THE INFLUENCE OF NEUROLEPTANALGESIC DRUGS ON CEREBROSPINAL FLUID PRESSURE

BY

W. Fitch, J. Barker, W. B. Jennett and D. G. McDowall

SUMMARY

The effects of the neuroleptanalgesic drug combinations, droperidol 5 mg + phenoperidine 1.5 mg, and droperidol 5 mg + fentanyl 0.1 mg, on the cerebrospinal fluid (c.s.f.) pressure, have been studied in patients with normal c.s.f. pathways during controlled ventilation. The influence of droperidol 5 mg + fentanyl 0.1 mg on intracranial pressure has also been investigated in patients with intracranial space-occupying lesions. In patients with normal c.s.f. pathways, droperidol and phenoperidine produced only small alterations in c.s.f. pressure in either direction, while droperidol plus fentanyl resulted in falls in c.s.f. pressure in each case studied, with a significant decrease in overall mean c.s.f. pressure. Similarly, in patients with intracranial space-occupying lesions, droperidol plus fentanyl produced decreases in c.s.f. pressure in all but one of the cases studied. The striking difference between the effect on c.s.f. pressure of these drugs and of the volatile anaesthetic agents could be of importance to the clinical anaesthetist dealing with head injuries or working in a neurosurgical unit, when under conditions of controlled ventilation these drugs could be used as adjuvants to nitrous oxide-oxygen anaesthesia.

In the past few years, it has been recognized that volatile anaesthetic agents can elevate the intracranial pressure even in the absence of hypercapnia (Hunter, 1964; McDowall, Barker and Jennett, 1966); and that the increases in intracranial pressure produced by these drugs are markedly greater in patients with intracranial space-occupying lesions than in patients with normal cerebrospinal fluid (c.s.f.) pathways (Jennett, McDowall and Barker, 1967; Jennett et al., 1969; Gordon, 1968; Fitch et al., 1969). Furthermore, in patients with intracranial space-occupying lesions these marked increases in intracranial pressure can occur despite arterial carbon dioxide tensions in the range 28–35 mm Hg (Jennett et al., 1969; Fitch et al., 1969).

There is, therefore, a strong case for seeking alternative agents as supplements to nitrous oxide-oxygen in neurosurgical practice. In the past neuroleptanalgesic drugs have been advocated for use in neurosurgery (Tasker and Marshall, 1965; Nilsson and Janssen, 1961; Brown, 1964), and it was therefore decided to investigate the effects of these drugs on cerebrospinal fluid pressure.

METHODOLOGY

As in our studies on the effects of volatile anaesthetic agents on c.s.f. pressure, two groups of patients have been investigated: those with normal c.s.f. pathways, and those with signs and symptoms of raised intracranial pressure due to intracranial space-occupying lesions.

Two combinations of neuroleptanalgesic drugs have been studied:

1. droperidol 5 mg + phenoperidine 1.5 mg;
2. droperidol 5 mg + fentanyl 0.1 mg.

In all cases, these drugs were administered intravenously to patients already anaesthetized with nitrous oxide-oxygen and relaxant, and being ventilated artificially.


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Measurements of both systolic and diastolic c.s.f. pressure were made and the mean c.s.f. pressure calculated as diastolic c.s.f. pressure + ½ pulse pressure. Similarly, mean arterial blood pressure was taken as diastolic blood pressure + ½ pulse pressure. Cerebral perfusion pressure (mm Hg) was then obtained by subtracting the mean c.s.f. pressure (mm Hg) from the mean arterial blood pressure (mm Hg).

Patients with normal c.s.f. pathways.

Twelve patients undergoing surgery for lumbar disc lesions were studied, of whom 6 were given droperidol and phenoperidine and 6 droperidol plus fentanyl. The informed consent of the patient was obtained in each case.

The detailed methodology was as described previously by McDowall, Barker and Jennett (1966), with the exception that in place of adding a volatile anaesthetic agent to the inspired gas mixture, the neuroleptanalgesic drug combination under study was given intravenously over a 2-minute period, and the resultant changes in the c.s.f. pressure followed for the ensuing 15 minutes.

