,5 prozentige Methoxyflurankonzentration unterschiedliche Reaktionen aus; bei manchen Patienten kam es zu einem leichten Liquor-Druckanstieg, bei anderen zu einem geringen Liquor-Druckabfall. Die 1,5prozentige Methoxyfluranauf-Konzentration dagegen verursachte bei allen Patienten einen erheblichen Liquordruckanstieg, der nicht mit irgend einer Veränderung der Kohlendioxid-Spannung oder des zentralen Venen-Drückes verküpft war. Bei den Patienten mit intrakraniellen, raumfordernden Prozessen kam es sowohl nach der 0,5prozentigen als auch nach der 1,5prozentigen Methoxyflurankonzentration zu Erhöhungen des Liquor-Druckes, die deutlich über den bei Patienten ohne raumfordernden Läsionen beobachteten Werten lagen. Der mittlere Liquor-Druckanstieg war von der Konzentration des verabreichten Wirkstoffes abhängig; er war nach Applikation der 0,5prozentigen Methoxyflurankonzentration gering, bei der höheren Konzentration jedoch sehr viel ausgeprägter. Eine mögliche Gefahr bei solchen Patienten besteht darin, daß die Verabreichung von Methoxyflurane zu einem Druckgefälle des intrakraniellen Druckes führen kann und solche Lagerveränderungen des Gehirns und eine Distorsion des Mesenzephalons verschlimmert werden.

BOOK REVIEWS


This manual is based on the organization of the Department of Inhalation Therapy at the University of Michigan Hospital, Ann Arbor, Michigan. The aim is to present techniques and equipment presently available to the inhalational therapist, to outline individual responsibilities of the inhalation therapy team and to serve as a basic instruction manual for the inhalational therapist.

The first section details the job descriptions of the technical staff of the inhalation department. This includes function, job contract and specifications, and promotion prospects. By far the largest part is devoted to the function, principles of operation and responsibilities of those dealing with certain types of equipment used in inhalation therapy. This is followed by a section concerned with drugs that may be required. A further chapter deals with forms and records and the book ends with a brief section on cleaning and sterilizing.

This book is obviously unlikely to have great appeal in Great Britain where inhalation therapy is not yet organized on the same basis as in the United States of America. Perhaps the greater lesson to be learnt from this book is that the physician has considerable responsibility for giving specific instructions for the type, method and duration of treatment. All too often oxygen and mist therapy are prescribed without adequate thought having been given to the actual requirements. As a manual it lacks diagrams which would be of considerable help. In view of the great importance that attaches to the sterilization and cleaning of the apparatus, this section could be materially enlarged, at the expense of the section devoted to forms and records, which is given disproportionately greater space relative to its significance.

Gordon H. Bush


This book, received by the reviewer only very recently, is dated Spring 1967 and since most of the references included precede 1965 much of its value is lost. The main purpose of such monographs is surely to present new ideas and to keep the reader informed of current progress in the selected field. Unlike a textbook, the main purpose of which is to present accepted doctrine, the monograph must meet its publication deadline if it is to make any impact.

The idea of a monograph on metabolism in relation to anaesthesia is excellent but the result is disappointing partly because there are many important omissions, for example the metabolism of the barbiturates and that of the opiates is not discussed, and partly because of the method of presentation chosen by some of the contributors. A well-written essay by an informed expert makes delightful reading in the week-end supplement of a favourite newspaper but it is less attractive when presented without supporting facts and references in an authoritative monograph.

Fundamentally the book lacks balance but many of the individual contributions make fascinating reading; that by Bosomworth and Morrow on the metabolic significance of catecholamines released during anaesthesia deserves special study and that by Little on the metabolism of the liver and anaesthesia, though less up-to-date and rather ineptly titled, provides fundamental background information. The book is nicely printed on good quality paper and it is well bound; some of the illustrations, however, are very poor and could have been redrawn with advantage. On the whole this is a monograph for the departmental library rather than for the anaesthetist's personal bookshelf.

J. P. Payne