DRUG THERAPY IN BRAIN ISCHAEMIA

S. E. GISVOLD AND P. A. STEEN

After many years of research, drug treatment in cerebral hypoxia is still controversial and no treatment appears to be firmly established. Not even the mechanisms causing damage have been established (Siesjö, 1981), only that they are linked to a disturbance in the oxygen demand: supply ratio.

Enthusiasm for new modes of therapy have waxed and waned. We have witnessed alternating enthusiasm for cerebral vasodilators, cerebral vasoconstrictors, cerebral metabolic depressants, free radical scavengers, membrane stabilizers, calcium blockers, drugs that improve blood rheology, and drugs that are reported simply to improve cerebral function in a “black box” fashion.

Part of the apparent conflicts in the literature may result from great variety in the models used to test pharmacological brain protection. To clarify some of the confusion it is important to differentiate between species, pre- and post-treatment and the main categories of cerebral hypoxia (table I).

<table>
<thead>
<tr>
<th>TABLE I. Categories of cerebral hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cerebral hypoxia</td>
</tr>
<tr>
<td>hypoxaemia</td>
</tr>
<tr>
<td>incomplete ischaemia</td>
</tr>
<tr>
<td>Regional cerebral hypoxia</td>
</tr>
<tr>
<td>incomplete ischaemia</td>
</tr>
<tr>
<td>Global cerebral anoxia</td>
</tr>
<tr>
<td>complete ischaemia</td>
</tr>
</tbody>
</table>

In global cerebral hypoxia, “global” pertains to the whole brain. This may result from hypoxaemia or incomplete ischaemia such as occurs with arterial hypotension or increased intracranial pressure. The second category comprises regional cerebral ischaemia, which always appears to be incomplete with some collateral circulation remaining.

The third category is cerebral anoxia or complete cerebral ischaemia, such as occurs following cardiac arrest.

The pathophysiology of these different types of hypoxia may vary greatly and thus a drug cannot necessarily be expected to have the same protective effect in all categories. As an example, some of the anaesthetic agents apparently reduce cerebral oxygen consumption (CMRO2) by reducing electrical activity of the brain as witnessed on the EEG (Michenfelder, 1974; Newberg, Milde and Michenfelder, 1983). This mechanism can therefore be expected to be protective only when there is electrical activity present that may be reduced. This would not be the case during complete cerebral ischaemia where the EEG becomes isoelectric within seconds (Steen, Milde and Michenfelder, 1978). However, this does not preclude a protective effect by some other mechanism.

Similarly, a drug that works by reducing increased intracranial pressure (ICP) can obviously act only in models where ICP is increased and in many types of ischaemia the magnitude and importance of oedema/ICP is still unclear (e.g. in global, complete ischaemia). A drug which vasoconstricts in normal parts of brain should shunt blood from normal to ischaemic parts (reverse steal or Robin Hood phenomenon) and this may occur in regional ischaemia such as stroke, but not in situations where the whole brain is hypoxic.

If the possible mechanism of action of different drugs is correlated with the types of hypoxia in this way, some of the apparent conflicts in the literature may become explicable. Other factors, including age, temperature, haematocrit and blood-sugar con-
centration should also be considered; not all studies are well-controlled in these respects.

A growing problem in studying literature in brain hypoxia is the vast number of books and journal supplements comprising manuscripts from a great number of symposia. Some of these secondary papers are good reviews of current literature, but many present results from investigations that have not passed peer review as original articles in a journal. One should be as careful in using these results and conclusions as in accepting abstracts as references. Many may prove valid, while others may not. One should also distinguish between reports from a drug manufacturer and from independent laboratories. Confirmation of results reported by the former should be required.

To guide the readers, in the reference list following this article, manuscripts from symposia are marked *, reports from the manufacturers †.

In this review, we discuss some drugs according to the classification and order noted in table II.

**TABLE II. Drugs which have been used in cerebral ischaemia**

1. Calcium entry blockers
2. Anticonvulsants and drugs depressing cerebral metabolism:
   - Barbiturates
   - Etomidate
   - Midazolam
   - Althesin
   - Gammahydroxybutyrate
   - Isoflurane
   - Phenytoin
3. Drugs promoting microcirculation post-ischaemia:
   - Vasopressors
   - Heparin, Streptokinase
   - Dextran 40, Fluosol DA
4. Prostaglandins and drugs affecting prostaglandin synthesis:
   - Prostacyclin (PGI-2)
   - Indomethacin
5. Free radical scavengers
6. Miscellaneous drugs:
   - Corticosteroids
   - Naloxone
   - Dimethyl sulphoxide (DMSO)
   - Piracetam

**CALCIUM ENTRY BLOCKERS**

Disturbed Ca\(^{2+}\) homeostasis resulting in increased intracellular Ca\(^{2+}\) concentrations has been incriminated during the past few years as a major trigger of tissue damage occurring during hypoxia (Siesjö, 1981; Raichle, 1983; White et al., 1983a) (see also Meldrum (1985)). Thus, the calcium entry blockers are currently being investigated for their potential protective effects against hypoxic damage.