Patients with intracranial space-occupying lesions.

Nine patients have been investigated (6 female, 3 male). All were given the combination of droperidol and fentanyl.

Following the technique previously described (Jennett, McDowall and Barker, 1967), measurements of intracranial pressure were made from the lateral ventricle. The effects of an intravenous injection of droperidol and fentanyl on the c.s.f. pressure were followed for 15 minutes. Immediately thereafter, 1.0 per cent halothane was added to the nitrous oxide-oxygen anaesthetic mixture and the resultant changes in the c.s.f. pressure produced by this volatile anaesthetic agent were then followed for a further 5 minutes. Thus in these patients with space-occupying lesions, the changes in c.s.f. pressure produced by the neuroleptanalgesic drugs could be compared subsequently with the effects of halothane on the same patient.

Arterial blood pressure was measured in all patients; in those with normal c.s.f. pathways by upper arm sphygmomanometry and in those with space-occupying lesions either by direct intra-arterial recording (5 patients) or by upper arm sphygmomanometry (4 patients). Central venous pressure was monitored in all patients by a catheter passed from an antecubital vein into the superior vena cava.

Throughout each investigation, end-tidal carbon dioxide concentrations were monitored continuously and, intermittently, samples of capillary or arterial blood were obtained for measurement of pH and Pco₂, the latter by the technique of Siggaard-Andersen and associates (1960). Oesophageal temperature was also measured, and all blood-gas results were subsequently corrected for temperature.

RESULTS

 Patients with normal c.s.f. pathways.

Droperidol 5 mg + phenoperidine 1.5 mg. All 6 patients given this combination of drugs were males: average age 37.3 years (range 18–59). The mean initial c.s.f. pressure, i.e. under nitrous oxide-oxygen anaesthesia alone, at a PaCO₂ of 39.9 ± 1.9 mm Hg, was 109 ± 55 mm H₂O; 15 minutes after the intravenous injection of droperidol and phenoperidine, the mean c.s.f. pressure had fallen to 90 ± 46 mm H₂O, but this change was not significant (0.9 > P > 0.80). The effect of the neuroleptanalgesic drugs on individual patients was variable, in that of the patients studied 4 showed a fall in c.s.f. pressure, whereas the remaining 2 patients showed a slight rise (fig. 1); the range of pressure change being from −60 mm H₂O to +30 mm H₂O (fig. 1).

Although there was no significant alteration in central venous pressure or carbon dioxide tension obtained before, and 15 minutes after the
### Table I(A)

<table>
<thead>
<tr>
<th></th>
<th>c.s.f. pressure (mm H$_2$O)</th>
<th>Systolic arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H$_2$O)</th>
<th>P$_{aco_2}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection NLA</td>
<td>109 ± 55</td>
<td>105 ± 9</td>
<td>4.4 ± 3.0</td>
<td>39.9 ± 1.9</td>
</tr>
<tr>
<td>15 min after NLA i.v.</td>
<td>90 ± 46</td>
<td>92 ± 4*</td>
<td>3.5 ± 3.3</td>
<td>38.9 ± 1.1</td>
</tr>
</tbody>
</table>

### Table I(B)

<table>
<thead>
<tr>
<th></th>
<th>c.s.f. pressure (mm H$_2$O)</th>
<th>Systolic arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H$_2$O)</th>
<th>P$_{aco_2}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection NLA</td>
<td>147 ± 64</td>
<td>108 ± 18</td>
<td>3.3 ± 0.6</td>
<td>39.6 ± 2.2</td>
</tr>
<tr>
<td>15 min after NLA i.v.</td>
<td>109 ± 49†</td>
<td>94 ± 14†</td>
<td>3.5 ± 0.5</td>
<td>40.6 ± 1.8*</td>
</tr>
</tbody>
</table>

Statistically significant difference: * P<0.05; † P<0.01.

injection of the drug combination (table I(A)), there was a significant fall in systolic arterial blood pressure from 105±9 mm Hg to 92±4 mm Hg (0.02>P>0.01).

