EFFECTS OF FENTANYL, DROPERIDOL, AND INNOVAR ON CANINE CEREBRAL METABOLISM AND BLOOD FLOW

BY

J. D. MICHENFELDER AND R. A. THEYE

SUMMARY

The effects of droperidol and fentanyl given individually and in combination (Innovar) on the rate of cerebral oxygen consumption (CMRO₂) and cerebral blood flow (c.b.f.) were studied in dogs anaesthetized with nitrous oxide (70 per cent) and oxygen. Fentanyl (0.006 mg/kg) decreased both the CMRO₂ and the c.b.f. (mean decreases at 15 minutes were 18 per cent and 47 per cent, respectively). The duration of effect was approximately 30 minutes. Droperidol (0.3 mg/kg) produced a decrease of 40 per cent in c.b.f. due primarily to a 30-40 per cent increase in cerebrovascular resistance, and this effect persisted for the period of observation (60 minutes). No significant change in CMRO₂ occurred after droperidol was administered. With the combination drug (Innovar), the effects were partially additive. After 15 minutes, CMRO₂ had decreased 23 per cent; c.b.f. had decreased 50 per cent; and cerebral vascular resistance had increased 85 per cent. After 30 minutes, the effects of Innovar were indistinguishable from those of droperidol alone. No significant changes occurred in the rate of cerebral glucose consumption or the oxygen-glucose index. The effect of increased and decreased PₐCO₂ on c.b.f. after Innovar was compared with that observed during halothane anaesthesia. With halothane, hypercapnia (PₐCO₂ = 60 mm Hg) increased c.b.f. 40 per cent and hypocapnia (PₐCO₂ = 20 mm Hg) decreased c.b.f. 40 per cent. Innovar at normocapnia reduced the c.b.f. 65 per cent. With hypercapnia, the c.b.f. doubled, but with hypocapnia, little further reduction in c.b.f. occurred. It is concluded that droperidol is a potent cerebral vasoconstrictor, that this effect dominates when it is given in combination with fentanyl, that hypocapnia causes little further reduction in c.b.f., and that the reduction in c.b.f. produced by Innovar is not accompanied by alterations in normal cerebral metabolic pathways.

The anaesthetic state produced by the combination of droperidol, fentanyl, and nitrous oxide has been termed "neuroleptanaesthesia". Fentanyl is a potent, short-acting narcotic whose clinical effect lasts about 30 minutes. Droperidol is a neuroleptic drug which produces its maximal clinical effects 10 minutes after administration and has a prolonged action (6-24 hours). Given in combination (Innovar), these drugs result in a sedated patient, emotionally detached from his environment, with a significant degree of analgesia (Lasser et al., 1966). The recognition that Innovar alone produces an analgesic state and, in the presence of nitrous oxide, an anaesthetic state clinically different from that associated with other analgesics or anaesthetics suggests the possibility of different effects on cerebral metabolism, or cerebral blood flow (c.b.f.), or both. Accordingly in this study, dogs were given fentanyl, droperidol, or Innovar, and the subsequent effects on c.b.f. and rate of cerebral oxygen consumption (CMRO₂) were observed.

METHODS

Twenty-one fasting, unpremedicated dogs weighing 12-16 kg were studied. Anaesthesia was induced and initially maintained with halothane (1.0 per cent, inspired) in nitrous oxide (70%) and oxygen. Suxamethonium (40 mg) was given to

Innovar is the trade name for a combination of droperidol and fentanyl in the U.S.A. The equivalent trade name in the U.K. is Thalamonal.
facilitate endotracheal intubation and, thereafter, at 150 mg/hr to maintain muscle paralysis. Ventilation was controlled with a Harvard pump. Cannulae were inserted into a femoral artery for pressure measurements and blood sampling, and into a femoral vein for drug administration and reinfusion of blood. Thereafter, the dog was placed in the prone position with the head supported on a block.

