

THE USE OF CERTAIN HORMONES OF THE HYPOPHYSIS AND ADRENALS IN THE PREVENTION AND TREATMENT OF SHOCK DUE TO PROLONGED COMPRESSION OF SOFT TISSUES

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 49,

No. 6, pp. 35-39, June, 1960

Original article submitted June 27, 1959

Hormone preparations are being increasingly used in surgical practice, especially in the management of shock [1-4, 8, 9, 10].

Nevertheless, the results of experimental and clinical trials of hypophyseal and adrenal hormones in shock, and the indications for their use have been insufficiently studied, and many points in this problem remain controversial. In the treatment of the sequelae of prolonged compression of soft tissues (the crush syndrome), so far as we know these preparations have not been tried.

The object of this research was to study the therapeutic value of the adrenocorticotrophic hormone of the hypophysis (ACTH), cortisone, desoxycorticosterone acetate (DOCA) and noradrenalin in the treatment of shock arising during prolonged compression of the soft tissues.

METHOD

Experiments were carried out on white rats weighing 130-200 g. The soft tissues of both thighs were compressed by the application of special screw-clamps for eight hours. The volume of tissue compressed in each thigh was 5-6 cm³.

The following items were studied: the behavior of the animals, the duration and rate of their survival, the body temperature and the number of eosinophils in the peripheral blood [5]. These indices were determined before, and 16-20, 48 and 72 hours after the application of the clamps. The results obtained were treated statistically.

The dosage of the hormones and the methods of their administration are mentioned in the description of the results.

RESULTS

The total number of experiments was 165, divided into 15 series (Table 1).

In the control experiments, the application of the clamps elicited a violent defensive reaction, which lasted for 1-2 hours. General depression then gradually developed and progressed. The body temperature fell to 35-30° 16-20 hours after application of the clamps, and in some experiments it fell even below 30°. The number of eosinophils was considerably reduced, and in most experiments

they disappeared completely. After 48 hours the changes described had progressed in some animals, and in others a relative degree of normalization was observed (Table 2). Compression of the soft tissues caused necrosis of the skin and muscles of the limbs, as a result of which in the majority of experiments the limbs sloughed off 2-4 days after application of the clamps. From the results of the 50 control experiments, the rate of survival was 24.6% and the duration of survival 32 hours. The presence of marked variations in the resistance to trauma in different branches of rats made it necessary for us to carry out special control experiments in every case.

It is seen from the results in Table 1 that the preliminary intramuscular injection of ACTH for a period of seven days before infliction of trauma (series 2), in a dose of 3 units/kg twice daily, increased the animals' resistance. Six rats of this series actually survived more than 5 days, and the duration of survival of the rest was on the average 55 hours, against a mean survival period of the control animals of 17 hours. The difference between the mean results was statistically significant (probability of not arising by chance 0.970).

In these series of experiments (series 3, 4 and 5) the therapeutic value of ACTH was studied. The drug was injected in various doses (1, 3 and 10 units/kg) one and nine hours after removal of the clamps, and then twice a day thereafter. The rate and duration of survival of the animals receiving ACTH were higher than in the control animals. The best results were obtained when the preparation was given in a dose of 3 units/kg. In this series of experiments a comparatively high survival rate (60%) was observed, together with a relatively long survival period (48 hours). Compression of the limbs caused less severe disturbances than in the animals of the other experimental series. The body temperature after trauma (see Table 2) remained at a higher level; the number of eosinophils 72 hours after trauma had returned to the initial level in the majority of the animals which survived, thus demonstrating the normalization of the functions of the hypophysis-adrenal cortex system. It must be pointed out that large doses of ACTH (10 units/kg) led to a more pronounced hypothermia after the infliction of trauma, by comparison even with the

TABLE 1. Influence of ACTH, Hydrocortisone and DOCA on the Survival Rate and Duration After Infliction of Trauma

