Present Status of Barbiturates in the Acute Stage of Cerebral Damage

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Introduction

Barbiturates, introduced into clinical practice in 1932 by WESE and SCHARRPPF (30), still have a definite place in the practice of anesthesiology. Barbiturates are the anesthetics of choice for the induction of anesthesia in neurosurgical risk patients. The latter are all patients with decreased intracranial compliance as well as patients with functional narrowing of arterial cerebral afferent vessels.

Effects of Barbiturates

The major effects of barbiturates are to decrease brain metabolism and brain circulation. The reduction of both these parameters can amount to 50%-65%, according to the dose given (4). The decrease of metabolism concerns solely the functional metabolism: If the EEG is isoelectric, the metabolism, i.e., the structural transformation, cannot be further decreased (3, 27). The coupling between metabolism and circulation remains intact, in contrast to the case with some volatile anesthetics. Further effects of barbiturates can partially be explained as a consequence of this, e.g., the decreases in intracranial blood volume, intracranial pressure, and body temperature. Barbiturates affect regional distribution of cerebral circulation, and especially in focal ischemia the regional distribution is most likely the decisive factor in their favorable influence. Barbiturates are antiedematous and anticonvulsive. The effects described up to now seem to improve the quotient between oxygen supply and requirement in situations of acute cerebral damage.

As regards the protective effects of barbiturates, further mechanisms are discussed which affect the cell or molecular level, such as seizing free radicals with a high membrane damaging potential, decreased release of lysosomal enzymes, reduction in the formation of free fatty acids, and decrease in intracellular potassium content. Decisive for a protective effect, in a limited sense, however, is the prevention of terminal membrane depolarization, recognized by the irreversible potassium outflow from the cells. Newer results from several centers have shown that barbiturates cannot stop the extracellular potassium increase following global cerebral ischemia; thus a protective effect in this respect applies only to hypothermia from a clinical point of view (2).
Experience with Barbiturates in Long-Term Therapy

Therapeutic doses of barbiturates are unsuccessful in treating global cerebral ischemia following arrest of circulation: the initial claims of their effectiveness by SAFAR's group (1978) (6, 20) have now been disproved by both animal experiments and multicenter clinical investigations (1, 10). Other individual centers have also found similar negative results (22, 25, 28). Therefore, long-term therapy with barbiturates cannot be recommended.

In the search for alternatives, some calcium antagonists have shown hopeful results in animal experiments, but only when given soon after the occurrence of global cerebral ischemia (12, 17, 26, 29). Combinations of barbiturates and calcium antagonists have not yet been reported on.

The situation in respect of focal or regional ischemia is quite different, in particular when the ischemia is not definite. Thus, barbiturates can to a certain extent play a part in cerebral circulation narrowing, in carotid surgery, cerebral aneurysm surgery, extra-intracranial bypass, and induced controlled hypotension (5, 11). In cerebral insults which cannot be cured surgically, barbiturate therapy has been of less value (21-23), although it might be that early administration of barbiturates would be of benefit.

A generally accepted indication for long-term use of barbiturates is a therapy-resistant increase in intracranial pressure, in particular in connection with severe skull-brain trauma. When all other drugs that decrease cerebral pressure have been exhausted, it has been proven by continuous measurement of intracranial pressure that barbiturates may decrease pressure (7, 8, 14, 15, 18, 19, 24, 31). Nevertheless, not all authors emphasize the use of barbiturates even for this indication (16).

Relative indications for limited treatment with barbiturates are the acute posttraumatic mesencephalic syndrome and occasional cases of posttraumatic or postoperative vegetative dysfunction when stabilization cannot be effected with sedatives (24). In addition, therapy-resistant status epilepticus is sometimes an indication for limited treatment with barbiturates (9).

Barbiturate Therapy

Barbiturate therapy is not without problems, on the one hand because of severe side effects, on the other because of a defective dose-effect relationship. Pharmacokinetic studies revealed that administration of 100 mg thiopental per hour effected a stable blood level of about 6 μg/kg. With 500 mg/h – about 30 μg/ml – in many cases a burst suppression pattern occurs in the EEG. This is the maximal possible metabolic decrease via barbiturate. For a decrease in intracranial pressure, doses between 100 mg and 200 mg thiopental per hour seem sufficient. However, considerable acute and chronic barbiturate tolerance has been reported (13), and in all, there are no definite dose recommendations.

Side-Effects of Barbiturate Therapy

Barbiturates lead to a spreading depression of all organic systems. Mechanical respiration of patients is a presupposition for long-term barbiturate therapy. Such therapy leads regularly to atonia of the gastrointestinal tract; spontaneous perforations may escape diagnosis. Further side effects are cholestasis hepatoses as well as hypersensi-