The surgical preparation used in our laboratory for the direct measurement of c.b.f. has been previously described in detail (Michenfelder, Messick and Theye, 1968). Valid measurement requires obliteration of the diploic channels that communicate with the sagittal sinus. This is accomplished without exposure of the dura. Thereafter, the sagittal sinus is cannulated about 1 cm anterior to the torcular and then occluded posterior to the cannula. The blood flow is diverted to a reservoir at the level of the sinus, measured by automatic, timed collection, and reinfused into the femoral vein. Flow measurements so obtained represent the drainage of 43 per cent of the total brain weight (primarily cerebral hemispheres). This percentage and the individual brain weights of the dogs studied are used to convert flow units from ml/min to ml/100 g/min. Validation studies showed excellent agreement between values obtained by these means and simultaneous measurements by the Kety-Schmidt method (Michenfelder, Messick and Theye, 1968).

The isolation, collection, and measurement of the venous drainage of a known portion of the brain provides, in addition, a ready source for sampling mixed venous blood, which is exclusively representative of the brain tissue from which flow is measured. Oxygen content of the cerebral venous (sagittal sinus) blood and of the arterial blood was calculated from measurement of haemoglobin, oxyhaemoglobin (IL180 CO-Oximeter), and oxygen tension (IL313 electrodes) (Theye, 1970). Glucose content of sagittal sinus blood and of the arterial blood was determined by an enzymatic method (Bergmeyer, 1965). Additional measurements included pH and PaO₂ (electrodes), arterial blood pressure (strain gauge), and brain temperature (parietal epidural thermistor). Cerebral metabolic rate for oxygen (CMRₒ₂), and for glucose (CMR₆₀₆) was calculated as the product of c.b.f. and arterial-sagittal sinus blood content difference [C(a-v)]. Oxygen-glucose index (o.g.i.) was calculated in the manner described by Cohen and associates (1967). Cerebral vascular resistance (c.v.r.) was calculated as the ratio of the mean arterial pressure (m.a.p.) to the c.b.f.

Ventilation and inspired oxygen concentration were adjusted to maintain a PaO₂ of 40 ± 2 mm Hg and a PaCO₂ greater than 90 mm Hg. Sodium bicarbonate was given to maintain a normal buffer base. Temperature was maintained at 37.0 ± 0.1°C by either infra-red heat or alcohol sponging. Haemoglobin level was maintained at 13.0 ± 1 g/100 ml and m.a.p. above 80 mm Hg by the infusion of either dextran or whole blood.

In twelve dogs, halothane was discontinued when the surgical preparation was complete. Control measurements were initiated 1 hour later. CMRₒ₂ was calculated from a minimum of ten consecutive measurements of c.b.f. and C(a-v)ₒ₂, and CMR₆₀₆ was calculated from three measurements of c.b.f. and C(a-v)₆₀₆ obtained during periods of steady c.b.f. Thereafter, four dogs each were given intravenously, during a 2-minute period, droperidol (0.3 mg/kg) or fentanyl (0.006 mg/kg) or Innovar (droperidol 0.3 mg/kg and fentanyl 0.006 mg/kg). Cerebral blood flow and C(a-v)ₒ₂ were then measured every 5 minutes, and C(a-v)₆₀₆ was measured every 15 minutes for 60 minutes.

In four additional dogs, halothane was not discontinued and, after control determinations, the effects of droperidol (0.3 mg/kg) were followed for a 30-minute period.

In five additional dogs, the effect of Innovar on response of c.b.f. to change in PaCO₂ was determined and compared to the response during halothane anaesthesia. In each dog, c.b.f. was measured at a PaO₂ of 20, 40, and 60 ± 1 mm Hg during halothane anaesthesia (0.8 per cent expired) and after halothane had been discontinued for 1 hour and Innovar (droperidol 0.3 mg/kg and fentanyl 0.006 mg/kg) was given. For these studies, ventilation was initially adjusted to result in a PaO₂ of 20 mm Hg and maintained unchanged thereafter. The other levels of PaO₂ (40 and 60 mm Hg) were obtained by adding carbon dioxide to the inspired gases. Sequence of carbon dioxide levels studied was randomized within and between dogs. When PaO₂ was steady, eight consecutive measurements of c.b.f. and two consecu-
TABLE I
Control situation (12 dogs); nitrous oxide (70 per cent) and halothane (<0.1 per cent).

