EFFECTS OF ALFENTANIL ON CEREBRAL VASCULAR REACTIVITY IN DOGS

R. W. McPHERSON, E. KREMPASANKA, D. EIMERL AND R. J. TRAYSTMAN

Alfentanil is a short acting analogue of fentanyl which is one-third as potent and has a higher therapeutic ratio than the parent compound as a result of its rapid elimination from plasma (Bovill et al., 1982). Alfentanil provides haemodynamic stability during anaesthesia in patients with cardiac disease when used either as an induction agent or during total i.v. anaesthesia, or both (Sebel, Bovill and Van Der Haven, 1982). Even after large doses of alfentanil, the time to awakening is short (DeLange, Stanley and Boscoe, 1981), and this short duration of action has led to its use as an infusion during prolonged anaesthesia (Bower and Hull, 1982).

The shorter duration of action of alfentanil makes it an attractive alternative to fentanyl, as a supplement to anaesthetic gases, in patients undergoing neurological procedures. Moreover, its more rapid termination of action compared with fentanyl makes retention of carbon dioxide after operation less likely (Stanski and Hug, 1982), would minimize postoperative narcotic-induced somnolence, and would allow more prompt evaluation of neurological function following surgery.

This study was undertaken to determine the effects of high doses of alfentanil (0.32 mg kg\(^{-1}\) i.v.) on cerebral blood flow and metabolism (CMRO\(_2\)) in the dog. In addition, the reactivity of the cerebral vasculature to hypercapnia and hypoxia, and to changes in mean arterial pressure, was determined.

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SUMMARY

The effects of high dose alfentanil on the cerebral vascular responses to alterations in mean arterial pressure (MAP), arterial oxygen tension (Pa\(_{O_2}\)) and arterial carbon dioxide tension (Pa\(_{CO_2}\)) were studied in 17 dogs, using the cerebral venous outflow technique. In six animals anaesthetized with sodium pentobarbitone 30 mg kg\(^{-1}\) i.v. bolus injection of alfentanil 0.32 mg kg\(^{-1}\) i.v. decreased MAP without a change in cerebral blood flow (CBF). In another group of animals (n = 5) anaesthetized with pentobarbitone 30 mg kg\(^{-1}\) i.v. the CBF responses to changes in MAP, Pa\(_{O_2}\), and Pa\(_{CO_2}\) were studied.

In a third group of animals (n = 6) anaesthetized with alfentanil 0.32 mg kg\(^{-1}\) i.v. plus pentobarbitone 1–2 mg kg\(^{-1}\) i.v. and an infusion of alfentanil 0.32 mg kg\(^{-1}\) h\(^{-1}\), the CBF response to alterations in MAP, Pa\(_{O_2}\), and Pa\(_{CO_2}\) were studied and compared with the barbiturate-anaesthetized animals. The CBF responses to hypercapnia and hypoxia in the alfentanil-anaesthetized animals were not different from those observed in animals anaesthetized with barbiturate only. The lower and upper limits of cerebral autoregulation in alfentanil-anaesthetized animals were not different from those observed in animals anaesthetized with barbiturate only. The data suggest that alfentanil, in doses sufficient to cause profound analgesia and anaesthesia, does not alter cerebral reactivity to changes in Pa\(_{O_2}\), Pa\(_{CO_2}\), and MAP.

MATERIALS AND METHODS

Animals and anaesthesia

Seventeen mongrel dogs (20–25 kg) of either sex were utilized in this study. Two basal anaesthetic
techniques were used. Eleven animals (group 1, \( n = 6 \); group 2, \( n = 5 \)) were anaesthetized initially with pentobarbitone 30 mg kg\(^{-1}\) i.v. bolus and supplemented with i.v. increments of 30 mg in response to pedal and ocular reflexes. Six animals (group 3, \( n = 6 \)) were anaesthetized with alfentanil 0.32 mg kg\(^{-1}\) i.v. plus pentobarbitone 1–2 mg kg\(^{-1}\) and an infusion of alfentanil 0.32 mg kg\(^{-1}\) h\(^{-1}\) was administered continuously throughout the investigation. Additional increments of alfentanil 1 mg were given if movement or cardiovascular response to stimulation occurred during the surgical preparation. Pancuronium 3–4 mg i.v. was administered in all groups to minimize muscle contractions related to the electrocautery. Heparin 500 u kg\(^{-1}\) i.v. was used in all groups as the anticoagulant.

