Corticosteroids in Ischemic Stroke

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IN THE PATIENT with completed stroke there are few specific management options. Once damage has been sustained, objectives are limited: patient survival, reduction of neurological deficit to a minimum, effective rehabilitation to realize the potential of brain compensatory mechanisms, and secondary prophylaxis in hopes of avoiding a further ictus. The physician's concern must be to minimize the extent of tissue damage incurred as a direct or indirect result of the original vascular process. The record of the many medical interventions which have been advocated with that objective in mind — carbon dioxide inhalation, vasodilating agents, hyperventilation, induced hypertension, and stellate ganglion blockade, to name but a few employed in ischemic infarction — has not been inspiring, and such measures are rarely used today. One intervention, corticosteroid administration, first reported in the late 1950's, however, continues to be routine in many centers. The purpose of our discussion will be to examine, once again, the rationale for the use of corticosteroids in stroke and to assess the evidence that they do, in fact, accomplish the ends for which they are prescribed. Since corticosteroids have been thought to ameliorate the pathological processes in various brain lesions by reducing associated brain edema, we will also consider the nature of ischemic cerebral edema and the evidence that edema contributes to tissue injury.

Nature of Ischemic Cerebral Edema

In 1967, Klatzo1 described two forms of cerebral edema occurring in dissimilar experimental conditions and also resulting from different pathological processes in humans. In both forms, relative tissue water content, measured by weight or by specific gravity determination, is increased. Further, it is assumed that edema causes an absolute increase of water content in brain tissue and, therefore, an increased brain volume; that is, a loss of solid components alone does not qualify as edema. So-called "vasogenic" edema, produced experimentally by intracerebral transplantation of tumor, by induction of focal infection, or by production of a cold injury, among other models, is held to result from initial disturbance of the "blood-brain barrier." Resulting "leakage" of osmotic constituents of plasma from the vascular compartment to brain extracellular space is followed by influx of water to brain parenchyma. Such edema resembles plasma, containing similar protein and electrolyte concentrations. Movement of edema fluid through the expanded extracellular space occurs by bulk flow, predominantly in white matter. Both extravasation of colloid and water and their migration in brain parenchyma are promoted by arterial blood pressure elevations. In many experimental examples of vasogenic edema, barrier disturbance and water content are reduced by corticosteroids.

A distinctly different form of edema, "cytotoxic" edema, is found in experimental water intoxication or following administration of metabolic poisons. Excess brain water is located intracellularly in cytotoxic edema in contrast to its extracellular location in the vasogenic form. Active transport systems responsible for normal distribution of electrolytes and water across the cell membrane are thought to be impaired in intracellular water accumulation. Increase of brain water, derived from both the vascular compartment and from cerebrospinal fluid, is not accompanied by a striking influx of colloids. The resulting edema is a predominantly gray matter process, little affected by blood pressure changes. Corticosteroids have not been effective in models of cytotoxic edema. Since Klatzo's classic discussion, other forms of edema have been described, including the "interstitial edema" of hydrocephalus, so-called "granulocytic edema" of pyogenic infection, and "ischemic cerebral edema."

A better understanding of the nature of ischemic cerebral edema has emerged over the past few years.2 The edema which follows cerebral ischemia and infarction is not exclusively vasogenic or cytotoxic but has characteristics of both. Increase of brain water begins soon after induction of ischemia in the experimental model. Early edema is confined to the intracellular compartment and presumably results from failure of membrane homeostatic mechanisms due to oxygen and substrate deficiency. Intracellular water increment accompanies rising cell sodium, while potassium moves outward to the extracellular space. Cell dimensions increase, augmenting total brain volume despite reduction of extracellular space. The integrity of the blood-brain barrier, presumably comprised of the vascular endothelium, is initially un-
affected. If ischemia continues, necrosis of brain cells occurs, resulting in the release of lysosomal contents to cytoplasm with breakdown of proteins, fats, and nucleic acids. Digestion creates new osmols, constituting a considerable gradient favoring movement of still more water to brain. Eventually, the blood-brain barrier shows signs of increased permeability. The route by which proteins and other large molecules gain entry to the extracellular space remains unclarified. There is persuasive evidence that enhancement of pinocytotic transport of protein across ischemic endothelium may be important. During the secondary phase of ischemic edema, characterized by brain cell death and loss of barrier integrity, the extracellular space reexpands. Consequently, edema fluid may move by bulk flow, particularly along white matter tracts, subject to pressure gradients, in turn influenced by arterial blood pressure. The evolution from early “cytotoxic” and intracellular edema to later “vasogenic” and extracellular edema, termed “maturation,” occurs hours and even days after the onset of ischemia and the peak increment of tissue water. Accompanying the foregoing processes are alterations of other indices such as bioamine and cyclic nucleotide turnover. It is unclear whether some observations represent critical causal factors or epiphenomena.