<table>
<thead>
<tr>
<th></th>
<th>Droperidol group</th>
<th>Fentanyl group</th>
<th>Innovar group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>CMR\textsubscript{O} (ml/100 g/min)</td>
<td>5.89</td>
<td>0.50</td>
<td>6.23</td>
</tr>
<tr>
<td>CMR\textsubscript{Glucose} (g/100 g/min)</td>
<td>9.8</td>
<td>1.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Oxygen-glucose index</td>
<td>0.84</td>
<td>0.07</td>
<td>0.85</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/100 g/min)</td>
<td>87</td>
<td>13</td>
<td>95</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>149</td>
<td>11</td>
<td>131</td>
</tr>
<tr>
<td>Cerebrovascular resistance (mm Hg/ml/100 g/min)</td>
<td>1.7</td>
<td>0.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>


tive measurements of \( P_{\text{CO}_2} \) in duplicate were done during a 10-minute period.

Statistical significance was tested by the Student \( t \) test for paired data (\( P<0.05 \) considered significant).

RESULTS

Control values 1 hour after discontinuing halothane and prior to administration of droperidol, fentanyl, or Innovar were not different in the three groups (table I) and were similar to those previously reported for this anaesthetic circumstance (70 per cent nitrous oxide and <0.1 per cent halothane) (Theye and Michenfelder, 1968b). The seemingly high metabolic and flow values are appropriate for the method which primarily measures drainage from grey matter of the cerebral hemispheres.

After droperidol was administered in the absence of halothane (fig. 1), CMR\textsubscript{O} decreased insignificantly while c.b.f. progressively decreased, reached 60 per cent of control at 30 minutes, and remained at this level for the duration of the study. The reduction in c.b.f. was accompanied by a significant increase in c.v.r. and an insignificant decrease in m.a.p. By contrast, the administration of droperidol in the presence of halothane (table II) resulted in no change in CMR\textsubscript{O} or c.v.r.; and the small insignificant reduction in c.b.f. at 30 minutes was accompanied by a significant decrease in m.a.p.

TABLE II
Effect of droperidol in the presence of halothane (0.8 per cent).

<table>
<thead>
<tr>
<th></th>
<th>Control (30 min)</th>
<th>Droperidol (30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR\textsubscript{O} (ml/100 g/min)</td>
<td>4.70</td>
<td>4.73</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
<td>0.29</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/100 g/min)</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>102</td>
<td>83*</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cerebrovascular resistance (mm Hg/ml/100 g/min)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Significantly different from control (\( P<0.05 \)).

After fentanyl was administered in the absence of halothane (fig. 2), c.b.f. decreased to 55 per cent of control at 15 minutes and returned thereafter toward control. The initial changes in c.b.f. were primarily due to a significant increase in c.v.r. CMR\textsubscript{O} paralleled c.b.f., decreasing to 82 per cent of control at 15 minutes and then returning to control at 30 minutes.

After Innovar was administered in the absence of halothane (fig. 3), c.b.f. decreased to 50 per cent of control at 15 minutes primarily because of an increase in c.v.r.; CMR\textsubscript{O} returned to 60 per cent of control at 40 minutes, and remained at this level owing to a persistent increase in c.v.r. and de-
crease in m.a.p. Initially, CMRO₂ decreased to 78 per cent of control at 15 minutes and after 40 minutes returned to 95 per cent of control. These changes are consistent with partial additive effects of droperidol (fig. 1) and fentanyl (fig. 2).

In all, changes in CMR, paralleled changes in CMRO₂ and were not significant. No significant changes in o.g.i. occurred.

The response of c.b.f. to changes in PaCO₂ after Innovar was different from that during halothane anaesthesia (fig. 4). In the presence of halothane, c.b.f. at a PaCO₂ of 40 mm Hg was high owing to a very low c.v.r. (0.9 mm Hg/ml/100 g/min). With an increase in PaCO₂ to 60 mm Hg, c.b.f. increased 40 per cent, and with a decrease in PaCO₂ to 20 mm Hg, c.b.f. decreased 40 per cent. These changes were due almost entirely to changes in c.v.r. After Innovar, c.b.f. at a PaCO₂ of 40 mm Hg was 65 per cent less than that observed during halothane anaesthesia because of increased c.v.r. (2.6 mm Hg/ml/100 g/min). When PaCO₂ was reduced to 20 mm Hg, little further reduction in c.b.f. or increase in c.v.r.

