Perioperative Stroke Prevention

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The definitions of commonly used terms are given in Table 1 (1–8). Stroke has been simply defined as any form of cerebral infarction (2), which includes those attributable to hemorrhage. The latter group is more likely to occur as a complication of specific surgical procedures (e.g., carotid endarterectomy) or the use of anticoagulants and is otherwise rare in the perioperative period (3). Hence, much of the information in this review pertains to ischemic cerebral events.

Incidence and Significance

In the general population, stroke is a significant cause of morbidity and mortality. It is one of the commonest causes of death in most Western societies. The annual incidence is age-related, rising from 2.2 per 1000 population at 55 yr to 9.6–24.2 per 1000 between 75 and 84 yr (4). Eighty-five percent of these patients survive their first stroke (9), leaving an aging surgical population that may be at increased risk of anesthetic complications.

In the general surgical population, the reported incidence of perioperative stroke varies from 0.02 to 0.7% (2–4,9–14). The data for most of the reported series was collected retrospectively, so it is likely that the true incidence is higher. The majority of perioperative cerebral events occur in the postoperative period (12,13) with the average time for occurrence being 7 days after surgery (4). Intraoperative cerebrovascular accident (CVA) is a much rarer occurrence. For example, a large retrospective analysis found only one case of intraoperative stroke in nearly 40,000 ambulatory patients, one quarter of whom were ASA class III (14).

The mortality in these series is approximately 30% (2,9,10), but rises to over 60% if the patient has had a previous stroke (9). One-third of those patients who survive a stroke require assisted care for living. Thus, although perioperative stroke is an uncommon occurrence, it has a large impact on the patient and their family and community. Indeed, the annual cost associated with perioperative cerebral dysfunction and stroke has been estimated at $6 billion in the US.

Risk Factors

Table 2 gives the risk factors for stroke in the general population (9,15). It is assumed that the anesthetic population is subject to the same risk factors. As it is known that the risk of stroke in the surgical population is up to six times higher than normal, consideration must be given to risk factors in the surgical environment.

A recent study by Wong et al. (10) examined the possibility that anesthesia and surgery per se may be a risk for perioperative stroke. After adjusting for identified risk factors, patients who had a surgical procedure in the previous 30 days were more likely than controls to have a CVA (odds ratio 3.9). Even when high-risk surgery (cardiac, vascular, and neurological procedures) were excluded, the odds ratio was still significant at 2.9. Thus, the perioperative period itself predisposes patients to stroke.

The type of surgery is a major factor. Compared with the incidence of CVA in the general surgical population (<0.2%), the incidence is reported as 0.8%–3.0% in vascular surgical patients (9) and 4.8% in one study of head and neck surgery (16). The highest incidence follows cardiac bypass procedures, in which the incidence of major ischemic complications is approximately 3%–5% and up to 80% of patients suffer intellectual or cognitive dysfunction (17). The specific associations and management in this group will not be covered in this review but have been recently reviewed elsewhere (17).

A number of coexisting conditions may play an important role in identifying at-risk patients. Early reports demonstrated the significance of previous cerebrovascular events as a risk for perioperative stroke (18). Subsequent investigation has shown the incidence in this group to be 1.5%–2.9% (9). As noted above, the mortality of perioperative stroke is doubled in patients who have had a previous event. Small studies have shown a correlation between the occurrence of transient ischemic attacks (TIAs) and strokes in surgical patients. One report by Ropper et al. (19) recorded a 3.1% stroke rate among 32 patients with TIA or amaurosis fugax before their operation, and a further study by Carney et al. (20) noted that 2 of 12