Interest was originally focused on cardiac use. The first drug reported to have a calcium entry blocking effect, verapamil (Fleckenstein, 1964), has been used for treating cardiac arrhythmia for more than a decade, and there are now extensive reports that the calcium entry blockers can protect the myocardium against hypoxic damage (Braunwald, 1982; Landmark and Refsum, 1983). In the heart, these drugs have many effects—improving coronary blood flow and reducing the myocardial oxygen demand both by reducing afterload and by a negative inotropic effect (Landmark and Refsum, 1983). In addition, these drugs may have a direct protective effect on cells (Braunwald, 1982).

A reduction in oxygen consumption does not seem to occur in brain (Harper, Craigen and Kazda, 1981), although the other actions may be important. Cerebral hypoxia thus reduces extracellular calcium in brain (Nicholson, 1980; Harris et al., 1981), presumably by cellular uptake. CBF may then be reduced by:

1. **Cerebral vasoconstriction** from an increased calcium concentration in vascular smooth muscle (Somlyo and Somlyo, 1968; Van Neuten and Vanhoutte, 1980; Vanhoutte, 1981).
2. **Disturbed blood rheology.** Blood viscosity may increase by decreased deformability of red blood cells secondary to accumulation of calcium in the cell membrane (De Cree et al., 1979), and calcium may have an effect on platelet aggregation (Vanhoutte and Van Neuten, 1980).

It also appears that increase in the free cytosolic calcium in brain cells activates many catabolic reactions with breakdown of proteins and phospholipids (Schlaepfer and Bunge, 1977; Schneute et al., 1979; Farber, Chien and Mittnacht, 1981). The latter causes release of free fatty acids, including arachidonic acid with production of eicosanoids such as prostaglandins and thromboxanes, factors that may induce further tissue damage by further vasoconstriction, platelet aggregation etc., depending on the “balance” between the various substances (reviews Farber, Chien and Mittnacht, 1981; Siesjö, 1981; Raichle, 1983).

Large concentrations of calcium may also uncouple mitochondrial oxidative phosphorylation during hypoxia so that the oxygen supplied is used for pumping calcium into the mitochondria directly instead of being used for ATP production (Siesjö, 1981).
There is now a rapidly growing family of drugs that may block these effects, at least in vitro. They include verapamil, D-600, diltiazem, nifedipine, nicardipine, nimodipine, prenylamine, terodiline, fendiline, perhexiline, caroverine, flunarizine, cinnarizine and lidoflazine. In contrast to cations such as manganese, cobalt and lanthanum which are non-selective competitive Ca\(^{2+}\) antagonists, these drugs act in nanomolar concentrations and exhibit stereospecificity, indicating a tight binding to specific structures (Braunwald, 1982). On the other hand, the diversity of molecular structure of these blockers indicates potentially different modes and sites of action.

Two types of study with calcium entry blockers may be distinguished. Some are concerned with one of the possible mechanisms for hypoxic damage such as vasoconstriction (spasm) or disturbed mitochondrial function, and thereby examine only some element(s) of the hypoxic situation. Others are concerned with the whole clinical entity of cerebral hypoxia and examine the eventual outcome.

In the first category are studies reporting dilatation of cerebral vessels, and this appears to be more effective than for other peripheral vessels as described for verapamil, diltiazem and nifedipine (Allen and Banghart, 1979; Shimizu, Ohta and Toda, 1980), nicardipine (Yamamoto, Otha and Toda, 1983) and nimodipine (Toward et al., 1982) after constriction caused by a variety of agents such as prostaglandins, serotonin, histamine, thromboxanes and blood constituents in vitro. There are indications that this tissue specificity may result from cerebrovascular muscle tone being more dependent on entry of extracellular calcium than on tone in other peripheral vessels (Allen and Banghart, 1979). Perhexiline, diltiazem and nifedipine failed to influence CBF in normal rats (Edvinsson et al., 1983). It is hypothesized that these calcium entry blockers do not affect normal cerebral vasculature protected by an intact blood–brain barrier.

It is thus of interest to note that, although nimodipine in vitro has been reported to dilate human pial arteries (Auer, Oberbauer and Schalk, 1983) and increase non-ischaemic CBF in dogs (Kazda et al., 1982a), the effect in primates was significantly greater if the blood–brain barrier was disrupted osmotically before drug infusion (Harper, Craig and Kazda, 1981). An increase in CBF for open- but not closed-skull primates was found by Harris and others (1982).

Calcium-induced stiffness of the red blood cells (RBC) may possibly be reduced by flunarizine and cinnarizine (De Crec et al., 1979; Van Neuten and Vanhoutte, 1980). Parker (1981) found no effect with verapamil and claims that the role of calcium in RBC deformability in hypoxia in vitro is not clear. We have previously studied pentoxifyllin (Steen, Milde and Michenfelder, 1982), a diesterase inhibitor supposed specifically to improve RBC deformability in hypoxia (Ehrly, 1978), and found no effect on CBF during MCA occlusion in cats.

There might be increased platelet aggregation in the brain during hypoxia (Aragno and Doni, 1976; Hossmann, Hossmann and Takagi, 1980). The importance of this or the modulating effects of calcium entry blockers is not clearly established, but a reduction in platelet aggregation factor release from human leucocytes has been described for nifedipine (Jouvin-Marche et al., 1983).