Effect of fentanyl (0.006 mg/kg) on c.b.f., CMRO₂, c.v.r., and m.a.p. Cerebral blood flow decreased almost 50 per cent after 15 minutes primarily because of an increase in c.v.r. Thereafter, c.b.f. returned toward control. CMRO₂ decreased 18 per cent initially and then returned to control. In the initial 20 minutes, the changes in c.b.f., CMRO₂, and c.v.r. were significant (P<0.05). After 30 minutes, none of the changes was significant.

Effect of Innovar on c.b.f., CMRO₂, c.v.r., and m.a.p. Cerebral blood flow decreased to 50 per cent of control at 15 minutes primarily because of an increase in c.v.r. Thereafter, c.b.f. returned toward control. CMRO₂ decreased 22 per cent initially and then returned to 95 per cent of control. Changes observed after 30 minutes are indistinguishable from those seen 30 minutes after droperidol. The changes in c.b.f. and c.v.r. were significant (P<0.05). After 40 minutes, the changes in CMRO₂ were insignificant.

Effect of PaCO₂ on c.b.f. during halothane anaesthesia and after Innovar. Cerebral blood flow values are plotted as the percentage of the flow measured during halothane anaesthesia at a PaCO₂ of 40 mm Hg. In the presence of halothane, c.b.f. increased or decreased 40 per cent in response to an increase or a decrease in PaCO₂ of 20 mm Hg, respectively. In the absence of halothane (0.1 per cent) and after Innovar, c.b.f. at a PaCO₂ of 40 mm Hg was 35 per cent of that during halothane anaesthesia. An increase in PaCO₂ of 20 mm Hg doubled c.b.f. A decrease in PaCO₂ of 20 mm Hg decreased c.b.f. slightly. All of the changes in c.b.f. that accompanied the changes in PaCO₂ were significant (P<0.05) and were due almost entirely to changes in c.v.r.
occurred. However, when $P_{a_o_2}$ was increased to 60 mm Hg, the c.b.f. doubled, owing to a decrease of 50 per cent in the c.v.r.

**DISCUSSION**

The effects of droperidol on c.b.f. and CMR$_o_2$ differ from those of any anaesthetic drug previously studied in our laboratory: halothane decreases CMR$_o_2$ and increases c.b.f. (Theye and Michenfelder, 1968a). Thiopentone, pentobarbitone, and pethidine decrease both CMR$_o_2$ and c.b.f. (Altenburg, Michenfelder and Theye, 1969; Messick and Theye, 1969) and ketamine increases both CMR$_o_2$ and c.b.f. (Dawson, Michenfelder and Theye, unpublished data). Droperidol did not significantly alter CMR$_o_2$ but resulted in a gradual decrease in c.b.f. to 60 per cent of control at 30 minutes, primarily from an increase in c.v.r. These effects of droperidol on c.b.f. and c.v.r. resemble those of hypocapnia and are comparable to the effect produced by a decrease of 20 mm Hg in $P_{a_o_2}$. As is true for this degree of hypocapnia, the reduction in c.b.f. after droperidol was not sufficient to alter either CMR$_{glucose}$ or the o.g.i. Thus, c.b.f., although reduced, was presumably adequate to meet normal aerobic metabolic requirements in the presence of normal haemoglobin and oxygen levels (Michenfelder and Theye, 1969).

Fentanyl decreased both CMR$_o_2$ and c.b.f. in a manner qualitatively similar to that of other narcotics. Significant effects lasted 20–30 minutes, corresponding to the clinical experience of others (Lassner et al., 1966). The magnitude of the decrease was greater than that previously observed for pethidine (2 mg/kg) in our laboratory (Messick and Theye, 1969). The reduction in c.b.f. was almost totally accounted for by an increase in c.v.r. and was not associated with changes in o.g.i.