Table 1. Definitions

Stroke	Defined by the World Health Organization as the "rapidly developing signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin"(1). It has been more simply defined as any form of cerebral infarction (2).
Transient Ischemic Attack (TIA)	A focal neurological deficit of sudden onset that resolves rapidly after a period lasting more than a few seconds but no longer than 24 hours (2,5).
Reversible Ischemic Neurological Deficit (RIND)	Neurological symptoms which last longer than 24 hours but which resolve within 72 hours (2).
Cerebrovascular Accident (CVA)	A term which encompasses all three of these conditions, but is commonly used as being equivalent to stroke.
Perioperative Stroke	One which occurs in the perioperative period, usually defined as intra-operative or within 3–30 days following surgery (4).
Cerebral Protection	Treatment which reduces the incidence or severity of cerebral ischemia which is initiated before, and often sustained throughout, the ischemic event (6–8).
Cerebral Resuscitation	Treatments commenced after the brain insult and which are given to restore brain function or limit secondary brain injury.
Focal Cerebral Ischemia	A local reduction in cerebral blood flow (CBF) below a threshold level which leads to localized abnormalities in brain metabolism and function.
Global Cerebral Ischemia	A fall in total CBF below a threshold level which leads to generalized abnormalities in brain metabolism and function. It may be complete, as in the case of cardiac arrest, or incomplete, as may occur following prolonged hypotension.

Table 2. Risk factors for stroke in the general population

Biological factors
Age
Male gender
Ethnicity
Heredity
Obesity
Atherogenic factors
Hypertension
Diabetes mellitus
Hyperlipidemia
Cardiovascular diseases
Valvular heart disease, especially mitral stenosis
Patent foramen ovale
Left atrial enlargement
Atrial fibrillation
Transient ischemic attacks
Previous CVA
Asymptomatic carotid stenosis (?)
Migraine
Thrombotic Risks
Polycythemia
Thrombocytosis
Increased fibrinogen
Decreased antithrombin III
Pregnancy
Oral contraceptives
Bedrest
Lifestyle factors
Smoking
Drug and alcohol abuse
Obesity
Physical inactivity
Diet
Acute stress

patients (17%) had TIA preoperatively. Conversely, Treiman et al. (21) did not find cerebral ischemic symptoms to be a risk factor. Arteriosclerosis has been noted to occur more commonly in patients who suffer perioperative stroke (12).

This should be contrasted with the poor correlation between perioperative CVA and asymptomatic carotid stenosis. The latter is known to occur in 15% of the surgical population over the age of 55 yr (3). Several studies have not found any difference in the incidence of stroke in this group (3,19–21).

Cardiac disease is associated with perioperative CVA. Atrial fibrillation is commonly found in the patients who suffer a perioperative stroke in common with the general stroke population, with most studies reporting its presence in one third of cases (12–14). Seventeen percent of cases followed acute myocardial infarction in one study (3). This emphasizes the importance of rigorous evaluation for the presence of cardiovascular disease at the time of preoperative assessment.

The age of the patient is an important determinate of the risk of neurological complications after anesthesia. A review of perioperative stroke demonstrated a six-fold increase in the incidence in patients over the age of 80 yr (9). This is in keeping with studies that show the frequency of cardiovascular complications to be age-related (22). Age remains a risk factor even when other disease states have been considered. This may reflect the reduction in cardiovascular reserve that occurs with advancing age.

Other factors that have been suggested as risks for cerebral ischemia include hypotension (9), dehydration (12), and the occurrence of a hypercoagulable state after surgery (see below). Emergency surgery may also be associated with an increased risk (12).

Pathophysiology

A cerebral ischemic event occurs when there is interruption to the cerebral blood flow. Most strokes that occur in the perioperative period are attributable to thrombotic or embolic events (3). Further, it has been shown that the majority of events occur in the postoperative period. This suggests that perioperative strokes are generally not caused by an intraoperative event, such as hypotension, as has been traditionally believed, although hypotension will certainly worsen an ischemic insult. Although prolonged and profound hypotensive episodes may indeed cause cerebral ischemia, postoperative processes are likely to be more important.

One important observation is the hypercoagulable state that occurs after surgery. It is evident after general, vascular, and cardiac procedures and has been demonstrated in patients undergoing general and regional anesthesia (23–25). Abnormalities are evident both in thromboelastographic patterns (23) and by measurable alterations in hematological parameters. Chief among these are an increase in fibrinogen and factor VIII and a decrease in antithrombin III and fibrinolytic activity (13). A reduction in red cell deformability that results in increased blood viscosity is also a factor. The notion of increased coagulation is supported by the high incidence of perioperative deep venous thromboses.

