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Effects of Steroids on Behavior, Electrophysiology, Water Content and Intracranial Pressure in Cerebral Cytotoxic Edema[1]

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JAMES, H. E. *Effects of steroids on behavior, electrophysiology, water content and intracranial pressure in cerebral cytotoxic edema.* PHARMAC. BIOCHEM. BEHAV. 9(5) 653–657, 1978.—The effect of therapy with methylprednisolone sodium succinate (5.33 mg/kg/day) and dexamethasone sodium phosphate (1 mg/kg/day) on grey matter of rabbits rendered edematous by a metabolic blocker, 6-aminonicotinamide, is presented. Methylprednisolone was observed to significantly reduce the water content of the grey matter ($p<0.001$), whereas dexamethasone had little effect. Both agents, however, were equally effective in reducing intracranial pressure ($p<0.001$) and improving intracranial elastance, when compared to untreated animals. However, in the dexamethasone-treated group, there was improved behavior and EEG findings in 50% of the animals when compared to the untreated controls, and similar improvement was present in less than 15% of the methylprednisolone group. The disparity between the effects on water content, behavior and EEG supports the thesis that in cerebral edema these agents have a metabolic effect out of proportion to their effect on tissue water.

Steroids Cytotoxic cerebral edema

THE MANAGEMENT of clinical cerebral edema continues to be one of the most challenging therapeutic endeavors to face the clinician. Since the routine application of continuous monitoring of intracranial pressure (ICP) in clinical practice [5, 12, 17, 18, 29, 30], the response of various therapeutic modalities for the management of intracranial hypertension could then be analyzed more effectively [17, 18, 30]. The institution of steroids in the management of clinical cerebral edema has been associated with a stabilization of ICP [1, 12, 29, 30], improvement of regional blood flow [46], clinical improvement and reduction of cerebral edema in patients with brain tumors [11, 28, 30]. An improvement in the outcome of patients with severe closed head injuries has also been noted [8,12].

Experimental brain edema has been produced in many ways [4, 16, 19, 20, 22, 24, 34, 36, 37, 39, 45] and two basically different types of brain edema have been proposed: vasogenic and cytotoxic [19,38]. In the former, the primary injury is to the vessels and a subsequent increase in blood-brain barrier permeability produces an increase in the passage of serum constituents into the extracellular space by hydrostatic pressure, and subsequent spread through the tissues due to bulk flow [19, 20, 37]. In cytotoxic edema active ion transport is impaired due to interference of cell metabolism, with subsequent intracellular uptake of fluid and swelling [1, 2, 19, 36]. Most of the therapeutic trials of steroids in experimental cerebral edema have been vasogenic edema [24, 25, 33, 38].

In previous work Baethmann *et al.* [2], administered 6-aminonicotinamide (6-ANA) to rats and determined an increase in sodium and water in brain tissue. Subsequently [3] by measuring electrical conductivity of the cerebral cortex and electron micrographs, the authors concluded that the metabolic inhibitor produced an intracellular edema and a moderate decrease in the extracellular space. The blood-brain barrier stability seemed to be unaffected.

In an effort to study a form of cerebral edema in which the primary lesion was not at the blood-brain barrier (BBB) level, and with the previous knowledge that different pharmacological steroid preparations may give varying results in the different models [13, 14, 15], the present study was undertaken to analyze the response of the two commonly applied steroids by observing multiple parameters associated with cytotoxic edema of the grey matter.

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TABLE 1
BEHAVIOR(*)

	6-ANA (n=19)	Dexamethasone Sodium Phosphate (1 mg/kg/day) (n=15)	Methylprednisolone Sodium Succinate (5.33 mg/kg/day) (n=15)
Normal examination (no. of animals)	2	7	2
Moderately hypoactive with paraparesis (no. of animals)	6	5	8
Very hypoactive listless paraplegic (no. of animals)	7	3	5
Expired (no. of animals)	4	0	0

*A total of 120 mg/kg of 6-aminonicotinamide (6-ANA) intraperitoneal in 2 successive days, with either dexamethasone sodium phosphate or methylprednisolone sodium succinate. The controls only received 6-ANA. Examination documented on the third.

METHOD

Adult albino rabbits (2–3 kg) were divided into controls, 6-aminonicotinamide (6-ANA) treated, 6-ANA with methylprednisolone, and 6-ANA with dexamethasone groups. Ten rabbits formed the control group, and these were anesthetized with pentobarbital sodium (20 mg/kg) intravenously, tracheostomized, paralyzed with gallamine triethiodide (4 mg/kg) and artificially ventilated on a small animal respirator (Harvard Model 661, Mills, MA) with 70% N_2O and 30% O_2 mixture. Femoral arterial and venous lines were placed and systemic arterial pressure (SAP) continuously recorded through a Statham Model B23D transducer and a Hewlett Packard 2-channel recorder. The animals were placed in a stereotaxic head holder and a single barrel short bevel 20 ga. needle introduced into the cisterna magna and ICP continuously recorded using a similar system to that of SAP. Four screw electrodes were placed in the calvarium, two anteriorly and two posteriorly, and the EEG recorded on an ink-writing Van Gogh (EP-8) electroencephalography unit. Temperature was maintained at 37°C using a heating pad. Frequent measurements of arterial blood gases were made and the $PaCO_2$ was maintained by adjusting the ventilator at 38–42 torr. No animal with a SAP of less than 80 torr was included in the study.

