ATROPINE IN THE TREATMENT OF CLOSED HEAD INJURY

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The accepted treatment of severe closed head injury is largely concerned with supportive measures, and no definitive therapy has been described that is directed at any specific reversal of the non-surgical pathophysiologic sequelae of trauma of the brain.

Information has slowly accumulated regarding the mechanism of concussion, including descriptions of the pathologic changes such as those described by Scheinker as “vasoparesis.” Studies regarding cerebral swelling have been controversial, and treatment by dehydration has now been largely discarded. On the basis of present knowledge, it would seem that prolonged coma is due, at least in part, either to unknown changes in the neurone or to alterations in the environment of the nerve cell which persist for long periods of time.

This would suggest the possibility that metabolic changes may occur in neurones as the result of trauma. Studies of this type have been carried out only in recent years and only a small amount of data is available. Gurdjian, Webster and Stone have studied the carbohydrate metabolism of damaged brain and have demonstrated that head injury in animals causes no significant changes in the cerebral arteriovenous differences in oxygen, carbon dioxide, and glucose. Specimens of cerebral tissue were obtained by freezing the brain in situ, and it was found that areas of contusion showed greatly increased lactic acid and inorganic phosphate with decreased phosphocreatine and adenosine triphosphate. They felt that these findings might be due to a combination of direct injury to cells and anoxia resulting from vascular damage. However, areas of cortex showing no macroscopic evidences of damage were often chemically normal, even in profoundly injured animals. Thus, it is evident that head injury causes no generalized disturbance in cerebral oxidations.

However, changes in acetylcholine metabolism do exist following brain trauma. Bornstein has pointed out that while free acetylcholine (ACh) is never normally present in cerebrospinal fluid, it is found in relatively large quantities shortly after trauma in the experimental animal. It appears that ACh is liberated in abnormal amounts by traumatized nervous tissue and that some of the liberated ACh escapes destruction, persists in the intercellular spaces and finally diffuses into the CSF where its presence may be quantitatively determined. He also felt that there was a positive correlation between the concentration of ACh in the CSF, the clinical signs of concussion and the post-concussion EEG changes. He concluded that “free ACh
may be one of the physiological factors underlying the acute paralytic and excitatory phenomena of cerebral concussion and more severe cranioencephral injuries.” Bornstein further reasoned that if the abnormal electrical activity of the cortex and the behavioral pattern following concussion are due, at least in part, to the activity of abnormal concentrations of ACh within the brain tissue, it should then be possible to reverse these effects by atropine, an anticholinergic drug. He found this to be the case in the experimental animal in that both the EEG patterns and the stuporous condition may be abolished by appropriate doses of atropine sulfate (0.5–1 mg. per kg.). Bornstein also demonstrated that intracisternal injection of ACh (0.02 to 10 gamma) produces behavioral and EEG changes similar to those noted following concussion, and these may also be abolished by atropine. Tower and McEachern have studied these factors following head injury in the human and found low cholinesterase activity with reversal of normal cholinesterase ratios as well as free ACh, which may be present in large amounts in severe cases. Recovery is associated with reversal of the above changes. In 3 patients they could demonstrate a correlation between cholinesterase pattern, acetylcholine level, EEG, and the clinical state of the patients. It is obvious that these findings clearly suggest a rationale of therapy specifically directed at the reversal of one of the pathophysiologic sequelae of trauma of the brain.

CLINICAL DATA

Since it is difficult to accurately forecast the clinical course of patients who have been subjected to relatively mild head injury, anticholinergic treatment was given initially only to those patients who obviously had sustained very severe brain trauma. All of the initial group of 20 patients had severely damaged brains as evidenced by depth of coma, focal neurological signs and grossly bloody CSF. It was recognized that anatomical damage to the CNS was present in these cases and that no physiological methods could reverse these changes; but since superimposed reversible physiological factors should also be playing a role, it was hoped that obvious and reproducible clinical improvement could be produced in certain cases by the administration of atropine. The atropine sulfate was administered subcutaneously in doses of 0.1 mg. per kg. of body weight, so that the average single adult dose was gr. 1/10.

In one of the most striking cases of this group, the clinical improvement could be directly related to the prior administration of atropine, and this was consistently reproducible over 5 cycles. The patient was initially in decerebrate rigidity and each cycle consisted of dramatic clinical improvement which became definite about 12 to 14 hours after atropine. This was maintained for about 10 hours or slightly longer. The state of consciousness would then slowly become depressed over a 24 to 48 hour period, approaching the original level, at which time atropine was again administered. This was one of the early cases treated in this fashion, and for that reason the rather