A protective effect of the calcium entry blockers directly on brain cells has not yet been established. Harris and others (1981) reported a decrease in extracellular Ca\(^{2+}\) with nimodipine compared with placebo during MCA occlusion in cats, indicating an increased cellular uptake (see below).

Whilst these effects may be important, the main question for the clinician is: how do calcium blockers affect the clinical outcome after cerebral hypoxia?

There are many reports of improved outcome in rodents exposed to a variety of insults (Hoffmeister et al., 1982; Karasawa et al., 1982; Kazda et al., 1982b; Van Reempts et al., 1983; Wauquier et al., 1983), but as most of the models are not clinically relevant and the studies are performed mostly in the manufacturers' laboratories, they serve only as screening investigations.

One study which may be clinically relevant was undertaken with MCA occlusion in rats (Mohamed et al., 1983), in which nimodipine significantly improved CBF in the ipsilateral auditory and parietal cortex with no effects on other parts of the brain. This indicated improvement in the periphery of a focal ischaemic lesion (the penumbra) with no adverse steal effect on the central core of ischaemia (frontal cortex, caudate nucleus).

To our knowledge there are no reports yet on the effect of calcium entry blockers in global cerebral hypoxia in larger animals, although in regional cerebral ischaemia there are several reports on cerebral blood flow, rather than outcome.

Nimodipine increased CBF by curtailing autoregulation during hypertension in primates.
both before and after cerebral arterial spasm had been induced by successive injections of blood to the basal cistern (Svendgaard et al., 1983). As CBF was measured by a xenon-133 technique, it cannot be concluded that nimodipine necessarily affected spasm. A "look-through" phenomenon may occur where the counter recording CBF in an area affected by spasm picks up an increase in CBF in a non-ischaemic area behind (Hanson, Anderson and Sundt, 1975). Nifedipine was found (by angiography) to reverse cerebral arterial spasm produced in dogs by blood injected to the cisterna 48 h apart (Allen and Bahr, 1979). Varsos and colleagues (1983) failed to confirm this.

In a prospective, double-blind, randomized study Allen and others (1983) reported fewer neurological deficits produced by vasospasm (verified on angiograms) with nimodipine than with placebo in patients with intracranial aneurysms. Fifty-six patients were treated with oral nimodipine for 21 days, commencing within 96 h of subarachnoid haemorrhage, compared with 60 placebo-treated controls. After 21 days, death or severe neurological deficit from arterial spasm occurred in significantly fewer of the nimodipine- than the placebo-treated patients: one of 56 compared with eight of 60. If all deficits attributed to spasm were included, including mild to moderate degrees (four nimodipine v. two placebo-treated), the difference was not significant. There was, furthermore, no difference in the degree of spasm for patients with normal outcome.

Even in this multicentre study, the total number of patients with deficits attributed to spasm is small, and a recent editorial (Editorial, 1983) suggested that the data presented did not justify the assertion that the clinical efficacy was a result of inhibition of spasm. On the other hand, CAT scans indicated that a larger amount of subarachnoid blood before start of treatment was associated with a worse outcome in the placebo group, but not in the nimodipine group (Allen et al., 1983) and this would link the effect to reduction in spasm, as there appears to be a close relationship between subarachnoid blood and spasm.

In an uncontrolled study (Auer et al., 1982) of 17 patients operated for ruptured aneurysm 48–72 h after subarachnoid haemorrhage, topically applied nimodipine produced vasodilatation. After operation, topical application through a cannula placed during the operation was reported to reverse spasm in one of two patients and cause vasodilatation in five of seven patients without spasm.

We conclude that the calcium entry blockers, at least nimodipine, seem to be promising therapeutic agents in regional ischaemia from spasm, but more studies are required to confirm the original reports.

The efficacy of calcium entry blockers in other focal ischaemic events is less well established. Verapamil had no effect on ischaemic CBF, blood-brain barrier breakdown or other pathological changes during MCA occlusion in cats (Reedy et al., 1983). On the other hand, nimodipine increased ischaemic CBF during MCA occlusion in primates (Harris et al., 1982), but at the same time nimodipine-treated monkeys required higher CBF values to avoid the development of cortical oedema and a disturbed ion homeostasis than did control monkeys. Although nimodipine greatly improved ischaemic blood flow, this effect obviated other deleterious effects of the drug. Topical application of nimodipine also produced vasodilatation of cortical arterioles contracted after MCA occlusion in cats (Harris et al., 1982; Brandt et al., 1983; Reedy et al., 1983), but none of these studies reported on the eventual outcome of the animals.

Nemoto and others (1983) and Kaneko and colleagues (1983) have reported reductions in increased ICP with nifedipine or D-600 after a cortical freeze injury in cats. Reduction of oedema and ICP may be related to a more rapid recovery of cellular function. For D-600 (Kaneko et al., 1983) there was no difference in oedema formation or blood–brain barrier breakdown, and, as the calcium entry blockers should not reduce ICP by vasoconstriction, these results lack adequate explanation. However, they do fit with a report on cortical freeze injury in rats. Heller and others (1983) found an increase in local CBF in the area 24 h after injury and nimodipine did indeed decrease this high CBF.