Other postoperative factors that may be important are extended bed rest, the presence of thrombogenic devices, and the possibility of patient dehydration, all of which may increase the chances of thrombotic events.

The brain relies on glucose as the main substrate for energy production. Efficient utilization of this energy source requires a constant supply of oxygen via the cerebral blood flow (CBF, normally 50–60 mL/100 g) as very little oxygen is stored in the brain. Normally, the high metabolic requirements (3–5 mL O_2/100g/min) are met by an oxygen delivery of 1.5–2 times the requirement.

When oxygen delivery fails to meet the metabolic requirement, a complex cascade of events takes place, the "ischemic cascade" (Fig. 1) (2,6,7). This will occur when the CBF decreases below the threshold level of approximately 10 mL/100g/min. As cellular energy levels decrease, ATP depletion leads to a failure of the Na-K ATPase ion pump allowing massive efflux of potassium and influx of sodium. This depolarizes the cell membrane and an influx of calcium occurs. The increase in free intracellular calcium is a pivotal event in neuronal injury. It activates membrane phospholipases leading to the breakdown of phospholipids to free fatty acids. The high calcium concentration causes proteolysis and dysfunction of cellular organelles and this is responsible for the cellular dysfunction and abnormal membrane permeability that results in cellular necrosis. Release of excitatory amino acids, such as glutamate, which follows membrane depolarization may be a key step in the influx of calcium via ligand-regulated calcium channels (NMDA receptors). In addition, anaerobic metabolism of glucose to lactate causes intracellular acidosis, which compounds enzymatic dysfunction.

During ischemia, cyclooxygenase and lipoxygenase activities are low, leading to the accumulation of arachidonic acid produced from free fatty acids. However, if some oxygen is available, prostaglandins may be formed in excess including thromboxane A_2, which produces vasoconstriction and platelet aggregation, thus worsening local blood flow. In addition, toxic oxygen free radicals are produced (7). These mechanisms may occur predominately during reperfusion.

Edema results from two processes (2). In animal models, the early edema is predominately intracellular and is thought to be caused by the influx of sodium that occurs with failure of the ion pumps. This is cytotoxic edema. With ongoing ischemia, the integrity of the blood-brain barrier is eventually compromised, and there is a massive influx of blood constituents including proteins, ions, and fluid, resulting in vasogenic edema. Edema formation decreases the local cerebral perfusion pressure and may extend the area of ischemic damage to adjacent areas of the brain, the so-called "ischemic penumbra." In this area, relative ischemia causes acidosis and maximal vasodilatation. Autoregulation of the cerebral blood flow is lost and carbon dioxide reactivity may be reduced. This area of abnormal cerebral physiology can be considered to be the "cerebrum at risk" (2) of permanent damage in the event of further ischemic insults or suboptimal anesthetic management. Viewed another way, this is the area that can potentially be saved.

In addition to this classical mode of cell death, it has recently been shown that a second series of events occurs in parallel (26). The binding of excitatory amino acids and influx of calcium into the ischemic cell initiates the expression of a series of genes known as Immediate Early Genes (IEGs). Activation of these genes results in two processes. Firstly, they code for the production of proteins that may protect the cell from further damage or assist in the recovery phase. Included are nerve growth factor, glucose transporters, brain-derived neurotrophic factor, and neurotrophin-3. These factors are predominately produced in cells that have not been exposed to a