Series no.	Series of experiments	No. of animals			Mean duration of survival (in hr)	Probability of significance of difference between mean survival period compared with control
		total	surviving	dying		
Trial of therapeutic and prophylactic action of ACTH						
1	Control.	17	4	13	17± 4,9	0,970 0,987 0,998 0,999
2	Prophylactic admin of ACTH (3 units/kg twice daily)	10	6	4	55± 6,9	
3	Ther. admin. ACTH (1 unit/kg)	15	5	10	39± 7,0	
4	Ther. admin. ACTH (3 units/kg)	15	9	6	43± 6,2	
5	Ther. admin. ACTH(10units/kg)	15	6	9	55± 10,9	
Trial of therapeutic action of hydrocortisone						
6	Control	10	—	10	36± 6,7	0,875
7	Admin. of DOCA (30 mg/kg)	10	—	10	55± 9,3	
Trial of therapeutic action of DOCA						
8	Control	10	6	4	66± 13,8	
9	Admin. of DOCA (2.5 mg/kg)	10	6	4	53± 19,0	
10	Admin. of DOCA (5 mg/kg)	10	3	7	54± 18,7	
11	Control	10	3	7	46± 16,3	
22	Admin. of DOCA (5 mg/kg)	10	2	8	46± 12,8	
Trial of therapeutic action of noradrenalin						
13	Control	10	2	8	33± 6,0	0,998
14	Noradrenalin (0.1 ml)	10	2	8	71± 8,3	
15	The same (0.2 ml)	10	3	7	45± 11,4	

control experiments, which was evidently due to the considerable decrease in the general reactivity of the animals resulting from the action of the drug.

Hydrocortisone was injected intramuscularly in a dose of 30 mg/kg one hour after removal of the clamps, again 8-10 hours later, and subsequently once daily. As a result of the injection of hydrocortisone the condition of the animals improved slightly. Whereas in the control animals the body temperature 20 hours after infliction of trauma had fallen on the average of 21.6°, the temperature of the animals receiving hydrocortisone remained at the level of 30.8°. (The difference is statistically significant.) The duration of survival of the animals receiving hydrocortisone was 55 hours, and that of the controls only 36 hours. Analysis of the results obtained shows that the use of hydrocortisone was less effective than the administration of ACTH for the same purpose. An obvious and characteristic action of the preparation was to decrease edema. Edema in the traumatized limbs of animals receiving cortisone was less marked than in the control animals.

The therapeutic efficacy of DOCA (a 0.5% oily solution) was studied in 50 experiments, 20 of which were controls.

Desoxycorticosterone acetate was injected intramuscularly in a dose of 2.5 mg/kg (series 9) and 5 mg/kg (series 10 and 12), one hour after removal of the clamps, and then once on each successive day after infliction of the trauma. As a result of administration of the drug after trauma, a marked edema of the traumatized tissues developed, and secondary hemorrhages appeared much more frequently after removal of the clamps. In the small dose, the drug had no appreciable effect on the rate and duration of survival of the experimental animals, but in the larger dose (5 mg/kg), on the other hand, it had an adverse effect, lowering the survival rate of the animals after trauma (see Table 1). The body temperature of the animals receiving DOCA was 1.7° lower than in the corresponding control experiments 20 hours after trauma, and 2° lower 48 hours after trauma (Table 2). The eosinophils, as a rule, disappeared completely from the peripheral blood.

Noradrenalin, in a dose of 0.1 ml (1:20,000), had no effect on the survival rate of the animals, although the duration of their survival after infliction of the trauma was appreciably lengthened, on the average from 33 hours to 71

TABLE 2. Changes in the Body Temperature and the Number of Eosinophils in the Peripheral Blood after Infliction of Trauma

Series no.	Series of experiments	Initial findings		Findings after trauma					
				after 20 hrs		after 48 hrs		after 72 hrs	
		body temperature	no. of eosinophils	body temperature	no. of eosinophils	body temperature	no. of eosinophils	body temperature	no. of eosinophils

