# THE EFFECT OF CORTISONE UPON TYPHOID INTOXICATION IN RABBITS

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During infectious illnesses medicines not possessing antibacterial actions are used at times as, for example, antihistamines and hormones, the goal sought being the alleviation of the manifestations of intoxication or the blockade of tissue pathological reactions.

From the literature, it is known that cortisone exacerbates the clinical course of tuberculosis [9,15], spirochetoses [16], mycoses [20] and many other infections. We established that cortisone speeds the clinical course of rabbit pneumococcal infections, hastening their death [4]. The question arises as to the reason for this negative influence of the cortisone upon so many infections: is it that it depresses those factors which act as barriers to the multiplication of the infectious agents within the organism or is it that it suppresses those mechanisms which prevent the intensification of developing intoxications?

Z.A. Ertuganova showed that cortisone suppresses the ability of the endothelial-macrophagic system to have its cells destroy the engulfed bacteria [5]. This fact may be one of the reasons why cortisone hastens the course of the infection and hasten the dissemination of the bacteria. Alongside with this observation, some authors have observed that cortisone lowers the febrile response in patients with typhoid fever and in animals in response to typhoid vaccine [13]. V.I. Goncharova showed that cortisone diminishes the percentage of deaths in mice and prevents the death of rats during the course of typhoid intoxication [1]. The author attributes this fact to increased resistance to the bacterial intoxication on the part of the organism receiving cortisone.

Having been convinced that cortisone intensifies the severity of rabbit pneumococcal infection [4], we set ourselves the goal of determining the effectiveness of the preparation in a pathological situation where there was only the factor of intoxication, the living microbial agent having been excluded. For this purpose we used the method of producing typhoidal intoxication in rabbits.

## EXPERIMENTAL METHODS

The experiments were performed on 28 rabbits weighing an average of 2.2 kg, the animals being divided into four equal groups. The first group received only typhoid vaccine, the second was given cortisone and typhoid vaccine, the third group was given cortisone only and the fourth group received physiological saline. The animals in the first two groups received in the ear veins a slow injection of warmed typhoid vaccine prepared from laboratory strain B. Typhoides abdominis #4446, the dose being 25 billion microbes per 1 kg body weight. Biddle, Sawyer & Co. cortisone acetate was used. The cortisone was given intramuscularly as 5 mg per 1 kg body weight, this dose being repeated twice daily until the death of the animal. The first injection was given 30 minutes prior to the injection of the typhoid vaccine. The physiological saline was given in the amount of 0.1 cc and administered in the same sequence as cortisone.

Blood sugars in the rabbits were done by the method of Hagedorn-Jensen; adrenalin in the blood and adrenals by the Utevsky method; while ascorbic acid content of blood and adrenals was determined by titration with 0.02% solution of 2, 6-dichlorphenolindophenol.

The blood for the determinations was taken from the ear vein of the fasting animal prior to injection of cortisone or typhoid vaccine, 24 hours after the injection of the vaccine if the animal was still alive and also at the moment of death. Two rabbits in the first group and 3 in the second which were in very poor condition were killed by means of air emboli. The rabbits of the 3d and 4th group were killed by means of air emboli in the same time intervals at which the animals of the 2d group died.

Immediately on the death of the animal , the adrenals of the animal were taken out and weighed, after which they were ground in quartz sand and prepared for further studies by having the proteins extracted with the aid of 10% solutions of trichloroacetic acid.

## EXPERIMENTAL RESULTS

The experiments of this investigation indicate that cortisone delays rabbit deaths resulting from typhoid intoxication an average of 38 hours (Table 1). It follows that cortisone did not suppress the mechanisms producing resistance to typhoid intoxication.

TABLE I

Survival Rate of Animals Subjected to Typhoid Intoxication and Both Treated and Untreated with Cortisone

| Preparation introduced | Total number of rabbits | Number of rabbits dying after | | | | | | | | sacrificed after | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 8 | 10 | 14 | 15 | 23 | 40 | 44 | 99 hrs. | 32 | 48 | 89 | 90 hrs. |
| Typhoid vaccine | 7 | 1 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Cortisone and typhoid vaccine | 7 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |

The normal blood sugar in rabbits is 108-117 mg %. In the first group the blood sugar level in the first 24 hours of observation remained normal.. In the rabbits of this group, dying at later times, there was noted a hyperglycemia, the concentration of the sugar rising 2- $2\frac{1}{2}$ times over the base figures reaching 267 mg %, 218 mg %.

