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Therapeutic coma or neuroprotection by anaesthetics

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Abstract

Some surgical patients are at an increased risk for developing cerebral ischaemia. A subset of these patients is believed to benefit from putative cerebroprotective effects of anaesthetic agents.

Therefore, in this setting these drugs could have therapeutic modalities, besides their auxiliary functions to make surgery possible. However, both animal and especially human data are very disappointing.

Only the barbiturates and isoflurane have an experimental record warranting further research to delineate proper indications for their use as neuroprotective agents in surgical patients.

Key words : Barbiturates ; etomidate ; propofol ; ketamine ; isoflurane.

Ischaemic stroke is the third leading cause of death in industrialized countries (Dirnagl *et al.*, 1999). Furthermore, it is the leading cause of serious disability (Polls, 1997). Many of these insults occur during the perioperative period (Toner *et al.*, 1996).

Central nervous system neurons are extremely sensitive to an impairment of the delivery of substrates, particularly oxygen and glucose (Dirnagl *et al.*, 1999). At normothermia, only a few minutes of anoxia is tolerated before irreversible damage occurs (Cheng *et al.*, 1997). With the restriction of the delivery of oxygen a series of events is initiated that contribute to the demise of tissue (Dirnagl *et al.*, 1999). These events include : energy failure and excitotoxicity, peri-infarct depolarisations, inflammation, and apoptosis (Dirnagl *et al.*, 1999). While all these mechanisms are potential targets for therapy, those therapies aimed at interfering with the early energy failure by reducing cerebral metabolic rate are confined within the very first minutes after the insult (Dirnagl *et al.*, 1999).

Conventionally, it is thought that the reduction of cerebral metabolic rate is pivotal to anaesthetic neuroprotection. Therefore, it is to be expected that anaesthetics can only offer protection from exacerbations of preexisting ischaemia or de novo intraoperative ischaemia when being given during the occurrence of the ischaemic insult (Cheng *et al.*, 1997). This, obviously, limits their therapeutic potential. Nevertheless, some high risk surgical groups have been identified that can benefit from the manipulation of anaesthetic agents. These groups include patients undergoing carotid endarterectomy, cerebral aneurysm clipping and cardiac surgery (Polls, 1997 ; Michenfelder *et al.* 1987 ; Kassel *et al.*, 1990 ; Slogoff *et al.*, 1982).

Before discussing the neuroprotective characteristics of anaesthetic agents, some introductory remarks are necessary.

Anaesthetic agents can be divided into two subclasses : those delivered by inhalation and those used intravenously.

Besides the gaseous nitrous oxide, the inhalational anaesthetics include halothane, a halogen-substituted ethane derivative and further the halogen-substituted, ether link containing enflurane, isoflurane, sevoflurane, and desflurane (Cheung *et al.*, 1998).

The drugs that are currently available for intravenous anaesthesia include the barbiturates thiopental and methohexital, the imidazole-containing anesthetic compound etomidate, furthermore propofol, and the phencyclidine related ketamine (Kennedy, 1998).

Although some interference with one (or several) of the injurious processes underlying cerebral ischaemia has been shown, and although the sum of different mechanisms may collectively attenuate the ischaemic injury, the reduction of cerebral metabolic rate forms the basis of cerebroprotection by anaesthetics (Polis, 1997). The prototype, by which this form of neurologic protection can be illustrated best, is provided by the class of barbiturates. It has been known for a long time that deep barbiturate anaesthesia mimics hypothermia to 30°C with respect to reduction in cerebral metabolic rate (Pierce *et al.*, 1962). Once the electroencephalogram has become isoelectric, the cerebral metabolic rate for oxygen and the cerebral blood

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flow are approximately halved (Michenfelder, 1974). Further administration lacks any additional effect on the cerebral metabolic rate (Michenfelder, 1974).

On theoretical grounds, barbiturates are expected not to be protective during global, complete ischaemia (Polis, 1997 ; Steen *et al.*, 1979). The argument for this belief resides in the observation that the physiological target for barbiturate-based neuroprotection, namely the neuronal electrical activity, is already abolished within seconds after the complete ischaemic insult (Steen *et al.*, 1979). Although animal models have produced conflicting results, the only human study demonstrated no benefit (Brain Resuscitation Clinical Trial I Study Group, 1986).

During cardiopulmonary bypass, a suitable human model for incomplete global (or multifocal) ischaemia, benefit of barbiturate treatment could be demonstrated (Nussmeier *et al.*, 1986). However, these findings may no longer be relevant for up to date anaesthesiological management of cardiopulmonary bypass. First of all, a bubble oxygenator with no arterial filter was used (Nussmeier *et al.*, 1986). This in itself predisposes to microembolic events (Slogoff *et al.*, 1982). Furthermore, in the barbiturate treated group, significantly more inotropic support was needed and prolonged ventilatory support was required (Nussmeier *et al.*, 1986).

