NEUROPHARMACOLOGY - INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

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ABBREVIATIONS
CBF Cerebral blood flow
ICP Intracranial pressure
CMRO$_2$ Cerebral metabolic rate
MAP Mean arterial pressure
h Hour
min Minute

INHALATIONAL AND INTRAVENOUS AGENTS
Reviewing new pharmacological agents and their effects on the brain has been a considerable challenge. Over recent years a number of new agents, both inhalational and intravenous have been introduced. Their advantages and disadvantages are debated, their availability is not uniform, but their costs are undisputedly increased. Should they be included in this review? I believe they should, as a decision on the use of a drug can only be made after consideration of all the facts, pharmacological, economic and availability by the clinician. Previously, anaesthetists used inhalational techniques almost exclusively. Today it is different, with the important advances in intravenous drugs, a significant number of anaesthetists use intravenous techniques either routinely or with certain indications. Thus both inhalational and intravenous agents will be considered, with a discussion of clinical considerations where relevant.

INHALATIONAL AGENTS
The conventional understanding is that anaesthetic agents reduce neuronal function and so depress metabolic demands. This in turn reduces cerebral blood flow (CBF). However it is well recognised that volatile anaesthetic agents cause cerebral vasodilatation with an increase in CBF. This direct effect is caused by a reduction in the tension of the isolated cerebral artery muscle. Volatile agents also produce some uncoupling of the normal relationship between metabolism and blood flow. Usually, when cerebral metabolic rate (CMRO$_2$) decreases, local blood flow falls as there is a reduced requirement for oxygen delivery and carbon dioxide removal. This is the indirect effect. Volatile agents uncouple or disconnect this relationship in a dose dependent way. The overall effect on cerebrovascular tone therefore, is the sum of both the direct vasodilatory effect and any indirect vasoconstrictor effect remaining.

The important consequence of this is that any dilatation in turn raises cerebral arterial volume and increases brain volume. When the brain is stiffer, in other words, compliance is reduced, intracranial pressure (ICP) will rise [1]. This was explained in the previous article to which the reader is referred and is demonstrated in fig 1. Note the different size of the rises in ICP which occur as the squishiness or compliance of the brain changes. At the left hand end, the brain is not stiff, the normal situation. Any change in cerebral volume results in a small increase in ICP. In contrast at the right hand end of the curve the brain is stiffer, due to oedema or a large space occupying lesion such as a blood clot, tumour or cyst. Note the larger increases in ICP at the right end of the curve in this situation.

![Fig 1 The pressure-volume curve of the intracranial contents. As the volume of an expanding mass increases, ICP rises only slightly until the compensatory mechanisms are overcome. This point is reached at the elbow of the curve when further expansion of the mass causes a steep rise in ICP](image)

It is important to consider the influence on two other physiological mechanisms, autoregulation and CO$_2$-CBF relationship. The normal autoregulatory mechanism is gradually abolished as the concentration of the volatile agent is increased, CBF becoming blood pressure dependent. Thus as blood pressure rises, CBF increases and cerebral
vasodilation occurs. In contrast when blood pressure falls, there is no mechanism to sustain flow by reducing cerebrovascular resistance (fig 2).

The CO₂-CBF relationship is also affected by the volatile agents, the curve being shifted to the left. Hypocapnia is still able to reduce cerebral blood flow and therefore to oppose the vasodilation. However if CO₂ is allowed to rise, there is a much more rapid increase in CBF (fig 3).

TEACHING POINT
It is well recognised that following a head injury where the patient has lost consciousness briefly, a technique with spontaneous breathing with a volatile agent should NEVER be used. Following the head injury there will be some cerebral swelling because of contusion. Compensation will have taken place and thus the patient may not appear to have any significant decompensation. If an anaesthetic is required and halothene is given with the patient breathing spontaneously, there will be a rapid rise in ICP following cerebral vasodilatation induced by the combination of a raised CO₂ and a volatile agent. In addition blood pressure may fall as well, the combination dramatically reducing cerebral perfusion. Postoperatively this will be seen as persistent unconsciousness.

Halothane is a moderately insoluble agent, blood:gas solubility 2.5 and a MAC of 0.75%. In the presence of cerebral swelling, it produces a large rise in ICP which can be prevented by hyperventilating the patient for 10 min before introducing it [2]. Cerebral autoregulation is reduced at 1% inspired concentration and abolished by 2% [3]. Halothane does not causes cerebral epileptic activity detected on the electroencephalogram (EEG). In practice therefore it is reasonably safe to use halothane in a hyperventilated patient up to a concentration of 0.5% in conjunction with nitrous oxide. It should be avoided, if possible, by using alternative techniques, before the dura is opened in patients who have severe intracranial decompensation [4] - in other words, massive brain swelling leading to unconsciousness preoperatively.

