ON THE USE OF ACTH FOR THE TREATMENT OF TRAUMATIC SHOCK

(UDC 616-001.36-085.814.3)

Yu. N. Tsibin

Laboratory of Experimental Surgery (Head—Professor M. G. Shraiber)
and Laboratory of Pathological Physiology (Head—Candidate of Medical
Sciences, S. A. Seleznev), I. I. Dzhanelidze Leningrad Scientific Research
First-Aid Institute (Director—Professor G. D. Shushkov)
(Presented by Member of the Academy of Medical Sciences USSR, S. V. Anichkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 58, No. 11,
pp. 36-39, November, 1964
Original article submitted May 7, 1963

The opinion of exhaustion of the adrenal cortex during shock, advanced by Corbett [6], Reed [12], and other authors, has recently been subjected to serious criticism [5, 7, 9].

The question of the possibility of using ACTH for the treatment of shock is closely related to the problem of the functional state of the adrenal cortex during traumatic shock. One of the first studies along this line was the investigation of Smith and D'Amour [16]. ACTH, used by the authors in experiments for the treatment of lethal traumatic shock, has proved more effective than cortisone and adrenocorticotropic extract. In the experiments of V. K. Kulagin, ACTH, used for therapeutic purposes in severe traumatic shock, gave a better effect than hydrocortisone. However, I. D. Kudrin [1] generally was unable to detect any favorable action of ACTH when it was used in a complex treatment of pleuropulmonary shock. Phillips and Cohen [11], considering the cause of operative shock to be acute adrenal insufficiency, recommend intravenous injection of hydrocortisone, rather than ACTH, as a means of pathogenic therapy. The same indications may be encountered in the work of Scherer [15].

PROCEDURE

In the first series of experiments, traumatic shock was induced in cats by pulsed current (voltage 300 V, duration of stimulus 0.1 m sec, frequency of pulses 4 per second), delivered to the right paw of the animal. The therapeutic effect of the preparations used was checked during light and severe shock, as well as in the terminal state. ACTH in a dose of 12 units and cortisone in a dose of 12 mg were injected intramuscularly in the case of light shock, and intravenously in the case of severe shock and in the terminal state. Dropwise intravenous administration of noradrenalin (1 mg per 125 ml of physiological solution), was used only in the terminal state.

In the second series of experiments, we used the model of traumatic shock according to Cannon, with the application of 180 shocks along the soft tissues of the right femur of the animal. Hormone treatment was begun in the erectile phase of shock: ACTH in a dose of 12 units and cortisone in a dose of 12 mg were injected intravenously in one group of experiments, and intraarterially in another (into the central end of the femoral artery under pressure).

The indicated doses of the hormone preparations, which were used in both series of experiments, were equivalent to the doses used in the clinic and were calculated considering the formula of Bazett and Erb [3].

RESULTS

Shock induced in cats by stimulation with pulsed current, depending on its severity, was distinguished as light and severe. In addition, we distinguished the terminal state, in which we conducted part of our investigations.

Light shock was characterized by a reduction of the arterial pressure to a level comprising an average of 60% of the initial; the duration of the stimulation was 41±3.3 min; 7 out of the 17 control animals died.

In severe shock, the arterial pressure was lowered to a level comprising an average of 40% of the initial; the duration of the stimulus was 61±5.3 min; 12 of the 13 control animals died.

TABLE 1. Effect of Hormone Therapy for Shock Induced in Cats by Stimulation with Pulsed Current

Severity of shock	Preparation used	Method of introduction	Number of animals			Reliability of differences from data on control group
			Total	Survived	Died	
Light	ACTH	Intramuscularly	14	14	0	<0.05
	Cortisone	The same	10	8	2	<0.05
	Control series	–	17	10	7	–
Severe	ACTH	Intravenously	10	8	2	<0.05
	Cortisone	The same	9	6	3	<0.05
	Control series	–	13	1	12	–
Terminal state	ACTH	Intravenously	4	0	4	>0.05
	Cortisone	"	3	0	3	>0.05
	Noradrenalin	"	11	0	11	>0.05
	ACTH with noradrenalin	"	8	2	6	<0.05
	Cortisone with noradrenalin	"	7	1	6	>0.05
	Control series	–	17	0	17	–

TABLE 2. Effect of Hormone Therapy of Shock Induced in Cats by Crushing of the Muscles of the Femur

Preparation used	Method of introduction	Number of animals			Reliability of differences from data on control group	Lifetime (in h)	Reliability of differences from data on control group
		Total	Survived	Died			
ACTH	Intravenously	5	0	5	$P>0.05$	6.4±2.4	$P=0.05$
"	Intravenously	8	6	2	$P<0.05$	–	–
Cortisone	Intravenously	7	0	7	$P>0.05$	7.6±2.9	$P<0.05$
"	Intraarterially	6	0	6	$P>0.05$	17.7±2.5	$P<0.01$
Control series	–	15	1	14	–	1.3±0.26	–

The terminal state was characterized by a lowering of the arterial pressure to a level comprising an average of 15% of the initial. Third-order waves were recorded on the kymographic curve of the arterial pressure; sharp disorders of the respiration were observed, which represented single spasmodic inhalations, separated by prolonged pauses; the duration of the stimulus was 59±3.9 min; all 17 of the 17 control animals died; the average lifetime was 1.2±0.1 h.