Droperidol 5 mg + fentanyl 0.1 mg. In this study there were 5 male patients and 1 female: average age 33.3 years (range 19–45 years). Under nitrous oxide-oxygen anaesthesia, at a P$_{aco_2}$ of 39.6±2.2 mm Hg the mean c.s.f. pressure was 147±64 mm H$_2$O; 15 minutes after the intravenous injection of the neuroleptanalgesic drug combination, there was a significant fall in c.s.f. pressure of 37±18 mm H$_2$O to a mean value of 109±49 mm H$_2$O (0.005>P>0.001). Indeed, in contrast to the findings with droperidol plus phenoperidine, droperidol plus fentanyl produced a fall in c.s.f. pressure in each patient studied (fig. 1).

As with droperidol and phenoperidine, there was a significant fall in systolic arterial pressure following the injection of droperidol and fentanyl from 108±18 mm Hg to 94±14 mm Hg 15 minutes after the injection of the drugs (0.005>P>0.001). Arterial carbon dioxide tension increased from an initial level of 39.6±2.2 mm Hg prior to injection to 40.6±1.8 mm Hg 15 minutes postinjection, a small but significant rise (0.02>P>0.01). There was no significant alteration in central venous pressure (0.95>P>0.90) (table I(B)).

Patients with intracranial space-occupying lesions.

Droperidol 5 mg + fentanyl 0.1 mg. Nine patients (3 male and 6 female) comprised this group. Their average age was 50.4 years and ranged from 19 to 77 years. All but one showed a fall in c.s.f. pressure 15 minutes after the intravenous injection of the drug combination (fig. 2). The mean initial c.s.f. pressure was 309±70 mm H$_2$O; 15 minutes after the injection of droperidol plus fentanyl, this value had fallen significantly to a final value of 244±57 mm H$_2$O (0.01>P>0.005). In addition, as can be seen from

![Fig. 2](image-url)

Change in mean c.s.f. pressure produced by droperidol plus fentanyl in patients with and without intracranial space-occupying lesions.
INFLUENCE OF NEUROLEPTANALGESIC DRUGS ON C.S.F. PRESSURE

TABLE II(A)

Mean c.s.f. pressure, mean arterial blood pressure, central venous pressure and PaCO₂ before, and 15 min after intravenous injection of droperidol 5 mg and fentanyl 0.1 mg to 9 patients with space-occupying lesions.

<table>
<thead>
<tr>
<th></th>
<th>c.s.f. pressure (mm H₂O)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Central venous pressure (cm H₂O)</th>
<th>PaCO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection NLA</td>
<td>309 ± 70</td>
<td>91 ± 12</td>
<td>4.5 ± 2.8</td>
<td>40.2 ± 5.7</td>
</tr>
<tr>
<td>15 min after NLA i.v.</td>
<td>244 ± 57†</td>
<td>78 ± 12‡</td>
<td>4.2 ± 2.6</td>
<td>38.9 ± 4.8</td>
</tr>
</tbody>
</table>

Statistically significant difference: † P<0.01; ‡ P<0.001.

In table II(A), this combination of drugs produced a significant fall in mean arterial blood pressure, from an initial value of 91 ± 12 mm Hg to 78 ± 12 mm Hg (P<0.001).

In this group of patients with space-occupying lesions, cerebral perfusion pressure was calculated as described previously. No significant change in this parameter was produced by this dosage of droperidol plus fentanyl (table III). Similarly, no significant differences were found in the values for central venous pressure (0.95>P>0.90) or for carbon dioxide tension (0.20>P>0.10), measured before and 15 minutes after injection of the drug combination (table II(A)).