Enflurane has less effect on CBF and ICP than halothane. Like halothane it reduces CMRO₂, but it does cause cerebral epileptic activity, particularly when the patient is hypocapnic [5]. Epileptic activity is harmful as it induces a massive increase in cerebral metabolism, which in turn increases blood flow and hence cerebral swelling. Neurosurgery itself can also induce epileptic seizures postoperatively, and thus drugs which induce this process should be avoided. Finally the rate of production and resistance to reabsorption of CSF are increased by enflurane, making any increase in ICP associated with its use worse.
Isoflurane is a methyl ethyl ether with a blood:gas solubility 1.4 and MAC 1.2%. It causes both respiratory and cardiovascular depression, the latter occurring predominantly due to a fall in systemic vascular resistance [6]. CBF and cerebral blood volume (CBV) are not affected by concentrations of 0.6-1.1 MAC isoflurane, but 1.6 MAC doubles CBF. Similarly it is only higher concentrations which cause an increase in ICP. There is less impairment of autoregulation and CO₂ reactivity when compared to halothane. A major property is the significant reduction in cerebral metabolic rate. There is evidence of uncoupling between the direct dilating effect and indirect vasoconstrictive effect, of isoflurane on the cerebral vasculature. Therefore, up to 1.6 MAC the vasoconstricting effect predominates preventing cerebral blood flow from rising. As the inspired concentration rises, the direct vasodilatory effect overrides the indirect vasoconstrictor effect. However, in damaged or pathological brains the indirect vasoconstriction due to the depression in cerebral metabolic rate does not occur. Therefore small concentrations of isoflurane will cause some cerebral vasodilation although it is not as marked as with equipotent doses of halothane.

In clinical practice, it has been demonstrated that 1.1% isoflurane significantly increases intracranial pressure in patients with intracranial tumours with midline shift, despite hyperventilating the patient to induce a low CO₂ [7]. Despite these side-effects, isoflurane has become a useful drug for neuroanaesthesia because of its ability to reduce cerebral metabolic rate and to cause less vasodilation than other volatile agents available.

Sevoflurane is a new volatile agent with MAC 1.7-2%, and a low blood:gas solubility 0.6 (isoflurane 1.4). It has similar properties to isoflurane on the brain, CBF, CBV and ICP [8,9]. A requirement of neuroanaesthesia is rapid recovery following surgery which may have lasted several hours. Low blood:gas solubility enables very rapid recovery even after many hours of surgery. Sevoflurane is also metabolised (5%), increasing blood fluoride concentration. So far no renal complications have been reported.

When sevoflurane is used with baralyme or soda-lime, in a circle system, Compound A, a toxic compound is produced. Again there have been no reports in man of problems, although some countries have set a minimum fresh gas flow of 2L/min. Sevoflurane is very expensive, but when used in a low-flow system is little more expensive than isoflurane. However this does require sophisticated monitoring, and there is the potential problem of complications arising from Compound A. Opinion is still divided on whether the use of low flow sevoflurane (<1L/min) is acceptable.

Desflurane is also similar to isoflurane when considering the brain. The MAC is 5-10% and blood:gas solubility, 0.4%, also very low. Thus, like sevoflurane the main advantage to the neuroanaesthesitist is rapid recovery. It too is expensive and is only economically viable if used in a sophisticated low-flow system. However in contrast to sevoflurane it is irritant to the tracheobronchial tree, requires a special vapouriser but is not metabolised or affected by soda-lime.

Ether (diethyl-ether) is still used as it is considered to be one of the safest agents because respiratory depression precedes cardiovascular depression. It is an irritant, soluble agent, blood:gas solubility 12 (c.f. sevoflurane 0.6) and MAC 1.92%. Thus induction is prolonged and can be stormy. Recovery is also prolonged. Considering the brain, ether causes a biphasic response; at low concentrations, 2.4%, it will lead to some reduction in CBF and a significant fall in metabolic rate. However at higher concentrations, 4.5%, there is an increase in CBF with CMRO₂ rising towards baseline values [10]. Ether liberates catecholamines and it is believed that initially the increased sympathetic activity reduces CBF, but at higher ether concentrations the direct vasodilatory effect becomes dominant. The increased sympathetic activity also stimulates the brain with a risk of inducing epileptic activity, which both increases brain oxygen needs as well as increasing the risk of postoperative convulsions.