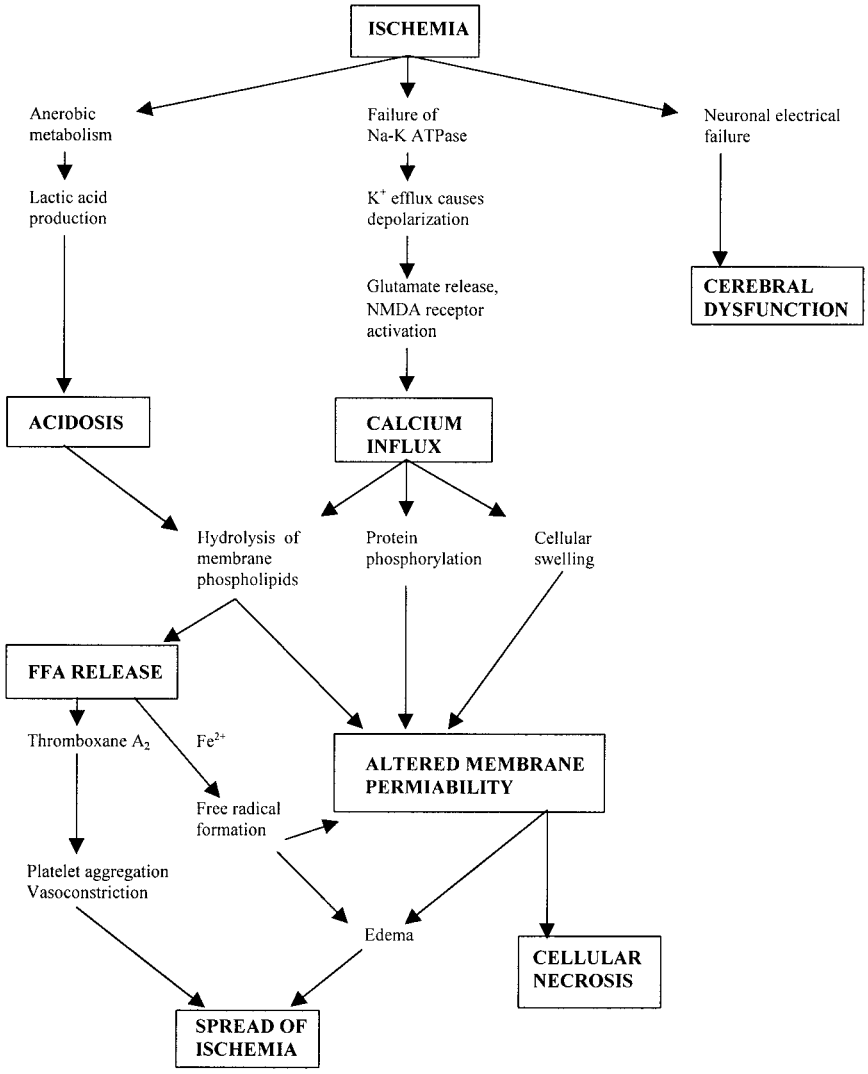

Figure 1. The ischemic cascade.

terminal ischemic insult. Secondly, IEGs induce an alternative mode of cell death known as programmed cell death (PCD), or apoptosis. In contrast to the process of necrosis described above, PCD is associated with the production of fewer toxic metabolites and no inflammatory response. Hence, ischemia results in the initiation of harmful as well as some potentially beneficial events. This raises the possibility that agents used for the purpose of cerebral resuscitation may, to some extent, increase the damage to neurons if they inhibit these protective pathways as well.

In summary, cerebral ischemia and the resulting cellular hypoxia lead to a complex and incompletely understood series of metabolic derangements that are, to some extent, self-perpetuating and tend to extend to adjacent areas of the brain.

Prevention

The primary prevention of perioperative stroke depends on identifying patients at risk and favorably altering risk factors to limit their impact on patient outcomes. In extreme cases this may require a case to be deferred until the risk has decreased, e.g., after a CVA. There is controversy regarding the time after a stroke during which a patient should be excluded from elective surgery. In 1962, Knapp et al. (18) recommended a period of 2 yr. More recently, authors have recommended periods ranging from 3 wk to 6 months, although these recommendations are not supported by clinical trials. Although there is animal evidence of abnormal autoregulation and CO_2 responsiveness for up to 3 yr after cerebral infarction, this would appear to be an unreasonable delay for even the most elective surgery. As the most severe physiological derangement occurs in the early recovery phase, it appears reasonable to delay surgery for 4–6 wk.