When cortisone was administered, hyperglycemia was observed within a day of introduction of the typhoid vaccine. Only in 2 rabbits of the second group (in one, at the moment of death) did the sugar concentration in the blood not rise within the first day. Subsequently, all the rabbits developed hyperglycemia. Compared with base level, blood sugars rose $1\frac{1}{2}$- 2 fold. Giving cortisone to healthy rabbits caused blood sugars to rise $1\frac{1}{2}$-2 times as compared with beginning readings. It follows that cortisone did not substantially affect blood sugar levels produced by typhoid intoxication as it produced hyperglycemia also in healthy rabbits.

The normal rabbit blood adrenalin concentration averages 0.027 mg %, fluctuating between 0.011 and 0.036 mg %. In the first day of observation, the rabbits of the first group maintained an adrenalin level within normal limits averaging 0.026 mg %. Rabbits of this group sacrificed in the second day or later had a 2-$2\frac{1}{2}$ fold adrenalin rise averaging between 0.063 and 0.047 mg % and being in agreement with similar data for the fourth animal group. In this fourth group of rabbits all indicators remain unaltered during the course of the experiment.

In rabbits of the second group hyperadrenalinemia was observed within the first day averaging 0.049 mg %. In the second day the adrenalin concentration in the blood attained still greater figures averaging 0.063 mg %; this level was also above normal averaging 0.044 mg % in rabbits dying at later times. Cortisone injected into healthy rabbits did not produce appreciable changes in the adrenalin content of the blood.

TABLE 2

Alterations in Adrenalin Content of Rabbit Adrenals Receiving Cortisone during Typhoid Intoxication

| No Group | Preparation being injected | Number of rabbits | Amount of adrenalin in the adrenals (in μg) | | | Weight of adrenals (in mg) per 1 kilogram body weight |
|---|---|---|---|---|---|---|
| | | | in 1 mg of tissue | in both adrenals | per 1 kg of body weight | |
| 1 | Typhoid vaccine | 7 | 0.041±0.009 | 13.08±2.00 | 6.19±1.27 | 197.80±19.53 |
| 2 | Cortisone and typhoid vaccine | 5 | 0.055±0.010 | 14.47±2.26 | 8.27±1.32 | 176.49±22.47 |
| | | 1 | 0.175 | 58.28 | 37.60 | 214.84 |
| | | 1 | 0.143 | 48.76 | 23.56 | 164.73 |
| 3 | Cortisone | 7 | 0.141±0.016 | 26,29±3.02 | 12.86±1.88 | 94.24±15.60 |
| 4 | Physiological saline (control experiment) | 7 | 0.131±0.017 | 37.37±3.02 | 15.90±3.05 | 116,96± 8,22 |

TABLE 3

Alterations in Ascorbic Acid Content in Rabbit Adrenals Receiving Cortisone during Typhoid Intoxication

| No Group | Preparation being injection | Number of rabbits | Amount of ascorbic acid in adrenals in μg | | | Weight of adrenals (in mg) per 1 kilogram body weight |
|---|---|---|---|---|---|---|
| | | | in 1 mg of tissue | in both adrenals | per 1 kg of body weight | |
| 1 | Typhoid vaccine | 7 | 0.66±0.077 | 251.82±70.41 | 115.68±22.43 | 197.80±19.53 |
| 2 | Cortisone and typhoid vaccine | 7 | 0.79±0.15 | 263.27±64.28 | 146.55±34.22 | 180.28±16.37 |
| 3 | Cortisone | 7 | 1.12±0.017 | 215.42±40.5 | 108.97±17.74 | 94.24±15.60 |
| 4 | Physiological saline (control experiment) | 7 | 1.84±0.16 | 353.10±33.77 | 223.82±13.21 | 116.96± 8.22 |

The average data on the adrenalin determinations in the adrenals is given in Table 2. Table 2 shows that adrenalin sharply diminishes in the adrenals as a result of typhoid vaccine administration, in spite of their increased weight. The adrenalin content of the adrenals was $2\frac{1}{2}$ to 3 times less while the weight of the glands was $1\frac{1}{2}$ times greater in the animals of the first group as compared with animals of the fourth group. In 5 rabbits of the second group the adrenalin content in the ardrenals was about 2 times lower than in animals of the fourth group, although somewhat higher than in animals of the first group. In 2 rabbits of the second group the cortisone fully prevented adrenalin depletion in the adrenal glands under the influence of typhoid vaccine. The corresponding adrenalin indicators were somewhat higher in them than in the fourth group (see Table 2) which may be attributed to individual fluctuations. When cortisone is administered to healthy rabbits, the adrenalin content of the adrenals remains unchanged while the weight of the glands diminishes slightly.