Thus, if there is a choice ether should be avoided. However, if there is no choice, then ether is better used as maintenance, following an intravenous induction, in a paralysed ventilated patient, in conjunction with a narcotic to reduce the ether requirements to a minimum.

Summary
Sevoflurane has great promise for neuroanaesthesia in those countries where it is available and can be
used with a low-flow system making it only slightly more expensive than isoflurane. The only question mark remains over the risk of the toxic substance, Compound A, which is formed when used with CO₂ absorber systems. Isoflurane is in general the “standard” volatile agent used for neuroanaesthesia. However the advantages of these different agents are relatively small and can be described as fine-tuning. Halothane or any of the less “ideal” agents are safe to use for neuroanaesthesia when there is no alternative provided that close attention to basic details required for neuroanaesthesia are adhered to. It is this that makes a major contribution to reducing the disadvantages of less suitable agents.

Nitrous oxide has been used for many years as a carrier gas and for its analgesic properties. It was believed that the effects on cerebral blood flow were minimal. However, in work with human volunteers nitrous oxide has been shown to cause a significant increase in cerebral blood flow acting synergistically with the volatile agents [11]. More importantly, the increase in CBF due to a combination of isoflurane and nitrous oxide is greater than simply increasing the volatile agent alone to provide the same MAC. As might be expected, an increase in ICP has been demonstrated when N₂O is used for patients with intracranial tumours. This has lead a number of centres to omit N₂O from their technique. However nitrous oxide is not contraindicated for most neurosurgical procedures when there is minimal cerebral swelling. In addition, patients have to be anaesthetised with some agent and before omitting nitrous oxide the clinician who normally uses it, must ensure that the alternative technique does not produce worse conditions. Volatile agents with oxygen enriched air have been used to maintain anaesthesia. Alternatively an infusion of thiopentone has been used, but there is a significant problem of hypotension and accumulation. More commonly propofol infusions are used, but they are expensive and require sophisticated infusion pumps.

HYPNOTICS
Drugs which induce general anaesthesia are cerebral depressants with the exception of ketamine.

Barbiturates reduce CBF by both direct cerebral vasoconstriction and indirectly by a reduction in metabolism. Pierce in 1962 showed there was a dose dependent reduction in cerebral metabolic rate and cerebral blood flow which ultimately led to a reduction in cerebral blood volume [12]. It is this change in cerebral blood flow and cerebral blood volume which causes a fall in intracranial pressure and has been used therapeutically. Thiopentone is used for induction and has been used for maintenance as an infusion with nitrous oxide, but without narcotic supplements [13]. Depending on patient age, weight and general condition 500-1500mg of thiopentone is put into 500ml. The infusion is commenced at 1-3mg/min, titrated against patient reaction and finally stopped as the dura is closed. The infusion rates used ranged from 28 to 800mg/h, with a mean rate 300mg/h. However large doses of barbiturates must be used with caution in patients with raised ICP as they also cause a marked fall in blood pressure which will lead to a fall in cerebral perfusion pressure, and will accumulate, leading to prolonged recovery.
the propofol effector site concentration was 1.8 mg.ml⁻¹ (95% confidence limits 1.4-2.34 mcg/ml; (14). Note the wide confidence limits, one of the factors that makes it more difficult to ensure the patient is not aware during a total intravenous technique.

A manual regimen has been described by Roberts et al[15] to achieve a maintenance level of propofol by commencing with a bolus, 1 mg/kg, and a rapid infusion rate (10 mg/kg/h for 10 min, 8mg/kg/h for a further 10 min). This is subsequently reduced to the baseline maintenance rate of 6 mg/kg/h. This technique requires both narcotic supplements and N₂O. Propofol is a very useful agent for maintenance of anaesthesia of the neurosurgical patient, particularly when nitrous oxide is to be avoided. It should be noted that propofol infusions are expensive and require sophisticated infusion pumps. More recently the concept of Target Controlled Infusions (TCI) has been introduced where a specially designed syringe pump using a pre-programmed algorithm injects the drug at a rate necessary to achieve the blood level set by the clinician.

**TEACHING POINT**

All available evidence suggests that ketamine should be avoided if possible for anaesthesia for neurosurgery especially in those with raised ICP, or cerebral swelling leading to a decreased compliance or squashiness.

Ketamine is a derivative of phencyclidine that induces dissociative anaesthesia, and stimulates the cardiovascular system with minimal respiratory depression. However in patients with intracranial decompensation because of oedema or space occupying lesions, in contrast to other anaesthetic agents, it increases CMRO₂, CBF and ICP. These changes can be reduced by pre-treatment with hypocapnia, thiopentone or a benzodiazepine.