Droperidol and fentanyl in combination (Innovar) appeared to have additive effects on CMR$_o_2$ and c.b.f. in the initial 30 minutes after injection. The onset of action was more rapid than that seen with either drug alone, the maximal reduction in CMR$_o_2$ was 23 per cent, the maximal decrease in c.b.f. was 50 per cent, and the maximal increase in c.v.r. was 85 per cent. In the second 30-minute period, the changes in mean CMR$_o_2$, c.b.f., and c.v.r. were indistinguishable from those observed during the same time period after the administration of droperidol alone. As in the other dog groups, there were no changes in o.g.i. suggestive of cerebral hypoxia.

These observations regarding the effects of fentanyl and droperidol on c.b.f. and CMR$_o_2$ are in partial agreement with those of others. Differences seem to be related to differences in the species studied, the presence of other anaesthetics, and methodologies. Pichlmayr (1969) used xenon 133 and measured regional c.b.f. in dogs anaesthetized with nitrous oxide, and he reported a decrease of 30 per cent in c.b.f. after a combination of fentanyl and droperidol was given in a dose that was three times the dose used in our study. Metabolic measurements were not reported. Kreuscher (1967) used a dye-dilution technique to measure c.b.f. in dogs anaesthetized with nitrous oxide and observed a reduction of 50 per cent in c.b.f. and a reduction of 50 per cent in CMR$_o_2$ after the combination of fentanyl and droperidol was given in doses of 0.28 and 0.007 mg/kg respectively. The validity of the methods may be questioned because the dye-dilution technique requires isolation of both the arterial and venous circulations of the brain. In the dog, isolation of the arterial system has been regarded as nearly impossible (Sokoloff, 1959) and, on the venous side, apparently no effort was made to interrupt the known extracerebral communicating channels. Miller and Barker (1969) studied dogs anaesthetized with trichloroethylene and measured regional c.b.f. ($^{85}$Kr). After administration of the combination of fentanyl and droperidol in doses similar to those used in our study, they observed no change in c.v.r. and an initial reduction of 24 per cent in c.b.f. which returned to control levels within 60 minutes. This response was nearly identical to the response which we observed after droperidol was given to dogs anaesthetized with halothane (table II). In these, only a modest reduction in c.b.f. occurred in the initial 30 minutes, which was totally secondary to a decrease in m.a.p. Thus, both halothane and trichloroethylene seem to prevent the cerebral vasconstrictor effects of droperidol. In the cat, droperidol, in the absence of other anaesthetics, had no effect on regional c.b.f. (Freeman and Ingvar, 1967) and fentanyl, in large doses, caused an increase of 20–30 per cent in regional c.b.f. (Freeman and Ingvar, 1967; Nilsson and Ingvar, 1966). These
The recognized similarity between the effects of droperidol and hypocapnia on c.b.f. and c.v.r. prompted an evaluation of the effect of $P_{a\text{CO}_2}$ on c.b.f. after the administration of Innovar, as compared with the effect of $P_{a\text{CO}_2}$ on c.b.f. during halothane. In the presence of halothane the expected response of c.b.f. to change in $P_{a\text{CO}_2}$ was observed, similar to that reported by Wollman and associates (1964) in man. A decrease of 20 mm Hg in $P_{a\text{CO}_2}$ caused a decrease of 40 per cent in c.b.f., and an increase of 20 mm Hg in $P_{a\text{CO}_2}$ caused an increase of 40 per cent in c.b.f. After Innovar, and in the absence of halothane ($<0.1$ per cent), the response of c.b.f. to $P_{a\text{CO}_2}$ was 35 per cent of that observed during halothane anaesthesia. After an increase of 20 mm Hg in $P_{a\text{CO}_2}$ c.b.f. approximately doubled, whereas a decrease of 20 mm Hg in $P_{a\text{CO}_2}$ caused little further reduction in c.b.f. Thus, as regards the adequacy of c.b.f. and on the assumption that haemoglobin and oxygen levels are normal, there would appear to be little or no hazard resulting from the combination of moderate levels of hypocapnia and Innovar.