When flow has been re-established after a period of complete cerebral ischaemia, a transient 5–15 min period of increased CBF is followed usually by a period of prolonged hypoperfusion with CBF down to 20–30% of control despite normal arterial pressure (Hossmann, Lechtape-Griiter and Hossmann, 1973; Steen et al., 1983a) It has been suggested that the magnitude of the neurological damage results in part from this delayed hypoperfusion (Siesjo, 1978; White et al., 1983a) and that increased calcium concentrations intracellularly might be responsible for this (Kazda et al., 1982a; White et al., 1983a). The effect of calcium blockers on this hypoperfusion has therefore been examined.

Flunarizine (White et al., 1982), lidoflazine, ver-
Apamil and magnesium sulphate (White et al., 1983b) appeared to abolish hypoperfusion in dogs when given after 20 min of complete cerebral ischaemia obtained by ventricular fibrillation with reflow established by cardiopulmonary bypass. Some uncertainty applies to these results as the control CBF values (mean 200–250 ml min⁻¹/100 mg) were two to three times that reported normally for dogs and validation of their thermal method used for CBF measurements is, to our knowledge, not yet published. In other studies flunarizine (Newberg et al., 1984) and lidoflazine (Dean et al., 1983) failed to influence the hypoperfusion period in dogs.

Nimodipine improved CBF in the hypoperfusion period in cats (Kazda et al., 1982a) and in dogs, both when treatment was commenced before (Steen et al., 1983a) and after ischaemia (Steen, Newberg et al., 1984). None of these studies reported on regional distribution of CBF however, and Smith and colleagues (1983) found that, although global CBF post-ischaemia was improved by nimodipine, there were great regional differences in rat brains, with a picture much like that obtained by hypercapnia in the same model. Smith and colleagues (1983) studied return of blood flow after 15 min of severe incomplete ischaemia and, although unlikely, a difference from the delayed hypoperfusion after complete ischaemia cannot be excluded. Whatever are the effects on CBF, neurological outcome is again the important issue.

In a controlled blind study (Winegar et al., 1983) lidoflazine was given as part of the resuscitation after 15 min of cardiac arrest obtained by potassium injection in dogs. This study indicated that lidoflazine might improve the neurological recovery in that all five treated dogs had spontaneous ventilation, reactive pupils, voluntary movements and response to tactile stimuli 12 h after resuscitation, while four of five control dogs had maximum neurological deficit scores. Lidoflazine also appeared to improve the outcome when given after 10 min ventricular fibrillation in dogs, but not after 7 or 10 min of asphyxial cardiac arrest (Vaagenes et al., 1983).

Flunarizine did not improve the outcome in dogs 48 h after ischaemia when it was given after 10 min of complete cerebral ischaemia obtained by cross-clamping the aorta (Newberg et al., 1984). In contrast, nimodipine commenced before ischaemia significantly improved the outcome 48 h after ischaemia (Steen et al., 1983a). When nimodipine was commenced after ischaemia, the neurological outcome was intermediate, not significantly different from either control or pretreated dogs (Steen, Newberg et al., 1984).

In a recent, controlled, blind primate study from Michenfelder's laboratory (Steen, Gisvold et al., 1984) nimodipine treatment was commenced 5 min after 17 min of complete cerebral ischaemia obtained by a neck-cuff inflated to 1500 mm Hg combined with arterial hypotension to 50 mm Hg. Com- pleteness of ischaemia was confirmed by a xenon-133 technique. The monkeys were given intensive care for 96 h, followed by neurological and pathological evaluation, and nimodipine significantly improved the outcome.

Thus, both lidoflazine and nimodipine may improve the outcome in models of complete cerebral ischaemia such as occurs with cardiac arrest. No human studies have been reported yet, but an international multicentre study is currently being launched.

Finally, there is one group of double-blind studies reporting on the effects of flunarizine on chronic cerebral dysfunction in geriatric patients (Staessen, 1977; Lehrl, Sollberg and Schumacher, 1978; Nelson et al., 1978; Zissis, Alevisas and Dontas, 1981). The criteria for patient selection are not well described in any of the studies, and in one (Nelson et al., 1978), more than 100 doctors were involved in the trial. All studies reported improvements in some cerebral function or symptom, compared with placebo, but often not the same effect and there was usually also a significant placebo effect.

There is no good explanation to account for improvement in the patients. It may be hypothesized that, in these brains with diffuse cerebrovascular disease, the drugs improved blood supply to parts which normally receive sufficient only to survive, but not enough for normal function. The existence of such areas has never been established, and with the great placebo-effects reported also in these studies, results should be interpreted with great caution.

We conclude that, at present, calcium entry blockers seem promising for treatment of patients with regional cerebral ischaemia, at least when this results from vasospasm such as in subarachnoid haemorrhage, and in treatment of patients with complete cerebral ischaemia such as occurs in cardiac arrest. In the former category, more human studies are needed, whilst in the latter, no human reports are available yet.