Following ischaemia the pathological mechanism which results in cerebral infarction involves the release of a number of neurotransmitters, a major one being N-methyl-D-aspartate (NMDA). Ketamine is a non-competitive antagonist at NMDA receptors and may therefore offer protection from the adverse effects of cerebral ischaemia. This is a field under intensive research at present.

**TEACHING POINT**

When presented with a patient who has a full stomach, safe establishment of the airway takes a priority. Despite the possible risks of raised intracranial pressure, in the emergency case, succinylcholine is the drug of choice for intubation.

Pancuronium does not affect CMRO₂, CBF or ICP during induction of anaesthesia. It may cause arterial hypertension and tachycardia which may make intracranial conditions difficult during surgery.

**TEACHING POINT**

Falls in blood and cerebral perfusion pressure are particularly risky in the elderly and emergency patient, when they will cause a significant fall in brain oxygenation. Any fall in blood pressure associated with the use of propofol can be avoided by reducing the bolus dose and titrating it cautiously in these vulnerable patients.

Vecuronium is an intermediate acting non-depolarising neuromuscular blocking drug. Its principal advantage is that it has no significant effects on cardiovascular parameters. A preliminary report in neurosurgical patients confirmed that there was no effect on intracranial pressure or cerebral perfusion pressure [18]. Following an induction dose of 0.15mg/kg the onset time for neuromuscular blockade is approximately 140 seconds which is adequate for elective procedures.

Thus, in summary, vecuronium appears to have useful properties for inducing neuromuscular blockade prior to intubation in elective cases. It can be used to maintain neuromuscular blockade using an infusion technique. Alternatively, neuromuscular blockade can be maintained perfectly satisfactorily with the more established long acting or intermediate neuromuscular blocking drugs with the anaesthetist taking into account the unwanted side-effects.
NARCOTICS
It has been well established that narcotics given to conscious patients with some degree of intracranial decompensation will cause a rise in intracranial pressure. However, if ventilation is supported then the direct effect of narcotics in general on cerebral blood flow is minimal.

Fentanyl is an established narcotic used in neuroanaesthesia, the peak effect occurring 4 minutes after injection and lasting for more than 15 minutes. Suppression of the cardiovascular response to painful stimuli can be achieved using 1.5-2.5 mcg/kg. There is no change in CBF or ICP, though if a large bolus is given a small decrease in arterial pressure can lead to a similar change in cerebral perfusion pressure. However, it has been shown that fentanyl does accumulate and the duration of action can be up to 60 minutes or more if used over a period of time.

Pethidine is a synthetic opioid with similar properties to other narcotics, with additional atropine like effects. It can cause marked hypotension (minimised by slow intravenous injection), an important consideration in a patient with high ICP. The length of action is intermediate, 2h with a plasma half life 3-4hours. The usual intravenous dose is 0.5mg/kg. Pethidine has two drawbacks for neuroanaesthesia. It is metabolised in the liver to norpethidine, which is a convulsant. Norpethidine relies on excretion in the kidney, and thus this problem is particularly relevant in someone whose renal function is impaired. Secondly, pethidine is lipid soluble, thus if large doses are used, in a long and stimulating procedure for instance, the action can be prolonged.

In summary, pethidine is not an ideal agent, but if it is the only narcotic available then it is safe to use it, but with caution, while considering the properties mentioned.

Alfentanil is a more recent opioid which is less potent than fentanyl but has a very rapid onset of effect with shorter duration due to rapid excretion. Alfentanil has a very low volume of distribution and because it is not widely distributed throughout the body the amount required to produce an adequate effective concentration is less - hence its rapid excretion. This happens despite the clearance rate being similar to that of the more soluble opioid, fentanyl. It is analogous to the rapid emergence from the effect of an insoluble inhalational agent.

Suppression of the cardiovascular response to painful stimuli can be achieved with 10-30mcg/kg which will be effective within 1 min and last for 12 minutes. However, a bolus of this magnitude can cause a fall in arterial pressure, especially in elderly or emergency patients with a compromised circulation. This is very important when intracranial pressure is raised.
Initially there were reports that CBF, and ICP were increased by alfentanil. There appeared to be no explanation for this and the rises were not considered clinically significant. However these changes were accompanied by falls in arterial pressure which had a significant effect on cerebral perfusion pressure. Looking at the mechanism of autoregulation provides the answer for this otherwise unexplained rise in ICP. If autoregulation is functioning, as arterial pressure falls, a compensatory increase in CBF occurs, as explained in the previous article. The increase in CBF will happen because of a decrease in cerebral resistance, caused by dilatation of the cerebral arterioles. In turn this increases cerebral arterial blood volume, causes cerebral swelling and increases ICP if the brain is already enlarged. If this explanation is correct, when the opioid is given to patients with some cerebral swelling and blood pressure maintained by catecholamines, there will be no change in ICP.