The fact that Innovar is a potent cerebral vasoconstrictor in the dog is consistent with observations in man regarding the effect of Innovar on intracranial pressure. Jennett and associates (1969) reported that in patients with intracranial mass lesions a reduction in intracranial pressure occurs with Innovar. This contrasts with the effects of volatile anaesthetics that were reported by the same investigators (Fitch et al., 1969) to increase intracranial pressure in such patients. These effects of anaesthetics on intracranial pressure are most conveniently explained by alterations in c.b.f. The volatile anaesthetics are known to be cerebral vasodilators in man. It is reasonable to conclude that Innovar in man, as in the dog, is a cerebral vasoconstrictor.

REFERENCES


LE S EFFETS DE FENTANYL, DROPERIDOL ET INNOVAR SUR LE METABOLISME ET LE FLUX SANGUIN CEREBRAUX CHEZ LE CHIEN

SOMMAIRE
Les effets de droperidol et fentanyl, administrés individuellement et en association (Innovar) sur le taux de consommation cérébrale d'oxygène (CMRO₂) et le flux sanguin cérébral (c.b.f.) ont été étudiés chez des chiens anesthésiés au protoxyde d'azote (70 pour cent) et oxygène. Fentanyl (0,006 mg/kg) diminua aussi bien le CMRO₂ que le c.b.f. (les réductions moyennes à 13 minutes furent resp. 18 pour cent et 47 pour cent). L'effet dura approximativement 30 minutes. Droperidol (0,3 mg/kg) causa une réduction de 40 pour cent du c.b.f., due principalement à une augmentation de 30 à 40 pour cent de la résistance cérébrovasculaire, et cet effet persista durant l'entièr période d'observation (60 minutes). Aucun changement significatif du CMRO₂ ne se manifesta après administration du droperidol. Les effets sous le médicament combiné (Innovar) s'additionnèrent partiellement. Le CMRO₂ avait diminué après 15 minutes de 23 pour cent; le c.b.f. avait diminué de 50 pour cent et la résistance vasculaire cérébrale avait augmenté de 85 pour cent. Les effets d'Innovar après 30 minutes ne s'additionnèrent plus de ceux du droperidol seul. Il n'y eut aucune modification significative du taux de consommation cérébrale de glucose, si de l'index oxygène-glucose. L'effet sur le c.b.f. d'un Paco₂ réduit ou augmenté après Innovar a été comparé à celui observé durant l'anesthésie à l'héptane. Dans ce dernier cas, l'hypercapnie (Paco₂=60 mm Hg) augmenta le c.b.f. de 40 pour cent et l'hypocapnie (Paco₂=20 mm Hg) diminua le c.b.f. de 40 pour cent. Innovar en normocapnie réduisit le c.b.f. de 65 pour cent. Le c.b.f. double sous hypercapnie. On en conclut que le droperidol est un puissant vasoconstricteur cérébral, que cet effet domine lorsqu'il est administré en association avec fentanyl, que l'hypocapnie cause peu de réduction supplémentaire du c.b.f. et que la réduction du c.b.f. causée par Innovar ne s'accompagne d'altérations des voies métaboliques cérébrales normales.

