

THE EFFECT OF URETHANE ON THE LYMPHOID ORGANS AND ON THE SUSCEPTIBILITY OF WHITE MICE TO TYPHOID FEVER POISONING

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According to many workers narcosis inhibits the development of several infections [4, 5, 6 and 2]. Drug-induced sleep in rabbits inhibits the development of local staphylococcal infection, smallpox and rabies and at the same time it aggravates the course of pneumococcal septicemia, tetanus infection (on infection with spores) and tetanus toxemia [7].

According to the findings of Alaverdian [1], local anesthesia with novocain and general barbiturate narcosis reduce the area of spread of the inflammatory reaction in the skin of experimental animals caused by staphylococcal autolyzate.

In the present work we studied the effect of urethane on the lymphoid organs and the susceptibility of white mice to typhoid fever poisoning.

In the first part of our work we studied the change in weight of the organs of white mice under the action of urethane.

EXPERIMENTAL METHOD

The investigations were made on white mice weighing 17-18 g. Urethane was injected subcutaneously twice a day in doses from 0.25 to 7.5 mg per injection.

At various intervals after injection of urethane the animals were killed. The liver, spleen, axillary glands, adrenal glands and thymus were weighed on spring scales and the weight of each organ calculated as a percentage of the total body weight of the animals. The results obtained were compared with the weights of these organs in normal mice not receiving urethane. The weights of the organs of normal animals were taken as 100 %.

EXPERIMENTAL RESULTS

Four series of experiments were carried out (with 10 mice in each series). Each mouse received a daily subcutaneous injection of 0.5, 5, 10 or 15 mg of urethane. As a result of the urethane, on the 3rd-4th day the weight of the thymus and spleen decreased. The weights of the remaining organs did not always decrease during this time and in some cases they even increased.

As seen in Fig. 1, the weight of the thymus decreased by 75 % on injection of 10-15 mg of urethane, by 50% on injection of 5 mg and by 25 % on injection of 0.5 mg.

The weight of the spleen decreased by 75 % on injection of 15 mg of urethane, by 50 % on injection of 10 mg. In smaller doses, urethane had no effect on the weight of the spleen.

The action of urethane on the weight of the lymphoid organs is thus the same as that of cortisone and other corticosteroids [10].

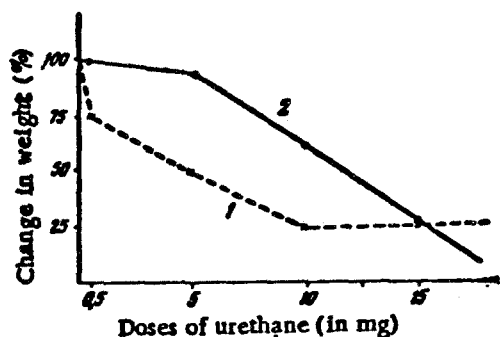


Fig. 1. Change in weight of the thymus and spleen due to urethane.

1) Weight of thymus; 2) weight of spleen.

As in the preceding experiments, as a result of the injections of urethane into the unoperated mice the weight of the thymus decreased by 75 %. Injection of urethane into the operated mice decreased the weight of the thymus by 33 %. The weight of the thymus of the operated mice, not receiving urethane, increased by about $1\frac{1}{2}$ times. The same effect of urethane was shown by the spleen (Fig. 2).

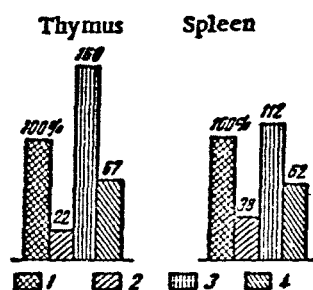


Fig. 2. Change in the weight of the thymus and spleen due to urethane given to normal and adrenalectomized mice.

1) In normal mice; 2) in normal mice receiving urethane; 3) in adrenalectomized mice; 4) in adrenalectomized mice receiving urethane.

taining 3×10^9 bacterial bodies. Urethane, in a dose of 10 mg per mouse was injected subcutaneously at the same time as the vaccine or 4-5 hours afterwards. Cortisone was injected intramuscularly at the same time as the vaccine in a dose of 0.1 mg per mouse.