Carotid endarterectomy (CEA) is unequivocally recommended by the American Heart Association (AHA) for symptomatic patients with 70%–99% carotid stenosis (15), and this should occur before other surgery

when possible. Repair of intracardiac defects and replacement of abnormal cardiac valves should be considered in the context of the risks of these procedures. In contrast, CEA for asymptomatic carotid stenosis is controversial. In the Cochrane analysis, examination of the six randomized trials led reviewers to conclude that there is "some evidence favoring CEA for asymptomatic carotid stenosis, but the effect is at best barely significant" (27). It has already been noted that asymptomatic carotid stenosis has repeatedly been shown not to correlate with perioperative CVA.

The consumption of aspirin (acetylsalicylic acid) in an effort to reduce the incidence of cardiovascular disease is increasing, with over 100 billion tablets consumed annually worldwide (28). The AHA recommends aspirin for all patients at risk of ischemic cerebral events, although the optimal dose is debated (15). Aspirin use is associated with only a slight increase in the risk of hemorrhagic strokes in the general population (28); however, there is obvious concern about continuing aspirin therapy in the perioperative period for fear of increased bleeding complications. One survey of neuroanaesthetists found that nearly half would administer a platelet transfusion to patients on aspirin who required surgery (29). Aspirin has been shown to reduce the incidence of cerebrovascular complications of CEA. In a randomized comparison, daily use of small-dose (81 or 325 mg) aspirin reduced the risk of perioperative stroke compared with the use of higher doses (650 or 1300 mg) (30). Because of its recognized benefits, it is the current practice of the surgical and anesthetic departments at the authors' institution to continue aspirin use in the perioperative period even with high-risk procedures such as carotid endarterectomy, major joint replacement surgery, and cardiac procedures.

Attention should be given to other modifiable risks for CVA in the general population, for example, control of hypertension.

Good anesthetic technique may play a role in reducing the incidence of cerebral complications. This may include careful positioning of the head and neck, and the early treatment of hypotensive episodes. Patients at risk should be well hydrated throughout the perioperative period. No study has shown a benefit for regional anesthesia versus general anesthesia in the prevention of stroke. There have been studies of the effect of anesthetic agents on postoperative hypercoagulability. One demonstrated increased fibrinolysis in volunteers given a propofol infusion but not in those given Intralipid, suggesting that propofol may lower the tendency for thrombosis (31). Another study by the same group indicated a reduction in coagulation with patients given extradural anesthesia compared with those given general anesthesia alone (32). However, another group has found that the use of epidural blockade did not prevent the postoperative hypercoagulability response after abdominal aortic bypass surgery (25).

Cerebral Protection

Techniques that are used to minimize the injury to the brain in the event of an ischemic insult can be thought of as having three broad purposes: to increase the supply of oxygen to the injured tissue, to reduce the metabolic demands, or to affect specific pathways in the ischemic cascade to reduce the production of unwanted metabolites (6).

Physiological

As areas of brain within the ischemic penumbra are maximally dilated, blood flow becomes dependent on maintaining an adequate cerebral perfusion pressure (2). Cerebral blood flow to the injured area has been shown to decrease considerably in previously hypertensive patients with acute ischemic stroke whose blood pressure was reduced by more than 16% (33). Furthermore, an analysis of patients enrolled in one trial of rt-PA thrombolysis (34) suggested that treatment of hypertension after stroke might be detrimental. In this trial, patients in the treatment arm who received antihypertensive therapy were less likely to have a favorable outcome than those whose hypertension was not treated. However, there are biases in this post hoc analysis and, except in the case of severe vasospasm, arterial hypertension is generally undesirable, as it may result in an increase in cerebral edema or hemorrhage (7). Hence we suggest blood pressure be maintained within 20% of the patient's normal range with a cerebral perfusion pressure greater than 70 mm Hg if possible.

Hemodilution has been suggested as a therapy after ischemic brain injury. Oxygen delivery has been shown to improve with a decrease in hematocrit to 30% via a reduction in viscosity. Unfortunately, current data do not support the routine use of hemodilution, except as an adjunct in the treatment of vasospastic ischemia.

