Hypothermia plus Barbiturates:
Apples plus Oranges?

Two apples plus two oranges certainly yields four, but four what? In this issue Lafferty et al.1 and Hagerdal et al.2 attack this particular problem of unit addition in relation to the cerebral metabolic depressive effects and the cerebral protective effects of hypothermia and barbiturates. In essence, Lafferty et al. tell us that two cerebral metabolic depressive units of hypothermia added to two such units of barbiturate-induced depression equal four units, whereas Hagerdal et al. provide evidence that the cerebral protective units cannot be so added. Are these results contradictory? Probably not.

The capacity of hypothermia to protect the brain during a period of decreased or absent oxygen delivery is well established both experimentally and clinically. Further, the magnitude of protection is directly related to the magnitude of temperature decrease, and this in turn, to the magnitude of cerebral metabolic depression. A reasonable conclusion is that the latter accounts for the former. Recognition that most anesthetics also decrease cerebral metabolic rates caused speculation that they too would provide cerebral protection appropriate to the magnitude of metabolic depression. Experimentally, barbiturates, which are the most potent pharmacologic depressants of cerebral metabolism, do provide protection. Other anesthetics have not been convincingly demonstrated to do so. The latter should of itself cause one to question the validity of equating metabolic depression to protection. This, however, has been dismissed by some on the grounds that at clinically safe concentrations inhalational agents are not potent metabolic depressants. Further, the inhalational agents produce cerebral vascular changes quite different from those produced by barbiturates (dilation rather than constriction), which might in turn adversely alter intracranial dynamics during a period of decreased oxygen delivery (for example: increase in intracranial pressure). Accepting this as a side issue (but a bothersome one), the question remains whether the metabolic and protective effects of hypothermia and barbiturates are additive.

One might anticipate that metabolic addition would occur so long as the brain is electrically active. This point is emphasized by Lafferty et al. The mechanisms whereby hypothermia and barbiturates decrease cerebral metabolism almost certainly differ. Hypothermia presumably acts by decreasing rates of biochemical reactions; this is a direct function of temperature unrelated to the electrical activity of the brain per se. Barbiturates presumably stabilize electrically active membranes in a much more specific fashion than does hypothermia, thus decreasing the work of the brain and hence, cerebral energy requirements. Since these mechanisms do not apparently overlap one another, their combined effect in the electrically active brain should be additive. However, if hypothermia were induced to the point of abolishing cerebral electrical activity (less than 22°C) one would predict that the addition of barbiturates could not further decrease cerebral metabolic rates.

Should, then, the cerebral protective effects be additive? Only if metabolic depression is the sole mechanism of protection and, if that is so, only if the experimental model of cerebral hypoxia is one that does not abolish cerebral electrical activity. The question as to whether metabolic depression is the basis for protection remains unresolved. In the case of hypothermia there is no convincing evidence to the contrary. In the case of barbiturates there are contradictory data. Barbiturates have been reported to protect the brain when
administered following a prolonged period of complete global ischemia at a time when all of the energy stores of the brain are depleted. Such protection on the basis of metabolic depression seems remote. Some (but certainly not all) have reported that very large doses of barbiturates are necessary to demonstrate protection experimentally. Since only clinical doses are needed to produce near-maximal metabolic depression, the reported need for much larger doses cannot be so explained. Thus, there is at least some reason to question whether barbiturate-induced metabolic depression is the basis for protection. If it is not, a simple additive protective effect with hypothermia might not be expected.

In the investigation reported by Hagerdal et al. there are at least two other reasons why they may have failed to observe an equal and/or additive protective effect. They chose to induce cerebral hypoxia by producing hypoxemia (as defined by \( P_{\text{O}_2} \)) rather than ischemia. As a result, with hypothermia the leftward shift of the oxyhemoglobin dissociation curve lessened hypoxemia (as defined by arterial oxygen content) compared with normothermic rats. Since the normothermic hypoxic model thus differed from the hypothermic hypoxic model, the magnitude of protection provided by barbiturates (as measured in the normothermic model) could not be expected to equal the protection provided in the hypothermic model. However, when examined separately, both barbiturates and hypothermia had protective effects when \( P_{\text{O}_2} \) was decreased to 25 torr. Since hypothermia alone completely protected animals at this oxygen tension, it was not possible to determine additive effects. That barbiturates alone did not protect completely normothermic rats at \( P_{\text{O}_2} \) 25 torr, despite a similar magnitude of metabolic depression, can be fully explained by differences in the extents of hypoxemia (that is, arterial oxygen content). The authors clearly recognize this possibility.

Because hypothermia (32 C) did completely protect the animals at \( P_{\text{O}_2} \) 25 torr, and thus obscured any possible additive effect of barbiturates, a second set of studies was done at \( P_{\text{O}_2} \) 15 torr. Here, the authors clearly failed to observe additive protective effects when phenobarbital was administered to rats maintained at 32 C. It seems entirely likely that at \( P_{\text{O}_2} \) 15 torr and 32 C the electrical activity of the brain would be abolished. If that is so, then it is reasonable to predict barbiturates would contribute no further protection (since further metabolic depression presumably would not occur), whereas a further lowering of temperature (which would further decrease metabolic rates) would contribute greater protection. Several conclusions appear justified. Both barbiturates and hypothermia decrease cerebral metabolic rates, but by different mechanisms; in an electrically active brain these effects are additive. Both barbiturates and hypothermia can protect the brain during a period of decreased oxygen delivery; depending on the nature and the extent of cerebral hypoxia, these effects may or may not be additive.

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References