As it follows from the data cited in Table 1, the use of ACTH protected all 14 animals with light shock from death. The use of cortisone for the treatment of shock of the same severity, although increasing the survival rate of the experimental animals in comparison with the control group, did not do so to the same degree as in the use of ACTH: 8 of the 10 cats survived.

The use of ACTH for the treatment of severe shock also gave somewhat better results than treatment with cortisone.

The use of intravenous injections of ACTH and cortisone for the treatment of shock in the terminal phase proved fruitless: death set in just as rapidly as in the animals of the control series, evidently before the ACTH or cortisone was able to manifest its action. The latter circumstance led to the idea of using simultaneous injection of ACTH or cortisone with noradrenalin for the treatment of shock in the terminal phase. As the results of a separate series of experiments using noradrenalin in the terminal state showed, this drug substantially lengthens the duration of this phase, without thereby increasing the survival rate of the animals: all 6 cats died.

In the combined use of intravenous injection of noradrenalin and ACTH for the treatment of shock in the terminal phase, two of the right cats survived, while in the case of the use of noradrenalin with cortisone, one out of seven cats survived (see Table 1).

In the second series of experiments, we studied the comparative action of ACTH and cortisone in the case of intravenous and intraarterial injection during the period of the erectile phase.

In numerous experiments conducted in the Pathophysiological Laboratory of the Institute, it was established that the trauma used in the experiments (180 shocks) is lethal: in the control experiments, 14 out of 15 cats died; the average lifetime was 1.3 ± 0.26 h.

The intraarterial injection of ACTH, which, as follows from Table 2, substantially increased the survival rate of the animals, both in comparison with the control series and in comparison with the series of experiments in which intraarterial injection of cortisone was used, proved the most effective (the differences are statistically reliable: $\chi^2 = 4.4$; $P = 0.05$).

The intravenous injection of ACTH and cortisone, as well as the intraarterial injection of cortisone only increased the lifetime of the experimental animals, without increasing their survival rate.

The idea that in traumatic shock the cortical layer of the adrenals is exhausted is disputable. A study of the indices of the functional state of the adrenal cortex, conducted by a number of researchers, has shown that the adrenal activity is increased during shock. The favorable results of the use of ACTH for the treatment of traumatic shock, obtained in our observations, give indirect evidence of the absence of exhaustion of the adrenal cortex during shock.

Of special interest is the more pronounced therapeutic effect of ACTH in comparison with the therapeutic action of cortisone, which was revealed in our experiments on cats. Evidently this is due to the fact that after the injection of ACTH, the adrenal cortex secretes not only hydrocortisone, but also a number of other hormones, which may be of significance in the protective reactions of the organism [16].

The results of the treatment of shock in the terminal phase, obtained in the simultaneous injection of ACTH or cortisone with noradrenalin, are probably explained by the fact that noradrenalin, which lengthens the agonal period to a considerable degree, makes it possible to gain time for the manifestation of the antishock action of ACTH or cortisone. The possibility of a potentiating influence of ACTH and cortisone with respect to the hypertensive action of noradrenalin still remains [8], although some researchers cast doubts upon a relationship of this type [13, 14].

We have found no indications in the literature devoted to questions of the hormone therapy of shock on the possibility of the intraarterial administration of hormones. The pronounced therapeutic effect of the intraarterial injection of ACTH during shock is difficult to explain. Evidently in this case a great role is played by the so-called peripheral or extraadrenal action of ACTH. According to the data of Berliner [4], independent of the presence of the adrenals, ACTH inhibits decomposition of glucocorticoids in the tissues, guaranteeing their economical consumption. Data are available on an extraadrenal action of ACTH on the carbohydrate metabolism [10].

LITERATURE CITED

1. I. D. Kudrin, Khirurgiya, 12 (1958), p. 20.
2. V. K. Kulagin, Voen.-Med. Zh., 7 (1961), p. 34.
3. H. C. Bazett and W. H. Erb, J. Pharmacol. Exp. Ther., 49 (1933), p. 352.
4. D. L. Berliner, N. Keller, and T. F. Dougherty, Endocrinology, 68 (1961), p. 621.
5. I. Carr, J. Path. Bact., 78 (1959), p. 533.
6. I. F. Corbett, J.A.M.A., 65 (1915), p. 380.
7. D. M. Hume and D. H. Nelson, Surg. Forum., 5 (1955), p. 568.
8. G. S. Kurland and A. S. Freedberg, Proc. Soc. Exp. Biol., 78, New York (1951), p. 28.
9. K. Markley, M. Bocanegra, E. Ego-Aguirre, et al., Surgery, 47 (1960), p. 389.
10. N. B. Marshall, F. L. Richardson, and F. L. Engel, Acta endocr., 41, Kbh. (1962), p. 227.
11. L. A. Phillips and R. I. Cohen, Anaesthesia, 14 (1959), p. 270.
12. F. R. Reed, Am. J. Surg., 40 (1938), p. 514.
13. M. M. Reidenberg, E. A. Ohler, and R. W. Sevy, Proc. Soc. Exp. Biol., 97, New York (1958), p. 889.
14. E. J. Ross, Quart. J. Med., 30 (1961), p. 285.
15. G. Scherer, Med. Klin., Bd. 52, S. 308 (1957).
16. D. L. Smith and F. E. D'Amour, J. Pharmacol Exp. Ther., 106 (1952), p. 429.