**Anticonvulsants and Drugs Depressing Cerebral Metabolism**

Various agents which depress cerebral metabolism...
have been investigated to examine the hypothesis that, in situations with limited oxygen supply, depression of cerebral oxygen demand may produce improved balance between oxygen supply and demand, thereby preventing detrimental metabolic effects.

Of these drugs, the most extensively investigated are the barbiturates, which are considered separately in this issue (Shapiro, 1985). Other drugs include etomidate, gammahydroxybutyric acid, Althesin, midazolam and isoflurane.

The most effective procedure for metabolic inhibition is probably hypothermia, which may enable the brain to tolerate prolonged periods of circulatory arrest. It is worth mentioning that the mechanism by which hypothermia depresses metabolism is probably different from that by drugs. Hypothermia appears to cause general depression of cerebral metabolism, whereas the barbiturates (and possibly also other drugs) depress only that part of metabolism related to active electric function (Michenfelder, 1974). Thus, barbiturates have no apparent metabolic effects when the EEG is isoelectric (Steen et al., 1983b). If this hypothesis is correct, hypothermia should be superior to drug-induced depression of cerebral metabolism in maintaining cellular viability during periods of limited oxygen supply. This appears to occur during short hypoxic episodes, while long-term hypothermia (48 h) has been reported to cause circulatory disturbances (Steen, Soule and Michenfelder, 1979).

**Etomidate**

Etomidate is a short-acting hypnotic with greater cardiovascular stability than barbiturates. It is a potent depressant of CMRO$_2$, possesses anticonvulsant properties, is a cerebral vasoconstrictor and can thus reduce an increased intracranial pressure both in animals and man (Moss et al., 1979; Wauquier, 1983). Etomidate has been investigated extensively in rodents with various brain ischaemic insults (Wauquier, 1983). As with the calcium entry blockers, the studies are mostly reported by drug manufacturers, are not directly clinically relevant and lack long-term evaluation of neurological function. Therefore they serve only as screening investigations.

To our knowledge, no well controlled studies have been performed evaluating the long-term neurological effects of etomidate.

**Midazolam maleate**

Midazolam is a water soluble benzodiazepine reported to have a shorter duration of action than diazepam, and with little action on the cardiovascular system. Midazolam greatly reduces CMRO$_2$ in dogs without severe haemodynamic depression (Nugent, Artru and Michenfelder, 1982).

We are unaware of any study of clinically relevant regional or global ischaemia with long-term neurological evaluation.

**Althesin**

Althesin is a rapidly acting, rapidly excreted i.v. agent, with anticonvulsant properties, which decreases CMRO$_2$ and CBF (Sari et al., 1978) and can thus also decrease increased intracranial pressure (Turner et al., 1973). It is therefore possible that this agent may be evaluated for brain protective effects.

**Gammahydroxybutyrate (GHB)**

Gammahydroxybutyrate is a naturally occurring inhibitory neurotransmitter and may be administered as gammabutyrolactone (GBL), which is hydrolysed by a lactonase present in blood and liver but not in brain. GBL can reduce the rate of glucose utilization in the rat brain to the same extent as the barbiturates (Wolfson, Sakurada and Sokoloff, 1977), but GBL/GBH offered only modest prolongation of survival in hypoxaemic mice, in spite of the fact that it has a strong depressant effect on CMRO$_2$ (Artru, Steen and Michenfelder, 1980). A possible limiting factor is that CBF seems to be reduced more than CMRO$_2$, and since there also is a reduction in cardiac output, this may create an unfavourable imbalance between oxygen supply and demand in the brain. In contrast, GBL significantly reduced neuronal tissue loss during experimental forebrain ischaemia in the awake rat (Lavynne et al., 1983). Furthermore, low dose GBL prevented both the early hyperaemia usually seen in non-treated controls during reperfusion after ischaemia, and the prolonged delayed post-ischaemic hypoperfusion (Lavynne et al., 1983).

A protective effect may be explicable if GBL directly inhibits glucose utilization and thus possibly reduces the formation of lactic acid during hypoxia. The same authors claim that GHB may produce seizures in experimental animals, however, and they advocate caution in neurosurgical situations.

**Isoflurane**

Isoflurane possesses some properties not common to the other volatile anaesthetics. It may produce an
isoelectric EEG at concentrations that are
haemodynamically well tolerated (approximately 2
MAC) and CMRO₂ is reduced gradually with
increasing concentration, down to approximately
50% of control when the EEG becomes isoelectric,
with no further effects in higher concentrations
(Newberg, Milde and Michenfelder, 1983). This
differs from halothane, with which approximately
4.5% (5 MAC) is required to achieve an isoelectric
EEG, a concentration not tolerated haemodyna-
mically without cardiovascular support. Furthermore,
CMRO₂ continues to decrease with higher concen-
trations of halothane in the face of an isoelectric EEG.
More than 2% halothane causes disturbances in the
cerebral energy state and an increase in lactate con-
centration and lactate:pyruvate ratio, indicating a
toxic effect, possibly by interfering with oxidative
phosphorylation (Michenfelder and Theye, 1975).
Isoflurane has therefore an effect on cerebral
metabolism qualitatively different from that of
halothane, and it has been reported to improve the
cerebral energy state in dogs during incomplete
global ischaemia to the same degree as barbiturates
when compared with controls (Newberg and
Michenfelder, 1983).