Consequences of Ischemic Cerebral Edema

Massive and fulminant cerebral edema is a serious and sometimes fatal complication of extensive cerebral infarction. Of patients sustaining large supratentorial ischemic infarctions, 20 to 25% manifest signs of brain stem compromise related to transtentorial herniation. Peak volume augmentation from cerebral edema occurs one and one-half to three days after infarction. Certainly, reduction of brain volume during the time of critical cerebral edema may be life saving in such settings. In the majority of ischemic infarctions, however, the quantity of edema is not sufficient to exhaust compensatory mechanisms, and brain herniations do not occur. Whether ischemic cerebral edema contributes to tissue injury is not clear in the more common, but less dire, circumstances of “submassive” infarction. However, local increases in tissue water may compromise survival of marginally viable, ischemic cells.

Progressive tissue edema may perpetuate and extend local ischemia by its effects on collateral microcirculation. It has been shown that clinical and electrical function of cerebral tissue or individual brain cells requires a minimum local cerebral blood flow in the range of 0.18 to 0.25 ml/g/min. For maintenance of viability of brain tissue, the lower limit of cerebral blood flow appears to be approximately 0.12 ml/g/min. After vascular occlusion the flow provided by collateral channels in areas of the ischemic distribution may be in these ranges. Edema may cause further reduction of local flow below the critical lower limits for tissue function and survival.

The adverse local effects of evolving edema are thought to result from several processes. One effect of an increase in local water content is the creation of pressure gradients. If brain tissue has sufficient structural integrity to maintain local elevations in tissue pressure, then the effects on local microcirculation may be quite significant, even when measures of “averaged” intracranial pressure are not elevated. Available techniques to assess pressure in one of several intracranial spaces provide “resultant” measures that may not be relevant to local circumstances. Expansion of perivascular astrocytic processes and of the endothelial cells themselves will reduce luminal dimensions, measurable by histological means or by assessment of blood volume in ischemic tissue. Impairment of local autoregulation would potentiate the deleterious influence of local pressure on luminal diameter and flow by making vessels unresponsive to local metabolic requirements. It has been shown that after experimental occlusion, measures of circulatory well-being, such as oxygen availability, undergo a secondary decline, corresponding temporally to the evolution of ischemic cerebral edema and presumably produced by its local effects on the microcirculation. By virtue of its increased total mass, edematous ischemic brain tissue will receive less blood per unit dry weight. Volume expansion increases intercapillary distances so that metabolites and cellular wastes must travel further. Finally, the phenomenon of “no reflow” after ischemic anoxia may be an absolute failure of microcirculation in edematous tissue. In summary, gross swelling leading to displacement of brain structures is an unequivocally adverse effect of ischemic cerebral edema. Additionally, there is accumulating evidence that edema may affect the survival of marginally viable tissue and cells in ischemic brain.

Proposed Mechanisms of Corticosteroid Action in Brain Edema

Several potential mechanisms have been advanced to explain how corticosteroids might act as “anti-edema” agents. Early attempts to define a role for corticosteroids in modification of ischemic brain edema involved assessment of effects on blood-brain barrier permeability to tracer particles. The implied conviction that brain water increment and barrier permeability are causally linked following ischemia is an example of the obsolete concept that ischemic cerebral edema is predominantly “vasogenic.” In experimental vasogenic edema corticosteroids have reduced tracer extravasation, presumably by their “membrane stabilizing” effects. Complex interactions of corticosteroid molecules with membranes have been held to confer protection following various insults by retarding membrane dissociation, lysosomal enzyme release, and free radical injury. Current concepts of ischemic cerebral edema suggest that peak water increment precedes significant disturbance of barrier permeability. The “membrane stabilizing” action of corticosteroids on the blood-brain barrier is therefore not relevant during the critical stage of
edema. It has also been suggested that a mineralocorticoid action of the drug might influence electrolyte alterations that occur early in ischemia across brain compartments separated by membranes. However, the ultimate status of cerebral electrolytes depends on corticosteroid action at multiple sites, making prediction of the resultant effect difficult.