After the induction of anaesthesia, the trachea was intubated and the lungs ventilated utilizing a positive pressure respirator (Harvard Respiration Pump 607). Tidal volume and respiratory rate were adjusted to give an alveolar (end-expiratory) carbon dioxide concentration of 4% as monitored by a carbon dioxide analyser (Beckman LB2). The analyser was calibrated regularly with mixtures of carbon dioxide in air analysed to a precision of 0.1%. One femoral artery was cannulated to permit the continuous monitoring of arterial pressure. The contralateral femoral artery was cannulated and utilized for the removal of blood during those parts of the study which dealt with alterations in arterial pressure. One femoral vein was cannulated and was utilized to return the cerebral venous outflow, while the other femoral vein was cannulated and used for infusion of fluids and drugs. Rectal temperature was maintained at 38 ± 1 °C using heating lamps. All pressures were measured with Statham P-23 transducers, and all data were recorded in a Gould–Brush recorder.

**Measurement of cerebral blood flow**

The technique used to measure cerebral venous outflow has been described previously (Rapela and Green, 1964). The confluence of the cerebral sinuses was cannulated, and the lateral sinuses and occipital emissary veins were occluded with bone wax to eliminate communication between intracranial and extracranial venous circulations. From the confluence of the sinuses, blood was passed through a previously calibrated electromagnetic flow probe, before being returned to the dog via the femoral vein. With this technique approximately 50–70% of the mass of the brain is drained at the confluence of the sagittal and straight sinuses (Rapela and Green, 1964). Cerebral venous outflow pressure was measured upstream from the flow probe. The venous outflow pressure was maintained near 0 mm Hg by manipulation of the reservoir level. This pressure measures the resistance to the flow of blood induced by the flow transducer, because the outflow cannula was set at the level of the right atrium and all pressures were referred to this common zero reference plane. Brain perfusion pressure was estimated as systemic arterial pressure minus cerebral venous outflow pressure. Intracranial vascular resistance was calculated by dividing brain perfusion pressure by cerebral venous outflow.

The verification of the measurement of CBF utilizing this venous outflow technique has been described in detail elsewhere (Traystman and Rapela, 1975); the viability and reactivity of the cerebral vasculature to hypoxia and hypercapnia (Traystman and Rapela, 1975), hypoxia (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981) and ability to autoregulate (Rapela and Green, 1964) using this technique has been previously demonstrated. In the absence of increased venous outflow pressures (>2 mm Hg), this method of CBF measurement compares favourably with CBF measured by the injection of microspheres (Wagner and Traystman, 1983).

**Hypoxia and hypercapnia, and blood-gas analysis**

Arterial hypoxia was produced through decreasing arterial oxygen content by introducing a gas mixture containing 6.5% oxygen and 93.5% nitrogen to the inspiratory limb of the respirator. Arterial carbon dioxide tension was maintained constant throughout. Hypoxia was maintained for 10–15 min to allow for measurement under near steady-state conditions. The CBF response to hypercapnia was evaluated by introducing likewise a carbon dioxide-containing gas mixture. Five and 10 percent carbon dioxide in air were utilized as the gas mixtures, and hypercapnia was maintained for 10 min at each concentration so that near steady-state measurements could be obtained.