After 20 min of a stable state they were sacrificed using a saturated KCl solution. A craniectomy was rapidly performed and the brain removed. After removing the pia arachnoid, samples of grey matter were dissected from the underlying white matter and placed in pre-weighed, air-tight vials. The vials were reweighed, then dried to constant weight in a heated vacuum dryer at 110°C. The water content was then calculated by the formula: (wet weight–dry weight/wet weight)×100. A measure of cerebral compliance ($\Delta P/\Delta V$) [21, 22, 30] was obtained by the injection of 0.1 ml bolus of sterile saline through the cisternal cannula [26]. The highest pressure recorded immediately after the infusion was subtracted from the resting pressure and this used to express the relative elastance (E_m) in torr.

Nineteen animals received intraperitoneal 6-ANA at a dose of 60 mg/kg/day, over two days, and four expired. In the remaining 15, a behavioral assessment was performed, and subsequently an experimental run similar to that of controls was performed. Two additional groups of 15 animals were studied. In one, 6-ANA (60 mg/kg/day) was simultaneously administered with 5.33 mg/kg/day of methylprednisolone sodium succinate (Solu-Medrol. The Upjohn Company, Kalamazoo, MI). The final group received 6-ANA (60 mg/kg/day) with 1 mg/kg of dexamethasone sodium phosphate (Decadron. Merck, Sharp and Dohme Laboratories, West Point, PA). On the third day, behavioral assessment was performed and then the experimental run was performed, as in the control groups.

Data was then available on behavior, EEG, ICP, E_m and water content of the grey matter, in all groups.

RESULTS

Behavior

Four basic categories of assessment were made: normal behavior and motor function, moderate hypoactivity with paraparesis, very hypoactive (often listless with paraplegia), and death. Four animals in the control group expired whereas no deaths occurred in the steroid treated groups.

Only two animals in the 6-ANA group were noticed to have a normal behavior and motor examination. A similar number was noted for the methylprednisolone treated group whereas 7 of the 15 in the dexamethasone treated group were normal (Table 1).

EEG

The EEG findings were graded as: normal, generalized

TABLE 2

EEG(*)

	Controls (n=15)	Dexamethasone Sodium Phosphate (1 mg/kg/day) (n=15)	Methylprednisolone Sodium Succinate (5.33 mg/kg/day) (n=15)
Normal (no. of animals)	0	7	3
Generalized slowing with high voltage (no. of animals)	2	6	2
Very slow (no. of animals)	8	2	6
Next to flat tracing (no. of animals)	5	0	4

*All 3 groups had 120 mg/kg of 6-aminonicotinamide intraperitoneal over 2 successive days, the recording being performed on the third day.

TABLE 3

WATER CONTENT OF GREY MATTER, ICP AND INTRACRANIAL ELASTANCE (E_m)

	Controls (n=14)	6-ANA (120 mg/kg/total) (n=18)	Dexamethasone Sodium Phosphate (1 mg/kg/day) (n=18)	Methylprednisolone Sodium Succinate (5.33 mg/kg/day) (n=46)
Water	79.99 ± 0.77%	81.73 ± 0.90%(*)	81.49 ± 0.72%(†)	80.74 ± 0.84(‡)
ICP	2.15 ± 1.53 torr	8.70 ± 4.34 torr(*)	4.63 ± 1.03 torr(‡)	4.15 ± 1.33(‡) torr
E_m	2.63 ± 1.27 torr	8.79 ± 5.31 torr	3.90 ± 0.97 torr	4.12 ± 1.36 torr

(*) $p<0.001$ for difference from controls.
(†) $p>0.01$ for difference from 6-ANA.
(‡) $p<0.001$ for difference from 6-ANA.

moderate slowing with high voltage, large slow waves, and essentially flat tracing.

No animal in the 6-ANA group had a normal tracing versus 41% of the dexamethasone treated and 20% of the methylprednisolone group. A next-to-flat tracing was noted in 33% of the controls, 26% of methylprednisolone group and none in the dexamethasone treated group (Table 3).