Recently, attention has turned to a potential role of corticosteroids in edema resolution. Excess water is removed either directly by primary reabsorption into the vascular space or indirectly after initial flow into the CSF compartment. The latter route appears particularly attractive since there is no known barrier between brain extracellular space and CSF. Removal of edema by the indirect route might be enhanced by reduction of volume of true CSF, either by decreased production or accelerated reabsorption. Both effects have been ascribed to corticosteroids. While each of these actions of corticosteroids has been suggested as a rationale for using the drugs as antiedema agents in ischemia, the mechanisms have been tested not in ischemia but in other models and, therefore, in other forms of brain edema. Indeed, if corticosteroids do affect ischemic cerebral edema, the means by which they do so are unknown.

Effects of Corticosteroids in Experimental Ischemic Infarction

Since the early 1960's, the effects of corticosteroids have been studied in several models of cerebral ischemia and anoxia using rabbits, gerbils, rats, cats, dogs, and monkeys. Global ischemic anoxia, focal ischemia, and combinations have been produced by various means. Dexamethasone has been most frequently studied, although methylprednisolone has also been used. Both agents have been administered in varying dosages and with different temporal relationships to the production of ischemia or anoxia.

Interestingly, brain tissue water content has not been determined in all models. Stroke frequency, infarct size, blood-brain barrier permeability, electrolyte changes, and clinical status including mortality, have also been examined. The experimental designs have differed sufficiently to make the studies not strictly comparable, but the weight of experimental evidence does not support the use of corticosteroids in ischemic stroke.

In those studies in which brain edema was measured, the results are in conflict. For example, in a squirrel monkey model in which focal ischemia was produced by middle cerebral artery occlusion, dexamethasone had no effect on edema, nor did it influence the clinical course or histological findings. Similarly, in microembolized rats treated with dexamethasone, there was no effect on edema or on cerebral electrolytes, isotope spaces, or survival in comparison with untreated controls. On the other hand, in a cat model with middle cerebral artery occlusion, dexamethasone reduced edema and evidence of blood-brain barrier injury in necrotic, but not ischemic brain. Studies in which only morbidity and mortality were assessed have also yielded disparate results, although, in most, steroids conferred no benefit. Thus, experimental work with animal models of ischemic and anoxic injury has yielded nonuniform results. It has not been established that corticosteroids alter the course of experimental ischemic cerebral edema or that they ameliorate the clinical course of ischemic injury in most animal models.

Effects of Corticosteroids in Human Ischemic Infarction

The beneficial effect of corticosteroids in human ischemic stroke has been thought to be the amelioration of ischemic cerebral edema. Despite that reasonably unanimous clinical conviction, the effects of corticosteroids on human ischemic cerebral edema have not been directly studied. Until the advent of computerized tomography, available techniques have not reliably demonstrated the presence and course of ischemic cerebral edema. Subarachnoid pressure monitoring at the lumbar space may inaccurately reflect intracranial pressure and has been considered potentially hazardous. Techniques for more direct measurement of intracranial pressure have been considered inappropriately invasive for a nonsurgical disease, and even they may yield misleading results. In clinical studies the presumed effects of corticosteroids on ischemic cerebral edema have been indirectly inferred from clinical outcome. Again, there is an implicit assumption that edema is harmful and that prevention or treatment of edema should improve the clinical outcome.