Although it may appear that any agent depressing
cerebral metabolic rate is a potential cerebral protec-
tive agent, this is not so. Although reducing
CMRO₂, halothane is harmful in regional cerebral
ischaemia (Smith et al., 1974). This might result
from other potentially detrimental effects, including
vasodilatation, with halothane overriding a poten-
tially protective effect. Furthermore, as noted
above, the reduction in CMRO₂ with high concen-
trations of halothane appears to indicate a toxic effect
with disturbances in oxidative phosphorylation. In
addition, in rats there was no apparent protective
effect during severe incomplete ischaemia with
clormethiazole (Carlsson and Rehncrona, 1979), a
potent depressor of cerebral metabolism, or with a
combination of diazepam and nitrous oxide which
depressed CMRO₂ to the same degree as barbitu-
rates with less cardiovascular depression (Berntman
et al., 1979). In these instance, the absence of a pro-
tective effect may result from lack of metabolic
effects. As suggested above, if the ischaemia is
severe enough to render the EEG isoelectric, these
drugs probably have no effects on cerebral
metabolism.

Phenytoin

Phenytoin was reported to improve neurological
recovery and histopathology in global cerebral
ischaemia produced with a pneumatic cuff in rabbits
(Aldrete et al., 1979). In another study of post-
ischaemic treatment, phenytoin also improved his-
topathology in comparison with placebo. Thiopen-
tone produced intermediate results, not signific-
antly different from either placebo or phenytoin
(Cullen et al., 1979). These results should be inter-
preted with caution. Post-ischaemic care was not
described in either study, and in the latter, no
physiological variables or neurological outcome
were reported and both the cerebral cortex and brain-
stem were excluded from the histopathological
reports.

In an uncontrolled study (Aldrete et al., 1981)
with phenytoin given after cardiac arrest which
occurred during or after anaesthesia, nine of 10
patients recovered almost completely. Before treat-
ment, the patients were comatose with dilated, aref-
lexic pupils and abnormal posturing, As this was
only a small, uncontrolled study in a patient group
where a reasonably good result might be expected
since the insult occurred in hospital, further studies
are necessary before any conclusion may be drawn.
Phenytoin may protect the brain by various
mechanisms. It has been reported to slow the release
of potassium from ischaemic neurones, and this
release may be an indication of ischaemic brain dam-
age (Artru and Michenfelder, 1981). The effects of
phenytoin on cerebral metabolism and blood flow
are unclear. Brodie and Nelson (1968) reported that
phenytoin reduced the high energy phosphate and
methanol utilization rate by approximately 50% after
decapitation in mice, while Artru and Michenfelder
(1980) failed to find any effect on cerebral
metabolism in the dog in vivo. It is possible that the
anticonvulsant effect of phenytoin may contribute to
a possible protective effect.

DRUGS PROMOTING MICROCIRCULATION

A no-reflow phenomenon, where parts of the brain
cannot be reperfused after periods of complete cere-
bral ischaemia has received much attention (Ames,
Wright and Kowada, 1968). Although others have
failed to find this phenomenon after complete
ischaemia lasting even 10 min or more (Marshall et
al., 1975; Steen, Milde and Michenfelder, 1978),
there is a pronounced reduction in overall post-
ischaemic CBF despite adequate arterial pressure
(delayed hypoperfusion discussed above), and it is
possible that the blood flow pattern is uneven
whether caused by red cell sludging, platelet aggre-
gation, pericapillary oedema or vasospasm. Much
interest has therefore focused on promoting the microcirculation after periods of complete cerebral ischaemia (see the discussion on calcium entry blockers above).

A rapid normalization of arterial pressure after ischaemia should be attempted, since post-ischaemia hypotension has been shown to cause additional brain damage (Cantu, Ames and DiGiacinto, 1969) and a post-ischaemic period of hypertension has been reported to improve reperfusion inhomogeneity (Fischer and Ames, 1972; Nemoto et al., 1979). It is not clear if transient hypertension with vasopressors should be induced; clinically, this concept is supported only by anecdotal reports (Wise, Sutter and Buckholder, 1972). Several investigators have explored further use of viscosity-reducing measures in order to improve post-ischaemic rheology. Heparin combined with hypertension and haemodilution given after cardiac arrest in dogs apparently improved outcome (Safar, Stezoski and Nemoto, 1976), as did heparin alone given immediately before or shortly after global cerebral ischaemia in cats (Stullken and Sokoll, 1976). In a model of multi-focal cerebral ischaemia in dogs, Hallenbeck and others (1982) found that prostacyclin and indomethacin improved neurological function after multifocal ischaemia in dogs, but only when combined with heparin. The combination of indomethacin and heparin given before ischaemia, or prostacyclin, indomethacin and heparin given after ischaemia also increased post-ischaemic CBF after complete cerebral ischaemia produced by spinal fluid compression in dogs (Hallenbeck and Furlow, 1979). Finally, streptokinase in combination with dextran 40 produced a more rapid return of EEG activity and higher cortical CBF after cardiac arrest in dogs than those receiving placebo or dextran 40 alone (Lin et al., 1978). Unfortunately, neurological outcome was not studied.

