ATROPINE IN THE TREATMENT OF CLOSED HEAD INJURY

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(Received for publication December 21, 1949)

THE accepted treatment of severe closed head injury is largely concerned with supportive measures,[15] 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,[3] including descriptions of the pathologic changes such as those described by Scheinker[12,13,14] as "vasoparesis." Studies regarding cerebral swelling have been controversial,[11] 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[6] 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[1] 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 craniocerebral 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[16] 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

large doses of atropine were given at rather cautious intervals.

Of the remaining 19 patients, 2 exhibited typical decerebrate rigidity on admission and both ultimately recovered. There were 5 fatalities in this group, and gross brain damage was present at autopsy in all instances. Of the 15 patients who recovered, it was felt that anticholinergic therapy was of dramatic benefit in 4 cases, of definite benefit in 7 cases, and of questionable value in 4 cases. Because of the satisfactory clinical results in this initial series of severely injured patients, anticholinergic therapy has been used in an additional series of 72 cases. These cases represented routine instances of closed head injury in patients admitted to the Neurosurgical Service in whom no improvement in the state of consciousness was noted during the first 3 hours after admission. In many of these the average adult dose of gr. 1/10 was administered daily as long as the patient was unconscious. Since the therapeutic benefit is more difficult to assess in such an unselected group of cases, no conclusions can be drawn in a small series other than the crude clinical impression that certain (but not all) patients recovered from the effects of trauma with greater rapidity than would otherwise be anticipated.

DISCUSSION

The ideal group of cases for a study such as this would be one in which the brain had been subjected to maximal "concussive" trauma without evidence of any gross brain damage whatsoever. Obviously this was not the case in any of the initial cases reported. Even so, anticholinergic therapy was of benefit in a significant number. This might tend to substantiate the conclusion of Denny-Brown and Russell[4] that "there is often no evidence to show that contusion prolongs the concussion disturbance of function." However, in those cases that were ultimately fatal, adequate pathological explanation of the cause of death was present. Obviously such changes cannot be reversed by anticholinergic therapy.

The mechanism by which acetylcholine is liberated by the mechanical energy of concussion remains unknown. Lorente de Nó[9] has shown that ACh is released from peripheral ganglia by mechanical damage alone. It is also conceivable that the observed free ACh might be the result of the intense neuronal discharge described by Walker, Kollros and Case[17] and Bornstein[1] suggested that this factor might be responsible for the presence of free ACh in his experimental animals. This is perhaps still open to question in view of the observation of Williams and Denny-Brown[19] that blows resulting in concussion always caused an instantaneous and generalized diminution in the cerebral electrical activity rather than hyperactivity, although blocking of amplifiers prevented recording during the first few seconds after trauma. It is known that cholinergic drugs injected into the subarachnoid space will cause many clinical signs similar to those seen in concussion, and these effects may be prevented by parenteral administration of atropine.[7,8] There is also some evidence that cholinergic compounds in

adequate concentrations will cause hemorrhages in the grey matter accompanied by diffuse gliosis, and subsequently by development of glial nodules, glial scars and neurone depletion.[2] These observations certainly do not disallow the concept that the presence of excess amounts of free ACh may contribute to clinical signs of head injury. We know that ACh is a powerful vasodilator and will cause increased permeability of the blood-brain barrier[5] and thus certain of the pathological changes described by Scheinker[12] may be on this basis. Since ACh may play some role in synaptic transmission, this disturbance of neuronal metabolism may also account for a part of the depression of neuronal activity seen clinically.

The dosage used in these series of cases was approximately 0.1 mg./kg., while Bornstein[1] used 0.5–1.0 mg./kg. in his experimental animals. On that basis, the human dose used should be considered minimal to produce the necessary anticholinergic effect. However, it was felt that a single dose of gr. 1/10 every 24 hours in these cases was close to toxic levels. In about 25 per cent of all cases some definite change in heart rate was observed, the pupils often became moderately dilated, there was a variable increase in temperature, and rarely a cutaneous flush was seen. In all instances these signs regressed within 4 to 6 hours and were no cause for concern. Because of the action of this drug on the heart, anticholinergic therapy has not been used in patients with proven cardiac disease. Sporadic reports of atropine poisoning appear in the literature,[10,18] but it is evident that this drug possesses a surprising factor of safety.

It is obvious that atropine does not represent the ideal anticholinergic drug for this particular purpose, and the search for a more satisfactory substitute is under way. In this study it would have been helpful, both in the matter of determining dosage and also in assessing the result of treatment, to have had serial EEGs on each patient. That was not done in the present series, but will be done in a future series.

Although certain very dramatic results have been achieved by anticholinergic therapy in patients with head injury, it is somewhat disappointing that unquestionable improvement due to medication alone could not be demonstrated in approximately 20 per cent of the cases. It is easy to hypothecate that the factor of organic damage was responsible for these doubtful cases. However, the essential fact is that we do not have sufficient knowledge to understand all the details of the pathophysiology of cerebral trauma and therapy must of necessity be somewhat empirical at present. It is hoped that the search for specific therapy will yield some of the needed data.

SUMMARY

1. It is known that following cerebral trauma, both in experimental animal and in man, free acetylcholine is found in the CSF in rather large amounts, whereas normally none is present. In the experimental animal both the EGG patterns and the stuporous condition resulting from cerebral trauma may be abolished by appropriate doses of atropine sulfate.

2. On the basis of the above data, anticholinergic therapy by atropine sulfate in doses of 0.1 mg./kg. (gr. 1/10 in adult man) has been used in a series of 20 patients who had sustained very severe closed head injuries. Dramatic and consistently reproducible clinical improvement was obtained in selected instances. Because of these favorable results, anticholinergic therapy has been used in an additional series of 72 consecutive patients with all grades of cerebral trauma.

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