WIRKUNGEN VON FENTANYL, DROPERIDOL UND INNOVAR AUF DEN GEHIRNSTOFFWECHSEL UND DIE GEHIRN DURCHBLUTUNG BEIM HUND

ZUSAMMENFASSUNG
An narkotisierten Hunden (70% Lachgas und 30% Sauerstoff) wurden die Wirkungen von Droperidol und Fentanyl, sowohl einzeln verabreicht als auch in Kombination (Innovar), auf den cerebraln Sauerstoffverbrauch (CSV) und die cerebrale Durchblutung (CD) untersucht. Fentanyl (0,006 mg/kg) führte zu einer Abnahme von sowohl CSV als auch CD (und zwar nach 15 Minuten durchschnittlich um 18 bzw. 47 Prozent). Die Wirkung hielt ungefähr 30 Minuten an. Droperidol führte zu einer Abnahme von CD um 40 Prozent, hauptsächlich infolge einer 30-40%-igen Erhöhung des cerebro-vaskulären Widerstandes. Dieser Effekt hielt etwa 60 Minuten an (Dauer der Beobachtung). Der CSV veränderte sich nach Gabe von Droperidol nur unwesentlich. Bei kombinierter Gabe (Innovar) addierten sich die Effekte teilweise. Nach 15 Minuten sank der CSV um 23 Prozent; die CD sank um 50 Prozent; der cerebrovaskuläre Widerstand wuchs um 85 Prozent. Nach 30 Minuten unterschieden sich die Wirkungen von Innovar nicht mehr von den Wirkungen von Droperidol allein. Der cerebrale Glucoseverbrauch und der Sauerstoff-Glukose-Index zeigten keine signifikanten Veränderungen. Die Wirkungen eines erhöhten oder erniedrigten arteriellen Paco₂, auf die CD nach Gabe von Innovar entsprachen den Beobachtungen bei Halothanaästhesie. Mit Halothan führte eine Hyperkapnie (Paco₂=60 mm Hg) zu einer Erhöhung der CD um 40 Prozent, eine Hypokapnie (Paco₂=20 mm Hg) zu einer Abnahme um 40 Prozent. Im Falle von Hypokapnie sank der c.b.f. um 40 Prozent. Bei Hyperkapnie verdoppelte sich die CD, bei Hypokapnie trat jedoch nur eine geringgradige weitere Abnahme der CD ein. Aus den Untersuchungen geht hervor, daß Droperidol ein starker cerebraler Vasokonstriktor ist, daß dieser Effekt bei Kombinationsgabe mit Fentanyl dominiert, daß eine Hypokapnie nur eine geringgradige weitere Abnahme der CD bewirkt und daß die durch Innovar hervorgerufenen Abnahme der CD die physiologischen cerebralen Stoffwechselvorgänge nicht beeinträchtigt.

EFECTOS DEL FENTANYL, DROPERIDOL E INNOVAR SOBRE EL METABOLISMO CEREBRAL CANINO Y FLUJO SANGUÍNEO

RESUMEN
Fueron estudiados los efectos del droperidol y fentanil administrados individualmente y en combinación (Innovar) sobre la tasa del consumo cerebral de oxígeno (CMRO₂) y el flujo sanguíneo cerebral (c.b.f.) en perros anestesiados con óxido nitroso (70 por ciento) y oxígeno. El fentanil (0,006 mg/kg) disminuyó de 18 a 47 por ciento el c.b.f. (las disminuciones medias a los 15 minutos fueron de respectivamente 18 por ciento y 47 por ciento). La duración del efecto fue de aproximadamente 30 minutos. El droperidol (0,3 mg/kg) produjo una disminución del 40 por ciento en el c.b.f. debida primariamente a un incremento del 85 por ciento en la resistencia cerebrovascular, y este efecto persistió durante el período de observación (60 minutos). No hubo ningún cambio significativo en la CMRO₂ después de la administración de droperidol. Con el medicamento combinado (Innovar) los efectos fueron parcialmente aditivos. Después de 15 minutos, la CMRO₂ había disminuido en un 23 por ciento; el c.b.f. había disminuido en un 50 por ciento; y la resistencia vascular cerebral había aumentado en un 85 por ciento. Después de 30 minutos, los efectos del Innovar eran indistinguibles de los del droperidol solo. No hubo cambios significativos en la tasa del consumo cerebral de glucosa o en el índice oxígeno-glucosa. El efecto de la Paco₂ aumentada y disminuida sobre el c.b.f. después de Innovar fue comparado con el observado durante la anestesia por halotano. Con el halotano, la hipercapnia (Paco₂=60 mm Hg) incrementó el c.b.f. en 40 por ciento y la hipocapnia (Paco₂=20 mm Hg) disminuyó el c.b.f. en 40 por ciento. El Innovar en normocapnia redujo el c.b.f. en 65 por ciento. Con hipercapnia el c.b.f. fue duplicado, pero con hipocapnia hubo poco aumento de la reducción del c.b.f.. Se concluye que el droperidol es un vasoconstrictor cerebral potente, que este efecto domina cuando es administrado en combinación con fentanil, ya que la hipocapnia provoca poco aumento de la reducción del c.b.f., y que la reducción del c.b.f. producida por el Innovar no es acompañada por alteraciones en las vías metabólicas cerebrales normales.