Compounding the usual difficulties of assessment of medical intervention in human illness is the clinical profile of cerebrovascular disease. The natural history of stroke is toward spontaneous improvement. To be proved clinically efficacious, a treatment must improve either survival or ultimate functional recovery. Given the expected trend to clinical improvement after ischemic cerebral infarction, functional recovery as a measure of the value of a treatment requires a larger number of patients, particularly when the effect of the treatment under study is of small magnitude or confined to an unidentified subgroup of a larger study population.

A number of human studies have addressed the question of whether corticosteroids are of benefit in acute ischemic infarction. Several agents have been employed, and they have been prescribed at various dosages and for various periods of time after ischemic infarction. One study suggested that in terms of graded clinical improvement, corticosteroids may be of benefit in treated patients compared with an untreated control group. The drug was of particular value among the most severely damaged stroke patients. Other controlled studies, however, showed no advantage for corticosteroids, and in one there were more deaths in the corticosteroid-treated group than in controls, although differences fell short of statistical significance. Representative of a number of other studies yielding negative results was one in
which corticosteroid-treated patients did not benefit in terms of improved survival or clinical recovery at four weeks. In three of seven corticosteroid-treated patients who died, but in only two of the five control deaths, cerebral edema was identified as the immediate cause of death. Hence, most clinical evidence suggests that corticosteroids are not of benefit in ischemic cerebral infarction. The suggestion that a subgroup, particularly those with large infarcts and extensive edema, might benefit has not been specifically examined but is not consistently supported. Again, it must be stressed that except for autopsied cases cerebral edema in human beings has been assessed only indirectly by clinical means.

If corticosteroids are not of proved benefit for the entire stroke population, are they, on the other hand, dangerous? Interestingly, in several experimental models of ischemic infarction, treated animals did less well than controls. As indicated previously, a slightly higher mortality among cortisone-treated patients compared with controls led one group to discontinue the study. An increased incidence of gastrointestinal bleeding, infection, and exacerbation of diabetes among corticosteroid-treated patients has been reported. By contrast, in another study the only three instances of gastrointestinal bleeding among patients with ischemic infarction occurred in controls. Virtually no work has been done on the effects of corticosteroids on the pituitary-adrenal axis following ischemic infarction. Certainly, such information should be sought given the high rate of stressful, late medical complications among stroke patients.

New Directions

While indiscriminate use of corticosteroids in all patients with ischemic infarction does not seem justified, subgroups that might benefit may be defined by newer techniques, and new programs of corticosteroid use may be worth pursuing. CT scanning provides a noninvasive means of assessing intracranial contents, and it may become possible to measure edema quantitatively. Two CT measurements might reflect the presence and quantity of brain water: (1) reduction of brain tissue density, represented by a decrease in X-ray attenuation, and (2) augmentation of brain tissue volume reflected by displacement of the ventricular system and obliteration of sulci. These two indicators are not infallible, however, since decreased density to X-rays may also result from the presence of free fatty acids, which are known to accumulate in infarcted brain, and increased tissue volume could result from an expanded vascular compartment during postischemic hyperemia. As we accumulate experience with CT scanning and newer generations of equipment are developed, areas of ambiguity may be resolved. Similarly, less invasive and hazardous techniques for local cerebral blood flow measurement and intracranial pressure monitoring are being developed. With the new techniques it will become possible to define edema and its consequences after ischemic infarction. The effects of a variety of agents, including corticosteroids, on measurable edema may then be assessed.

The implications of recent reports describing the efficacy of “superpharmacological” doses or “megadoses” of corticosteroids in traumatic cerebral edema have not yet been explored in stroke. Also, there is increasing enthusiasm for “combined therapy” for cerebral edema. The administration of corticosteroids and diuretics together, effective in animal models, deserves a trial in human ischemic cerebral edema.

We have attempted to summarize current concepts of ischemic cerebral edema and the evidence that corticosteroids influence its course. At the same time we have reviewed available information regarding the effects of corticosteroids on other processes of ischemic infarction in both animal models and humans. While the available evidence does not support the indiscriminate use of corticosteroids in ischemic infarction, they may be valuable in some situations, particularly those patients with large infarcts. Future studies incorporating more direct measures of the effects of corticosteroids on cerebral edema should help to resolve the question. Additionally, corticosteroids may be effective in combinations with other drugs, particularly diuretics, or when administered alone in extremely high dosage.

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