It follows that introduction of cortisone during typhoid intoxication did not interfere with the rise of adrenalin in the blood and exerted no appreciable influence on the decrease of the adrenalin in the adrenal glands of the majority of the rabbits. Giving the cortisone to healthy rabbits did not materially alter the adrenalin concentration in the blood and adrenals, although slightly decreasing the weight of the glands.

The ascorbic acid concentration in the blood of normal rabbits averages 0.35 mg %. In rabbits of the first group there was observed a tendency for a rise in the concentration of the ascorbic acid. In the second group of animals the concentration of the ascorbic acid did not alter in the first 24 hours, averaging 0.33 mg % but was above normal in rabbits dying in the second day, averaging 0.97 mg % and, still later, 0.6 mg %. In the third group there was noted a rise in the ascorbic acid of the blood, being about 2 fold the base level, as well as in rabbits sacrificed in the second day and later.

The averages on the ascorbic acid adrenal gland contents are presented in Table 3. Under the influence of the typhoid vaccine the adrenal content of the ascorbic acid falls sharply. In rabbits of the first group the ascorbic acid content of the adrenal averages some $1\frac{1}{2}$ to 2 times less than in rabbits of the fourth group. The adrenals of the rabbits of the second group had about the same amount of ascorbic acid as the adrenals of the rabbits of the first group. The adrenals of healthy rabbits receiving cortisone had 40-50% less ascorbic acid than the adrenals of the control animals. Thus, it appears that cortisone raised the ascorbic acid concentration in the blood and diminished the adrenal content in healthy rabbits but had no influence on the quantitative changes of ascorbic acid in the blood and suprarenals of animals during typhoid intoxication.

## DISCUSSION OF RESULTS

The delay produced by the influence of cortisone in the death of the animals as a result of typhoid intoxication may be due to two reasons: decreased permeability of the walls of the blood vessels and tissues and the antihistaminic action of cortisone. This latter diminishes the permeability of blood vessel walls [2, 7] and tissues [6,8,11,12,14,17,18] which, apparently, decreases the rate at which the intravenously administered typhoid endotoxin leaves the blood to enter the tissues.

The antihistaminic action of cortisone is manifested by its ability to activate histaminase [19] and, in the opinion of some authors, by the hindering of histamin formation [10]. These important properties of cortisone determine its role in the pathogenesis of intoxication as histamin and histamin-like substances forming in the organism as a result of endotoxin action are determining factors in some of the manifestations of intoxication [3].

The influence of cortisone in preventing adrenalin loss from the adrenal glands of rabbits intoxicated with typhoid vaccine may be attributed to the antihistaminic properties of the preparation. This effect is less evident with typhoid intoxication than with pneumococcal intoxication where the cortisone completely prevents adrenalin depletion in the glands keeping the actual levels within normal limits. The differences between the influence of cortisone during typhoid and pneumococal intoxication may be explained by the fact that, in the first instance, the blood receives a lethal dose of the endotoxin and all its manifestations develop quite rapidly, within a few hours, while with pneumococcal infections the intoxications develop more slowly requiring several days. It is also quite probable that the inhibiting effect of cortisone on adrenalin depletion in the adrenal glands may be different in pneumococcal infection from typhoid intoxication because of the specific actions of the toxin.

## SUMMARY

The introduction of cortisone in the dose of 5 mg per kilogram of body weight to rabbits twice a day in lethal typhoid intoxication prolonged the life of these animals up to 38 hours, on the average. However, it had no effect on the disturbance of the sugar concentration, blood level of adrenalin and the level of ascorbic acid in the blood and suprarenal glands. It had a certain retarding effect on depletion of adrenalin in the suprarenal glands.

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