The use of barbiturates in the setting of focal ischaemia seems more promising. However, although the majority of animal studies has clearly demonstrated protection, comparable results in humans are lacking (Polis, 1997). For instance, barbiturates used for surgical clipping of intracranial aneurysms did not improve outcome when compared with untreated patients (Mc Dermott *et al.*, 1989).

Although the barbiturates have failed to live up to expectations and many, if not all, of their putative indications for cerebroprotection have proved to be wrong, some well defined circumstances may exist where their use can be of limited value. Especially in the setting of cardiac surgery, their use could be beneficial, although even there firm evidence is lacking.

Etomidate shares many features with thiopental when it concerns its effects on the cerebral metabolic rate for glucose and oxygen (Davis *et al.*, 1986 ; Newberg Milde *et al.*, 1985). Although etomidate is less circulatory depressant than thiopental, adrenocortical suppression associated with its use in continuous infusion hampers its application as a cerebroprotective agent (Moore *et al.*, 1985). Furthermore, although high doses of etomidate are anticonvulsant, myoclonic activity can be observed after its administration (Modica *et al.*, 1990). This phenomenon can misdirect medical treatment (Polis, 1997).

Some animal studies have demonstrated modest neuroprotective effects of etomidate (Watson *et al.*, 1992). Although these findings were substantiated with histologic evidence, outcome studies failed to demonstrate a beneficial effect of etomidate (Polls, 1997). Furthermore, in an animal model with spontaneously hypertensive rats, larger infarct volumes were found when etomidate was given in comparison with halothane or thiopental (Drummond *et al.*, 1995). Taken together, especially in the perspective of the lack of valid human data, the use of etomidate for its putative cerebroprotective properties should be advised against.

Propofol is an alkylphenol intravenous anaesthetic characterized by a short duration of action. It is very suitable for administration in continuous infusion and hence very popular as an anaesthetic for neurosurgical procedures (Ravussin *et al.*, 1991). Although its use in this setting has been validated numerous times, there is no convincing evidence that propofol offers additional protection besides that present when an agent of any subclass suppresses cerebral metabolic rate for oxygen. There are wide discrepancies between some animal studies focusing on well defined deleterious mechanisms of ischaemic damage and studies addressing outcome (Cheng *et al.*, 1997). In humans, firm evidence of the superiority of its cerebroprotective properties with respect to other intravenous anaesthetics is lacking. Furthermore, when it is used in particular circumstances of increased risk of cerebral ischaemia, for instance in the case of temporary clipping during the surgical treatment of intracranial aneurysms, its titration towards burst suppression is accompanied by hypotension, necessitating the use of vasoactive substances (Ravussin, 1993). Therefore, although its use is well established, it is very doubtful that the choice for propofol against another anaesthetic can be based on the argument of superiority with regard to cerebroprotection of the former.

Ketamine is related to phencyclidine. It produces a so called ‘dissociative’ type of anaesthesia with a pronounced component of somatic analgesia (Cheng *et al.*, 1997). Although ketamine is a NMDA receptor antagonist and as such a suitable candidate for a neuroprotective anaesthetic, many unfavourable characteristics make it very unsuitable in patients with neurologic disease (Cheng *et al.*, 1997). Especially, the increase of cerebral blood flow, cerebral metabolic rate for oxygen and intracranial pressure associated with its use make its administration contra-indicated in patients with intracranial pathology (Cheng *et al.*, 1997). However, in patients affected by other pathology, which puts them at risk for developing cerebral ischaemia, further research may be warranted.

The volatile anaesthetics reduce the cerebral metabolic rate of oxygen. Therefore, there has been a longstanding interest in these agents as neuro-

protective anaesthetics. There is evidence that volatile anaesthetics prolong the time to terminal depolarization in animals subjected to near-complete forebrain ischaemia (Verhaegen *et al.*, 1992). Although there is also evidence that the time to terminal ischaemic depolarization is directly proportional to the potency in reducing cerebral metabolic rate of oxygen, some data do not support this statement (Verhaegen *et al.*, 1992 ; Warner *et al.*, 1993 ; Doyle, 2000). Nevertheless, recent experimental work in rats subjected to bilateral carotid occlusion and controlled hypotension has shown that the anaesthetic effects on cerebral metabolic rate predict histologic outcome (Nellgård *et al.*, 2000). But, while these findings provide firm evidence that the reduction in cerebral metabolic rate offers a clear benefit, the observed effect is probably of limited value (a delay of 1.5 min. in time to depolarization under experimental conditions) (Verhaegen *et al.*, 1992 ; Nellgård *et al.*, 2000).

The therapeutic role of anaesthetics as cerebroprotective agents is probably very small. Furthermore, with the exception of ketamine, the relative benefit of one anaesthetic versus another with regard to neuroprotective potential is unlikely to form a rational basis of choice.

The only advantage of preferring general anesthesia to locoregional techniques (for instance in the case of carotid endarterectomy) is the delay to terminal ischaemic depolarization, thereby offering a small therapeutic window for emergency intervention might ischaemia occur.

The role of anaesthetics in sedative doses in the setting of an ICU is less well defined. The effects of sedation on outcome in neurological critical care certainly warrant further research.

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