Arterial and cerebral venous blood samples were taken directly from the femoral artery and cerebral venous outflow cannulae, respectively. The design of the study was such that each dog acted as its own control for hypoxia and hypercapnia. Arterial oxygen tension (\(P_{aO_2}\)), carbon dioxide tension (\(P_{aCO_2}\)) and pH were measured at 37 °C immediately after the withdrawal of the samples (Radio-
Group 3 (n = 6)
Group 2 (n = 5)
Group 1 (n = 6)

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<th>Plan of investigation and data analysis</th>
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<td>The direct effect of alfentanil 0.32 mg kg⁻¹ i.v. on CBF and ( \text{CMRO}_2 ) was studied in group 1 animals (n = 6) anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v. In group 2 animals (n = 5) anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v. and in group 3 animals anaesthetized with alfentanil 0.32 mg kg⁻¹ i.v. plus pentobarbitone 1–2 mg kg⁻¹ i.v. and a continuous infusion of alfentanil 0.32 mg kg⁻¹ h⁻¹, the responses to hypoxia and hypercapnia were studied.</td>
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Fig. 1. Responses of cerebral blood flow (CBF), cerebral vascular resistance (CVR) and cerebral oxygen consumption (CMRO₂) to hypoxia in groups 2 and 3. Group 2 animals were anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v. and group 3 animals were anaesthetized with alfentanil 0.32 mg kg⁻¹ i.v. plus pentobarbitone 1–2 mg kg⁻¹ i.v. and a continuous infusion of alfentanil 0.32 mg kg⁻¹ h⁻¹. Each bar represents the mean ± SEM. *P < 0.05.

Fig. 2. Responses of cerebral blood flow (CBF), cerebral vascular resistance (CVR) and cerebral oxygen consumption (CMRO₂) to two levels of hypercapnia are shown. Group 2 animals were initially anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v. and group 3 animals were anaesthetized with alfentanil 0.32 mg kg⁻¹ i.v. plus pentobarbitone 1–2 mg kg⁻¹ i.v. and continuous infusion of alfentanil 0.32 mg kg⁻¹ h⁻¹. Each bar represents the mean ± SEM. *P < 0.05.

RESULTS

Haemodynamic, blood-gas and pH changes for all groups of animals are presented in table I. In group 1, alfentanil 0.32 mg kg⁻¹ i.v. decreased mean arterial pressure (MAP) to 68 % of control 2 min following injection. CBF and CMRO₂ remained unchanged from their control values, whereas cerebral vascular resistance (CVR) had decreased to 66 % of control 2 min following the injection.

In the animals in group 2, PaO₂ was decreased from 12.6 ± 1.1 to 3.2 ± 0.13 kPa, and CBF increased to 285 % of control and CVR decreased to 57 % of control. In group 3, as PaO₂ was...
Discussion

In this study, the cerebral venous outflow technique (Rapela and Green, 1964), in which transient changes in CBF could be monitored continuously, was used and the response of CBF and CMRO₂ to any intervention observed. While one advantage of this technique is that it measures CBF nearly devoid of extracerebral contamination, a disadvantage of this model is the need for anaesthesia during the surgical preparation. Therefore, we have no observation of the effects of alfentanil in the unanaesthetized animal. Baseline CBF in this study was similar to our recent study of fentanyl (McPherson and Traystman, 1984) but was somewhat higher than those previously reported (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981). As in our previous study (McPherson and Traystman, 1984), control CBF was around 30 ml min⁻¹ whereas in the earlier studies control flows were 20–23 ml min⁻¹. Basal CBF in this study was at a lower baseline arterial oxygen content (15 vol%) whereas in previous studies, baseline arterial oxygen content was about 19 vol% and CBF was somewhat lower. In fact, a CBF of 30 ml min⁻¹ at an arterial oxygen content of 15 vol% is consistent with our previous studies of the effect of decreased arterial oxygen content on CBF (Traystman, Fitzgerald and Loscutoff, 1978; Traystman and Fitzgerald, 1981).

Alfentanil 0.32 mg kg⁻¹ i.v., a dose twice that shown to cause profound analgesia and anaesthesia in both animals and man (Nauta et al., 1983), did not alter CBF despite a substantial decrease in MAP (40 mm Hg). An advantage of the venous outflow technique is the ability to observe transient changes in CBF. Observations were made immediately after the administration of the alfentanil and, although CBF was unchanged, CVR decreased significantly. This was a consequence of the decreased MAP and unchanged CBF and suggests that the decrease in CVR was a normal adjustment to maintain CBF constant in response to a decrease in MAP within the autoregulation range.