Halothane 1.0 per cent. In comparison to the effects of the neuroleptanalgesic drugs on the c.s.f. pressure in these patients with intracranial space-occupying lesions, the addition of halothane 1.0 per cent to the inspired gas mixture resulted in increases in c.s.f. pressure in each of the 9 patients. The mean increase in c.s.f. pressure was 137 ± 96 mm H₂O (0.005 >P>0.001). In association with this rise in c.s.f. pressure there was a fall in mean arterial blood pressure (table II(B)), with a consequently significant decrease in perfusion pressure (table III). From an initial value of 61 ± 13 mm Hg, the perfusion pressure fell to a value of 44 ± 16 mm Hg after 5 minutes of halothane administration (P<0.001).

DISCUSSION

Patients with normal c.s.f. pathways.

Patients with normal c.s.f. pathways showed no significant change in c.s.f. pressure after droperidol and phenoperidine, but a slight decrease in pressure following droperidol and fentanyl. This finding contrasts sharply with our previous findings of a rise in c.s.f. pressure in patients with normal c.s.f. pathways during the administration of any of the volatile anaesthetic agents, trichloroethylene, halothane, or methoxyflurane (McDowall, Barker and Jennett, 1966; Fitch et al., 1969).

The lack of significant c.s.f. pressure change with droperidol and phenoperidine, as compared with the small fall in c.s.f. pressure found with
droperidol and fentanyl, may indicate a difference in the action of these drugs on cerebral blood flow and cerebral metabolic rate. It is also possible, however, that the failure to detect a significant fall in c.s.f. pressure with droperidol and phenoperidine was due to the fact that the initial c.s.f. pressure was lower in this group of patients than in those given droperidol and fentanyl. It is known that the effect of any factor influencing c.s.f. pressure is greater when the initial pressure is high. The mean fall in c.s.f. pressure with droperidol and fentanyl was 38 mm H$_2$O from a steady initial pressure of 147 mm H$_2$O (i.e. a 26 per cent decrease), while the fall with droperidol and phenoperidine was 19 mm H$_2$O from a steady pressure of 109 mm H$_2$O (a 17 per cent decrease).

Patients with intracranial space-occupying lesions.

In patients with space-occupying lesions there was also a definite, though small, decrease in c.s.f. pressure with droperidol and fentanyl, a feature which contrasts with the large increases in c.s.f. pressure found when volatile anaesthetic agents were administered under similar conditions to patients with intracranial space-occupying lesions (Jennett, McDowall and Barker, 1967; Jennett et al., 1969). This contrast is highlighted by the direct comparison of the actions of halothane with those of droperidol and fentanyl in the present study (table II(B)). Although the increases in c.s.f. pressure in these patients following the halothane administration were not as great as those found in our previous studies, it should be noted that in the present investigation, halothane was administered for 5 minutes as compared with 10 minutes in the previous investigation, and also that in this study the patients had already been given droperidol 5 mg and fentanyl 0.1 mg prior to the exhibition of the halothane.

The increases in c.s.f. pressure produced by volatile anaesthetic agents are probably the result of drug-induced cerebral vasodilatation leading to increased cerebral blood flow and cerebral blood volume (McDowall, 1966). Similarly, it may be that the reduction in c.s.f. pressure noted with droperidol and fentanyl in these investigations is consequent upon a reduction in cerebral blood flow, possibly secondary to a decrease in cerebral metabolism. This hypothesis is supported by the finding of Kreuscher (1965) of a 50 per cent reduction in both cerebral blood flow and cerebral metabolic rate with associated slowing of the e.e.g. with droperidol and fentanyl. Similar findings of the disappearance of alpha waves and the appearance of slow waves on the e.e.g. have been reported following the administration of droperidol plus fentanyl to patients (Bushart and Rittmeyer, 1964; Nilsson and Ingvar, 1967; Marshall and Gordon, 1968). Against this possible explanation are the findings of Nilsson and Ingvar (1966) and Freeman and Ingvar (1967) of an increase in cerebral blood flow with accompanying e.e.g. activation following the administration of fentanyl to cats. However, as indicated by the authors, this is likely to be a species difference related to the well-known excitatory actions of morphine and morphine-like compounds in cats (Wikler, 1944).