Recently, haemodilution using the oxygen-carrier fluosol DA has been reported to reduce infarct size and improve neurological outcome in a model of focal ischaemia (Peerless et al., 1981). Takagi and colleagues (1983) found that fluosol DA improved outcome after 30 min of severe, global ischaemia in rats when judged by restoration of EEG and histology. Sutherland and Farrar (1983) found that treatment with fluosol DA increased oxygen availability in the brain after ischaemia.

It should be noted that, although possible, there is no definite evidence that the hypoperfusion occurring after complete cerebral ischaemia is harmful to the brain, except in the case of a true no-reflow phenomenon. Attempting to improve the collateral circulation during regional ischaemia may be a more established indication for promoting the microcirculation.

PROSTAGLANDINS AND DRUGS AFFECTING PROSTAGLANDIN SYNTHESIS

The normal biosynthesis of prostaglandins, thromboxanes and leukotriens may be affected during and after ischaemia. These products are metabolites of arachidonic acid, and oxygen is necessary for normal synthesis. The enzyme cyclo-oxygenase catalyses the formation of prostaglandin intermediate PGG-2 from arachidonic acid in a reaction requiring oxygen. Once formed, PGG-2 is converted to other prostaglandins, of which some are vasoconstrictors while others vasodilate. It is interesting to note that active oxygen species (free radicals) are generated as normal byproducts. Prostacyclin (PGI-2) is a potent vasodilator which also prevents platelet aggregation.

Thromboxane (primarily thromboxane $A_2$) synthesis is also dependent on the enzyme cyclooxygenase. Thromboxane $A_2$ has an effect opposite to that of prostacyclin; it promotes platelet aggregation and vasoconstriction. Normally, a delicate balance exists between these two systems (for excellent reviews, see Raichle, 1983 and Siesjo, 1981).

The synthesis of both substances is reduced after pretreatment with indomethacin which is a cyclooxygenase inhibitor. Gaudet and Levine (1979) found that treatment with indomethacin before bilateral carotid occlusion not only inhibited the increase in prostacyclin and thromboxane, but the treated gerbils recovered more rapidly and were more active than controls.

The effects of prostacyclin (PGI-2) and indomethacin on post-ischaemic circulation and recovery have been studied in various types of ischaemia. As reported above, Hallenbeck and colleagues (1982) found that a combination of prostacyclin, indomethacin and heparin improved neurological function after multifocal ischaemia in dogs. In another study, pretreatment with indomethacin increased CBF after global ischaemia in rabbits and focal ischaemia in cats, but failed to influence the return of EEG activity (Boulu et al., 1982). Again, long-term neurological outcome or pathology was unfortunately not reported. In an interesting study in heparinized rabbits subjected to 20 min of complete cerebral ischaemia, a (synthetic
polymeric prostaglandin given after ischaemia improved the neurological outcome when evaluated 24, 48 and 60 h after ischaemia (Kolata and Polis, 1980). At 24 h, seven of 10 recovered compared with three of 10 in the placebo-treated group. Recovery was strikingly rapid in the treated animals—very different from the controls. The mechanisms of action are not established, and CBF was not measured.

Pickard (1981) found that CBF was reduced by indomethacin under normal conditions, but increased during post-ischaemic recirculation. Thus it appears that, contrary to normal conditions, thromboxane synthesis is inhibited more strongly by indomethacin post-ischaemia than prostacyclin synthesis, thereby favouring prostacyclin.

Treatment with prostacyclin has been utilized also in patients with stroke (Gryglewski et al., 1983). The patients were treated with prostacyclin between 1 and 5 days after hospital admission and all had dramatic improvement in neurological function. As there was no control group, no clear conclusions can be drawn.

FREE RADICAL SCAVENGERS

It is still not clear which components of the complex post-ischaemic pathophysiology are the most important in causing neuronal destruction and death. The importance of calcium ions in addition to prostaglandins and other metabolites of arachidonic acid have been discussed above. Another possibly important component is an increased concentration of free radicals during or after ischaemia (Siesjo, 1981; Raichle, 1983).

A free radical is defined as any atom, group or molecule with one unpaired electron occupying an outer orbital. This implies a high energy state and thus renders the free radical highly reactive. They have the capacity to initiate destructive reactions in biological membranes and other cellular structures, and may be of central importance in causing further damage during or after ischaemia (Demopoulos, Flamm and Pietronigro, 1980). Hence, it has been suggested that treatment with so-called free radical scavengers (thiopentone, vitamin E, mannitol, DMSO, vitamin C and many other substances) may reduce or prevent further damage during this period. To our knowledge, there are no controlled experimental data on cerebral ischaemia (focal or global) indicating a therapeutic effect of free radical scavengers. It is interesting, however, that current research is focused on calcium, prostaglandin synthesis and free radicals. These represent different approaches to the same problem (free oxygen radicals are normal by-products of prostaglandin synthesis), and it is possible that the calcium ion holds a key position in this chain of reactions.