Trial of therapeutic and prophylactic action of ACTH

1	Control	36,8°	45	35,0°	0	33,1°	265	—	—
2	Prophylactic admin. of ACTH	37,9°	250	36,5°	0	37,4°	0	36,5°	320
3	Ther'ic admin. ACTH (1 unit/kg)	37,8°	280	34,6°	134	31,6°	0	—	—
4	Ther'ic admin. ACTH (3 units/kg)	37,0°	278	35,2°	22	34,8°	45	—	185
5	Ther'ic admin. ACTH (10 units/kg)	37,2°	344	33,6°	—	32,8°	0	36,3°	34

Trial of therapeutic action of hydrocortisone

6	Control	37,5°	78	21,6°	0	—	—	—	—
7	Admin. of hydrocortisone (30 mg/kg)	37,5°	58	30,8°	0	—	—	—	—

Trial of therapeutic action of DOCA

8	Control	36,7°	555	34,2°	10	37,3°	45	35,3°	—
9	Admin. of DOCA (2.5 mg/kg)	37,4°	465	35,1°	22	36,4°	144	35,6°	—
10	Admin. of DOCA (2.5 mg/kg)	36,9°	665	34,5°	0	36,7°	0	35,7°	22
11	Control	37,0°	110	36,2°	0	36,0°	0	—	—
12	Admin. of DOCA (2.5 mg/kg)	37,4°	665	34,5°	0	34,0°	0	—	—

Trial of therapeutic action of noradrenalin

13	Control	37,0°	1200	32,1°	12	—	—	—	—
14	Admin. of noradrenalin (0.1 ml)	37,1°	600	34,3°	12	36,4°	45	35,0°	33
15	Admin. of noradrenalin (0.1 ml)	37,7°	368	30,7°	33	36,6°	0	34,0°	156

hours (the difference between the mean values is significant). In a larger dose (0.2 ml) noradrenalin was less effective. The duration of survival of the experimental animals in this series of experiments was increased by only 12 hours over that of the control animals. Whereas small doses of noradrenalin improved the condition of the animals, large doses of the drug had the opposite effect. For instance, 20 hours after infliction of the trauma, the average body temperature of the animals in the control group was 32.8°, and after administration of noradrenalin in series no. 14 (0.1 ml) 34.3°, and in series no. 15 (0.2 ml) 30.7°. The difference between the mean values of the body temperature in the series in which noradrenalin was given in different doses was statistically significant (the probability of not arising by chance 0.984). Other conditions being equal, according to our observations the change in the body temperature in

small animals after infliction of trauma fairly accurately reflects the degree of severity of the general disturbances.

The results of the work thus showed that ACTH and, to a lesser degree, hydrocortisone improve the animal's condition after infliction of severe trauma, as a result of which the rate and duration of survival of the traumatized animals are appreciably increased. The positive effect of these preparations is evidently due to their anti-inflammatory action and also to their influence on the permeability of the vascular walls, as a result of which the development of massive edema of the traumatized tissues is prevented.

In contrast to this, DOCA, which is a relative antagonist of the glucocorticoids, does not improve the condition of the traumatized animals but, on the contrary, in large doses it aggravates it.

Noradrenalin maintains the vascular tone and lengthens the survival period of the animals. These findings are in agreement with clinical observations showing the value of noradrenalin in shock [6, 7].

SUMMARY

Experiments were performed on 165 rats. The therapeutic efficacy of ACTH, hydrocortisone acetate and noradrenalin was tested in prolonged crush-syndrome. Special clamps were applied to the thigh for a period of 8 hours.

Prophylactic and therapeutic administration of ACTH improved the condition of the animals; as a result of this, survival rate and the life span were considerably increased. Cortisone also improved the state of the animals and lengthened their lives. Analogous results were obtained in noradrenalin administration. DOCA aggravated the animals' condition by increasing edema of the injured tissues and hemorrhages. In large doses DOCA exerted a negative effect on the survival and the life span of experimental animals.

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