Similarly, normocarbia should be maintained. There are theoretical benefits to hypocarbia, by causing vasoconstriction in areas of normal brain and hence directing flow toward the injured area. However, hyperventilation has not been shown to improve outcome in focal or global ischemia in either clinical or animal trials (7). Hyperoxia has the potential advantage of increasing the oxygen delivery to the ischemic cortex. However, no studies have shown its effectiveness and there is the possibility that the production of damaging metabolites such as free oxygen radicals could occur.

The ischemic tolerance of the normothermic brain is around 4–6 min, after which permanent injury occurs.

However, patients can tolerate up to 60 min of cardiac arrest at 18°C with no neurological dysfunction. Widespread use of profound hypothermia is limited by the need for cardiopulmonary bypass. It would seem reasonable to investigate moderate degrees of hypothermia. Unfortunately, the use of hypothermia of 25°C–30°C in both animal and clinical studies has shown a high incidence of adverse affects in the absence of cardiopulmonary bypass (35). Problems include arrhythmias, cardiovascular collapse, and increased mortality. It is proposed that recirculation of accumulated metabolites occurs with the vasodilatation associated with rewarming and that these metabolites induce cardiovascular complications. Better results have been shown with temperature >30°C. Although conclusive human studies are lacking, animal studies of both focal and global ischemia have demonstrated improvements in neurological function and histopathological change (35). Furthermore, a randomized prospective pilot study has suggested that mild hypothermia may be beneficial in patients undergoing cerebral aneurysm surgery after acute subarachnoid hemorrhage (36). For maximal benefit, the onset of hypothermia should be immediately before or immediately after ischemia. Evaluation of metabolic changes in the hypothermic injured brain has shown that, in addition to a simple reduction in metabolic rate, improvement in outcome may be related to altered ion fluxes, reduced phospholipase activity, reduced glutamate release, and reduced oxygen free radical production. Conversely, hyperthermia even to mild degrees has been unequivocally shown to worsen outcome. Thus, fever should be aggressively treated in a patient who has had an ischemic event.

Careful control of blood glucose is thought to be an essential part of cerebral protection. Hyperglycemia can increase cellular acidosis by increasing lactic acid production. Experimental models of global ischemia have consistently demonstrated poorer outcome in hyperglycemic subjects, although the data has been inconsistent in focal ischemia (7).

Anesthetic Agents

In addition to their effect of reducing the cerebral metabolic rate (CMR), barbiturates have several other potentially beneficial actions in the ischemic cortex. Reported effects include blocking calcium channels, membrane stabilization, free radical scavenging, and reducing intracranial pressure (7). There is evidence that barbiturate use is not warranted after complete global ischemia (cardiac arrest) (37). However, in cases of incomplete ischemia, whether global or focal, the evidence for barbiturate use is not clear. The majority of studies showing a benefit with barbiturate use have been in animals (38); however, the extent to which the ability of these agents to lower body temperature was a confounding factor is not clear (39). The one human study that showed a decrease in neuropsychological complications after cardiopulmonary bypass has been challenged on methodological grounds (6). Hence, it remains that there are no adequate prospective human trials to justify the use of barbiturates in incomplete global and focal ischemia. It has been suggested that nitrous oxide may have attenuated the beneficial effects of barbiturates and that the use of nitrous oxide caused bias in the conduct of these trials (39).

Of the volatile anesthetics, most attention has been given to isoflurane as it has metabolic effects that are similar to those of the barbiturates. Animal studies into its utility in global and focal ischemia have shown mixed results. Some investigators have shown a benefit for isoflurane over other anesthetic agents in delaying the onset of ischemic depolarization in global (40) and focal (41) ischemic models. Yet studies to date have shown no benefit in neurological or histological outcome. This may be because isoflurane delays the onset of the ischemic cascade by seconds or minutes, but once the process has commenced it does not alter the ischemic cascade (6).

Propofol depresses cerebral metabolism, decreases CBF, reduces extracellular glutamate concentration that normally occurs with ischemia, and is a potent antioxidant (42). Studies into the effects of propofol have demonstrated some benefits in that it restores CBF in a global ischemic model (43), but improvement in neuropathological changes was not achieved. In focal ischemia, studies have shown a reduction in infarct size with propofol anesthesia (44). Although propofol and barbiturates have not been directly compared, some feel that propofol is unlikely to be more efficacious except from a pharmacokinetic perspective (39).