This study has been carried out by Werner [19] who noted that when BP was sustained there was no change in ICP following sufentanil, but when it was allowed to fall ICP rose. Although this work was carried out with sufentanil, another opioid with similarities to alfentanil, the mechanism is believed to be the same.

**Remifentanil** is an ultra-short acting esterase metabolised, mu-opioid receptor agonist. It is able to produce intense analgesia rapidly, and has potency similar to fentanyl. It has typical opioid effects of respiratory depression, bradycardia and skeletal muscle hypertonus. The major difference with this drug is that it is rapidly broken down by circulating and tissue non-specific esterases. Thus the $\beta$ half-life is 10-20 min with a plasma clearance of 3-4 L.min$^{-1}$. As recovery is so rapid, it is unaffected by the dose or the length of time that it has been given. The concept of context sensitive half-life has been introduced and will be considered below.

Early experimental work has shown that there is little difference between remifentanil and alfentanil on CBF or ICP. Studies in patients undergoing craniotomy have compared fentanyl, alfentanil and remifentanil [20,21]. A bolus administered over 1 min did not cause a significant rise in ICP (2-3 mmHg), but depressed blood pressure to an extent which was related to the dose (MAP 8 mmHg lower dose). One of the problems with remifentanil is that the remaining analgesic which is very useful in the immediate postoperative period even for craniotomies does not occur. Therefore the problem of providing postoperative pain relief needs careful consideration.

**Context sensitive half-time** was discussed in a recent editorial [22] where it was defined as the time for plasma concentration to decrease by 50% after terminating an i.v. infusion designed to maintain a constant plasma concentration. Context refers to the length of the infusion. It has been demonstrated that the context sensitive half-time of both anaesthetic agents and opioids could differ markedly from elimination half-lives and that it is dependent on the duration of the infusion. The offset of action of a drug is not only a function of the elimination half-life but also of a number of complex factors which include the rate of equilibration between plasma and effector site, the method of administration and duration of infusion. It is also more relevant than simple elimination half-life data to clinical anaesthetists who give drugs over a period of time.

The method of administration can be either a continuous infusion or intermittent boluses. The context sensitive half-lives for different narcotics are illustrated (fig 4) and it can be seen that the half-life for remifentanil is unaffected by time. This would be expected, since there is no accumulation as it is rapidly metabolised. It is interesting to note the rapid increase in the context sensitive-half-life for fentanyl when used for more than a 2h period. When the drug is used over a long period of time, as it has a large volume of distribution and is fat soluble, a large amount is stored in the fat stores. It therefore takes a long time to be eliminated from the body, particularly as it is released slowly. Clinical experience supports this when fentanyl is used in long cases. Clinicians know that if they give large doses of fentanyl, even when the patient needs more analgesia, recovery will be slow. In contrast, although alfentanil does accumulate to some extent, it is predictable, appearing to level off at 60 minute context sensitive half-life after an infusion of 180 min. Thereafter longer infusions make little difference, again born out by clinical experience in long cases.
When propofol infusions are used for more than 3-4 hours, recovery becomes longer. This can be understood by examining the context sensitive half-life (fig 5). Note that after an infusion of 6 hours the context sensitive half-time is 20 minutes.

**REFERENCES**

INTRODUCTION
During routine anaesthesia the incidence of difficult tracheal intubation has been estimated at 3-18%. Difficulties in intubation have been associated with serious complications, particularly when failed intubation has occurred. Occasionally in a patient with a difficult airway, the anaesthetist is faced with the situation where mask ventilation proves difficult or impossible. This is one of the most critical emergencies that may be faced in the practice of anaesthesia. If the anaesthetist can predict which patients are likely to prove difficult to intubate, he may reduce the risks of anaesthesia considerably. This paper reviews clinical techniques used for predicting difficulties in intubation and suggests different approaches to manage these patients.

Fig. 1 The classification of the views at laryngoscopy.
In class I the vocal cords are visible, in class II the vocal cords are only partly visible, in class III only the epiglottis is seen and in class IV the epiglottis cannot be seen.

There have been various attempts at defining what is meant by a difficult intubation. Repeated attempts at intubation, the use of a bougie or other intubation aid have been used in some papers, but perhaps the most widely used classification is by Cormack and Lehane [1] which describes the best view of the larynx seen at laryngoscopy (figure 1). This should be recorded in the patient’s notes whenever an