ICP

The control group's ICP was 2.15 ± 1.53 torr. The ICP in the 6-ANA group was 8.70 ± 4.34 torr and a significant decrease was noted in the methylprednisolone (4.15 ± 1.03) and dexamethasone groups (4.63 ± 1.03) (Table 3).

Elastance Measurement (E_m)

In the control animals the mean E_m was 2.63 ± 1.27 torr. In the 6-ANA group, the mean E_m was 8.79 ± 5.31 torr, whereas in the steroid groups, the E_m was higher than controls but lower than the 6-ANA group, 3.90 ± 0.97 torr for the dexamethasone group and 4.12 for the methylprednisolone (Table 3).

Water Content

The mean water content in the control animals was 79.99 ± 0.77% and in the 6-ANA group 81.73 ± 0.90% ($p<0.001$). In the dexamethasone group the water content was not different from the 6-ANA group (81.49 ± 0.72%), but the methylprednisolone group showed a significant decrease of water content, 80.74 ± 0.84% ($p<0.001$).

DISCUSSION

As previously described by Baethmann *et al.* [2,3], these studies demonstrate a significant edema in the grey matter following the administration of 120 mg/kg of 6-ANA over a two-day period, associated with poor behavior, changes in the EEG, elevation of ICP and poor intracranial elastance. The authors suggested that the possible mechanism of action of 6-ANA was competitive inhibition of NADH electron receptor sites, and thus decreased tissue ATP. This in turn would lead to an energy deficit, interference of the sodium-potassium pumping and ultimate cell swelling. They also showed that the simultaneous administration of nicotinic

acid, theophylline or nicotinic acid alone with 6-ANA, inhibited the cell swelling [2].

The control animals showed a dramatic alteration of level of consciousness, hind leg function and EEG activity (Tables 1 and 2). In the dexamethasone group, just under 50% of the animals presented a normal behavioral and EEG examination, whereas only 15% of the methylprednisolone animals manifested a similar response. On the other hand, intracranial elastance and ICP were significantly below 6-ANA treated values, in both groups (Table 3).

The water content which was significantly higher in the 6-ANA treated over the control animals, was not significantly different in the dexamethasone group from the 6-ANA group, though elevated over control values (Table 3). In contrast, in the methylprednisolone group the water content was significantly lower than the 6-ANA group ($p<0.001$).

It was previously felt by other investigators that the pure anti-edematous effect of steroids is limited while the clinical efficiency is felt to be considerable [23, 28, 29, 41, 43, 44, 46], and the present study supports that concept. The behavioral and EEG changes were far less in the dexamethasone group when compared to the methylprednisolone group, though the latter agent was the only one to significantly reduce the water content in the grey matter (Table 3). It is felt that steroids may improve cell metabolism by improving cell membrane [7,33], and blood-brain barrier integrity [1, 7, 24, 33], improve intracranial elastance [29] and normalize and stabilize cerebral blood flow [46]. However, the intrinsic mechanism of action can only be postulated, and further research is needed.

In another model of cytotoxic edema, that induced by triethyltin administration, behavioral improvement was noted in rabbits [43,44] and rats [41] following the administration of dexamethasone. The water content of the brain was also noted to be significantly reduced with this therapy [41, 43, 44]. In the rats, a reduction of the levels of triethyltin was documented in the brain, blood and liver [41], suggesting a direct effect of dexamethasone on the metabolism of this metal. The authors suggest that this in itself could account for the reduction in mortality and improvement of behavior.

The differing response between the two steroids studied here needs discussion. It has been documented that the pharmacological steroid preparations may differ in their anti-inflammatory response [13], adrenal suppression on oral administration [15], response to inhibition of cobra venom factor induced neutropenia [32], in preventing in animals the effects of nicotinamide deficiency [14], to vary the levels of NAD in livers [14], and to alter the amount of edema fluid in cerebral edema induced by cold lesion [33]. It is therefore not unexpected to see a discrepancy in the response in the agents here studied. What seems most significant has been the better understanding of dose related responsiveness to a given steroid, and the recognition that dosage adjustment has to be constantly revised in reference to the desired effect. Thus dosage increases have been made for the therapy of shock, brain tumors, cerebral edema, and other clinical syndromes.

Methylprednisolone has been noted to have different effects pharmacologicallly when compared to dexamethasone: no sodium retention or edema at pharmacological doses [6, 10, 31, 42], short adrenal suppressive activity [9,40], rapid intracellular penetration [35], higher inhibition of glial tumors [27]. In the combination of these effects together with other unknown actions, we may find the differing response in the present series.

It is very likely that the dosage equivalents of 0.75 mg/kg of dexamethasone versus 4 mg/kg for methylprednisolone employed for this series, though similar in activity for anti-inflammatory response, are not appropriate for the brain. The fact that the anti-edematous effect of methylprednisolone was superior to dexamethasone in these animals indicates that further work is needed in higher dosages for both agents.

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