Ketamine blocks the NMDA receptors in the central nervous system and also inhibits glutamate release (45). There are some animal studies to suggest a beneficial effect with the use of ketamine in focal or incomplete global ischemia (39). No human studies have been undertaken at this time. S-ketamine is a single enantiomer of ketamine that, it is hoped, might provide the benefits of cerebral protection without the adverse effects, such as dysphoria, associated with the R-enantiomer. Improved neurological outcome with S-ketamine has been shown in one study of incomplete ischemia in rats (46).

Any biochemical improvements achieved with etomidate in animal studies have not translated to improved functional or histological outcomes (6,47).

Recently developed models of focal ischemia allow the comparison of infarct size in awake animals and anesthetized animals. Propofol, halothane and sevoflurane all reduce infarct size compared with stroke in

awake animals (44,48). It is likely that all general anesthetics except nitrous oxide have this effect. There are, however, differences between drugs in the magnitude of this effect and these differences may reflect their pharmacological characteristics other than ability to reduce metabolic rate.

Another component of the ischemic cascade that has been targeted is the role of sodium influx in the initial pathological depolarization of ischemic cells. Use of a sodium channel-blocking agent such as lidocaine may delay the onset of ischemic depolarization and should also decrease the cerebral metabolic rate. Lidocaine has also been shown to reduce the accumulation and degranulation of leukocytes (49). In a study of cardiac surgical patients, a 48-hr infusion of lidocaine reduced the incidence of intellectual and memory deficits up to 6 months postoperatively (50). Improved outcome has been demonstrated with the prophylactic use of lidocaine in a feline model of focal cerebral ischemia (51). In this study, lidocaine use was associated with reduced infarct size and more normal somatosensory evoked potentials. In models of global ischemia, the results have been variable and this may be attributable to the beneficial effects of lidocaine occurring primarily in the ischemic penumbra (52).

Other Pharmacological Agents

The central role of intracellular calcium levels in the pathophysiology of cerebral ischemia has led investigators to assess the role of calcium antagonists. Calcium channel blockers are obvious candidates for studies because they may restore normal cerebral blood flow to ischemic areas as well as reduce cellular enzyme dysfunction and lipid membrane breakdown. Studies into the efficacy of these agents for cerebral protection have given mixed results (7). Some of the studies have likely been affected by the use of agents with limited CNS penetration (6). One particular agent that readily crosses the blood-brain barrier is nimodipine. Improvements in neurological outcome have been demonstrated in animal studies (8) but it is not clear whether the beneficial effects were a result of direct metabolic effects or restoration of regional blood flow. Two studies in human subjects have suggested a benefit for the use of nimodipine in acute focal cerebral ischemia (53,54). Magnesium is a physiological calcium antagonist and reduces calcium influx into neurons, suggesting it might have a beneficial effect. A clinical trial investigating its efficacy is currently underway.

A number of other agents are under investigation for their effect in ameliorating the ischemic cascade (6,7,39). Prostanoids, such as indomethacin, may inhibit the production and effects of prostaglandins, particularly thromboxane A_2. Free radical scavengers and iron chelators have been used with the intention of removing harmful end products. The lazaroids (21-aminosteroids) are inhibitors of lipid membrane peroxidation and also act as free radical scavengers. The most extensively studied of these agents is tirilazad, which is frequently used in Europe for reducing vasospasm and infarct size after subarachnoid hemorrhage. Promising results in experimental stroke models have failed to translate into improved outcome in clinical trials to date (55,56). Excitatory amino acid inhibitors, including experimental NMDA receptor antagonists, have been investigated. An interesting recent development has been the experimental use of antibodies to the NMDA receptor (57).

Summary

Perioperative stroke is an uncommon event but one that can have devastating consequences for the patient, family and health care providers. Knowledge of important risk factors and measures that may be taken to prevent ischemic cerebral events will help to reduce the impact of this important complication. A number of current and experimental pharmaceutical agents may limit the neurological deficit seen after a stroke.

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