We studied the effect of alteration in MAP on CBF using haemorrhagic hypotension and noradrenaline-induced hypertension. Noradrenaline has been shown not to cross the blood–brain barrier and thus has no direct cerebral vascular effect when given i.v. (O'Neill and Traystman, 1977). The limits of autoregulation were similar to those reported by others (Rapela and Green, 1964).
and in our previous study of fentanyl (McPherson and Traystman, 1984). These data suggest that increases in CBF in the presence of alfentanil and small amounts of barbiturates would be less with hypertension than that noted in the presence of inhalation agents, which have been shown to decrease the ability of cerebral vessels to autoregulate in a dose-dependent manner (Miletich et al., 1976; Morita et al., 1977; Todd and Drummond, 1984).

The lower limit of autoregulation found in this study was also comparable to those reported previously (Rapela and Green, 1964; McPherson and Traystman, 1984). CVR was decreased to a similar value in animals anaesthetized with barbiturate and animals anaesthetized with alfentanil plus small amounts of barbiturate, and the CBF was unchanged. This suggests that alfentanil plus small doses of barbiturate does not interfere with maintenance of CBF at relatively low arterial pressures. Thus these data suggest that alfentanil anaesthesia would be an acceptable anaesthetic in situations in which cerebral perfusion pressure is low, such as hypovolaemic hypotension or carotid surgery.

We have demonstrated an essentially linear increase in CBF with increases in \( P_{\text{aCO}_2} \) in animals anaesthetized with alfentanil and small doses of barbiturate which did not differ from the effect in animals anaesthetized with barbiturate only. This differs from situations when anaesthetic doses of anaesthetic gases are administered, in which the CBF response to carbon dioxide is altered (Miletich et al., 1976). These data suggest that alfentanil anaesthesia would allow manipulation of ICP by inducing alterations in \( P_{\text{aCO}_2} \).

Hypercapnia resulted in a decrease in CMRO\(_2\) in both barbiturate- and alfentanil-anaesthetized animals. This decrease in CMRO\(_2\) occurs in anaesthetized but not sedated animals (Berntmann and Dahlgren, 1979). The mechanism of maintenance of CMRO\(_2\) in unanaesthetized animals was considered to be an increased catecholamine turnover as a result of hypercapnia and a resultant increase in CMRO\(_2\). Both anaesthesia and propranolol have been shown to prevent the increase in CMRO\(_2\) caused by hypercapnia (Berntmann and Dahlgren, 1979); the mechanism of the decrease in CMRO\(_2\) remains unclear.

CBF increased in response to hypoxia both in animals anaesthetized with barbiturate and animals anaesthetized with alfentanil. CBF increased to 3 times control during hypoxia in both groups; however, CMRO\(_2\) was not decreased by hypoxia in animals anaesthetized with barbiturate only. CMRO\(_2\) was decreased during hypoxia in animals anaesthetized with alfentanil. This occurred because the \( P_{\text{aO}_2} \) and arterial oxygen content were decreased more in the alfentanil-anaesthetized animals than in barbiturate-anaesthetized animals, and the CBF response in those animals was insufficient to offset the reduction in oxygen delivery. These data suggest that alfentanil plus small doses of barbiturate is not different from moderate doses of barbiturate in its lack of adverse affects on the cerebral hypoxic response.

In summary, our data demonstrate that high-dose alfentanil in the presence of small doses of pentobarbitone does not alter cerebral haemodynamic responses to hypoxia or hypercapnia. In addition, the lower and upper limits of autoregulation are not altered by alfentanil. Since the normal cerebral compensatory mechanisms appears to be intact with high doses of alfentanil and since there is a well documented cardiovascular stability with alfentanil, this suggests that high doses of alfentanil would be an acceptable anaesthetic technique in neurosurgical patients.

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REFERENCES