MISCELLANEOUS DRUGS

Corticosteroids

The value of corticosteroids is controversial in ischaemic cerebral insults and brain trauma. Most interest has focused on the effect on oedema formation and the reader is referred to the article by Klatzo (1985) in the present Symposium. Recent investigations in large series of patients seem to indicate that there is no difference in outcome between steroid-treated and other patients with severe head injury (Cooper et al., 1979). However, the evidence is controversial with respect to focal ischaemia. Prophylactic steroid therapy was found to decrease oedema and improve regional cerebral blood flow after middle cerebral artery occlusion in cats (Bartko et al., 1972); Others have failed to confirm this when dexamethasone was given after onset of ischaemia in cats (De la Torre and Surgeon, 1976) and either before or after onset of ischaemia in primates (Lee et al., 1974).

Fishman (1982) stated in a review article that there is no proof of beneficial effects of steroids on oedema associated with hypoxia (or ischaemia) or in head injury. However, he speculated that they may have a beneficial effect by inhibiting the release of arachidonic acid from cell membranes.

There are studies indicating that steroids may stabilize lysosome membranes, prevent release of lytic enzymes and stabilize mitochondria and capillary walls. White, Hoehner and Wilson (1980) suggested that dexamethasone may improve ATP synthesis and partly protect the mitochondria from uncoupling. Marcy, O'Connor and Welsh (1981) demonstrated improved recovery of ATP synthesis with dexamethasone treatment when recirculation was re-established after 30 min of bilateral carotid artery occlusion in cats.

Naloxone

Several reports indicate that the opioid antagonist naloxone can improve neurological function in various types of cerebral insult. In two patients with focal cerebral ischaemia, naloxone completely reversed the neurological deficits, while morphine re-induced the hemiparesis in one (Baskin and Hosobushi, 1981). In gerbils with occlusion of one
carotid artery, the level of immunoreactive beta-endorphin-like material was 40–80% higher in the ischaemic hemisphere than on the control side, and repeated administration of naloxone consistently reversed all neurological deficits. As the deficits tended to revert after 20–30 min, they implanted 10-mg pellets of naloxone subcutaneously, and this produced a sustained reversal of the neurological deficit (Hosobushi, Baskin and Woo, 1982). These studies suggest that endorphins may be involved in this type of ischaemia. However, there are also negative reports on the use of naloxone in focal ischaemia. Shigeno and others (1983) found no effect of naloxone on local cerebral glucose utilization when given after MCA-occlusion in rats, and Cap de Ville and colleagues (1983) found no effect on neurological function when it was given during or 60 min after 30 min of severe global ischaemia in rats (four vessel ischaemia).

We are not aware of any studies of naloxone in complete global ischaemia such as occurs in cardiac arrest.

**Dimethyl sulphoxide (DMSO)**

DMSO is a water soluble organic solvent used industrially since the 1940s. There are a substantial number of possible beneficial effects of DMSO. It has diuretic actions and has therefore been used in control of ICP after failure of other osmotic agents and barbiturates (Waller et al., 1979). It is a free radical scavenger, may improve post-ischaemic blood flow by vasodilatation, and rheology by an anticoagulant effect and reduced platelet adhesiveness and aggregation (Kligman, 1965). In MCA occlusion in Rhesus monkeys, DMSO significantly reduced the neurological deficits after ischaemia (De la Torre and Surgeon, 1976). In this study, DMSO had a strong diuretic effect, and caused a reduction in brain swelling after ischaemia. The latter was found also with dexamethasone treatment, but this did not affect the clinical outcome. De la Torre and Surgeon speculated that the most important effects of DMSO may be those on blood rheology, but so far a protective effect of DMSO has not been firmly established.

**Piracetam**

Piracetam was first reported to have possible protective effects in hypoxia by Giurgea, Mouraviev-Le-Suisse and Leemans in 1970. Richardson and Bereen (1977) reported a beneficial effect compared with placebo on the level of consciousness after neurosurgery, in a study including 106 patients with various intracranial lesions. The authors noted that piracetam is a cyclic derivative of gamma-aminobutyric acid, which is a neurotransmitter, and that the effect of piracetam may be linked to this effect. We are not aware of any published studies on piracetam in experimental focal or global brain ischaemia.

**CONCLUSION**

Many drugs have been suggested to protect the brain against hypoxic damage. Despite the huge investment of resources in this field, no accepted drug therapy has yet emerged. The only undisputed therapeutic principle is to improve the oxygen demand:supply ratio. A reduction in oxygen demand may be accomplished with drugs in some instances; an improvement in blood flow and oxygen supply has been suggested with others, but no controlled human studies with unequivocal results have emerged so far. When we have achieved greater understanding of the mechanisms of hypoxic damage, it will be possible to explore systematically potentially protective drugs, and we may then expect to make more rapid progress in this field.

**REFERENCES**

*Manuscripts or abstracts from symposia/other meetings; † reports from manufacturers.*


---


---


Hoffmeister, F., Benz, V., Heise, A., Krause, H. P., and...


Reedy, D. P., Little, J. R., Caprono, J. A., Slugg, R. M., and


— Winegar, C. D., Wilson, R. F., Hoechner, P. J., and Trombley, J. H. jr (1983a). Possible role of calcium blockers in...