The lack of significant change in c.s.f. pressure with the combination of droperidol plus phenoperidine may indicate that this combination of drugs has less effect on cerebral blood flow and cerebral metabolic rate than droperidol and fentanyl. Certainly, Barker and associates (1968) found that the cerebral blood flow in patients anaesthetized with droperidol and phenoperidine was not significantly different from values obtained in unanaesthetized patients. However, as discussed earlier, the lack of change in c.s.f. pressure with this drug combination may be related to the lower initial pressure in this group of patients.

Clinical significance.

The administration of a volatile anaesthetic agent to patients with intracranial space-occupying lesions may lead to significant falls in cerebral perfusion pressure consequent upon the raised intracranial pressure and reduced arterial blood pressure. In this present study there was a fall in mean arterial blood pressure 15 minutes after the injection of droperidol and fentanyl (table II(B)), but this was associated with a small decrease in c.s.f. pressure which reduced the change in perfusion pressure. The initial value for intracranial pressure in this group of patients with space-occupying lesions was considerably higher than that found with any of the volatile anaes-
In addition, in no case given neuroleptanalgesic 0.9 per cent trichloroethylene (53 ± 20 mm Hg). This lower initial perfusion pressure may have been a factor in the reduced fall in perfusion pressure found in this study. None the less, it must be noted that the final perfusion pressure 15 minutes after injection of droperidol and fentanyl (60 ± 14 mm Hg) was considerably greater than that found after 10 minutes administration of either 1.0 per cent halothane (39 ± 19 mm Hg) or 1.5 per cent methoxyflurane (32 ± 11 mm Hg), and was moderately higher than that previously found with methoxyflurane (32 ± 11 mm Hg), and was shown in this study between the volatile and the non-volatile anaesthetics, which presumably means that in these patients the pathological lesion was more advanced and that the patient had entered the decompensated phase. As a consequence of this high intracranial pressure, the cerebral perfusion pressure under nitrous oxide-oxygen alone was lower (68 ± 16 mm Hg) than in our previous studies (81 ± 19 mm Hg). This lower initial perfusion pressure may have been a factor in the reduced fall in perfusion pressure found in this study. None the less, it must be noted that the final perfusion pressure 15 minutes after injection of droperidol and fentanyl (60 ± 14 mm Hg) was considerably greater than that found after 10 minutes administration of either 1.0 per cent halothane (39 ± 19 mm Hg) or 1.5 per cent methoxyflurane (32 ± 11 mm Hg), and was moderately higher than that previously found with 0.9 per cent trichloroethylene (53 ± 20 mm Hg). In addition, in no case given neuroleptanalgesic drugs did the cerebral perfusion pressure fall below 50 mm Hg; it was therefore at all times above the value of 40 mm Hg at which Zwetnow, Kjallquist and Siesjo (1968) found evidence of cerebral hypoxia in dogs.

This difference in the perfusion pressure between the volatile and the non-volatile anaesthetic agents is further emphasized by the contrast shown in this study between the perfusion pressure changes following the neuroleptanalgesic drugs and those obtained after halothane administration. As can be seen from table III, the perfusion pressure fell significantly after only 5 minutes halothane administration.

The clinical importance of these falls in cerebral perfusion pressure produced by volatile anaesthetics is debatable since these occur as a consequence of increase in cerebral blood flow. However, the large increases in intracranial pressure produced by these drugs in patients with space-occupying lesions may lead to the development of intracranial pressure gradients, and so increase the likelihood of internal brain herniation when the skull is closed, or external brain herniation and difficulty of surgical access once the skull has been opened.

For these reasons there may be occasions when neuroleptanalgesic drugs are preferable to volatile anaesthetic agents as supplements to nitrous oxide-oxygen anaesthesia in neurosurgery.

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Freeman, J., and Ingvar, D. H. (1967). Effects of fentanyl on cerebral cortical blood flow and e.e.g. in the cat. Acta anaesth. scand., 11, 381.


Des traumatisms de la tête ou qui travaille dans un service de neurochirurgie, lorsque ces médicaments pourraient être utilisés sous ventilation contrôlée comme adjutants de l’anesthésie au protoxyde d’azote-oxycène.

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