In series I (control) the mice were injected with typhoid vaccine alone, without urethane.

In series II, 10 mg of urethane was injected at the same time as the vaccine, and this was continued for the following 3-4 days in a dose of 10 mg twice daily.

In series III, the administration of urethane in the same dosage began 4-5 hours after the injection of vaccine and was continued for the following 3-4 days.

In order to discover whether urethane acts directly on the thymus and spleen or whether its action is effected through the adrenal glands, experiments were performed on 30 white mice. These mice were divided into 3 groups, 10 in each.

From the mice of the first and second groups the adrenals were extirpated, after which the mice of the first group were injected with urethane in a dose of 10 mg twice a day. The total dose of urethane per day was 20 mg. The mice of the second group did not receive urethane.

The unoperated mice of the third group received injections of the same doses of urethane. After 3 days all the mice were killed and the weights of the thymus and spleen were studied.

It may be suggested that urethane acts not only directly on the thymus and spleen but also, by stimulating the adrenal cortex, causes secretion of a large amount of corticosteroids, the action of which is added to that of urethane and thereby causing still greater decreases in the weight of these organs.

In the second part of the work we ascertained whether urethane is like cortisone in raising the resistance of mice to typhoid poisoning. As an additional control in this group of experiments we set up a series in which the animals were injected with cortisone. We know from the literature [8, 9] and also from our own investigations [3] that cortisone, injected simultaneously with a bacterial vaccine, increases the resistance of the animals to a toxic dose of the vaccine. In order to solve this problem we set up 4 series of experiments on white mice, with 20 in each series.

The investigations were carried out on white mice weighing 17-18 g. Typhus poisoning was produced by administration of a typhoid culture (strain 265), killed by heating to 56-58° C for 1 hour. In all cases the killed culture was injected intraperitoneally in a volume of 0.5 ml, con-

In series IV (control), 0.1 mg of cortisone was injected intramuscularly at the same time as the vaccine (see Table).

EXPERIMENTAL RESULTS

The results of these experiments are shown in the Table.

The Effect of Urethane on the Resistance to Typhoid Poisoning of White Mice

No. of experiment	Series of experiments	Number of mice	Date of injection of vaccine	Time of death (in days)					Number of mice surviving
				1	2	3	4	5	
				Number of mice dying					
40	I	20	5/29	14	2	—	—	—	4
40	II	20	5/29	12	2	—	—	—	6
	III	20	5/29	14	0	—	—	—	6
40	IV	20	5/29	4	0	—	—	—	16

While in series IV of the experiments 16 of the 20 mice injected with cortisone simultaneously with the vaccine survived, in control series I only 4 mice survived. In series II and III, i.e. in experiments with mice receiving urethane injections, 6 mice survived in each group, and the rest died in the first two days after the injection of the vaccine.

On repeating this experiment two further groups of 10 mice each were added. In one group, each animal was injected with 10 mg of urethane daily, in the other, with 0.1 mg of cortisone 3-4 days before the injection of vaccine and for 3 days afterwards. As before, the greatest number of deaths was observed among mice treated with urethane.

Thus the injection of mice with urethane in these doses resulted in a considerable reduction in the weight of the thymus and spleen and did not improve the course of typhoid poisoning.

Reduction of weight of these organs was observed to a greater degree in normal mice than in adrenalectomized mice. We may suppose that urethane has a destructive action, both directly on lymphoid tissue and through the adrenal cortex, stimulating the secretion of corticosteroids.

Both in the previous experiments with cortisone [3] and in the present experiments the protective effect of this drug was established in experimental bacterial poisoning.

In experiments with urethane we were unable to observe a similar effect, in spite of the outward resemblance in the action of these two substances on the lymphoid organs. On the contrary, prolonged administration of urethane lowered the resistance of the animals to bacterial poisoning.

This increased susceptibility is evidently due either to disturbance of adrenal function as a result of excessive stimulation from the effect of urethane, or to destruction of the lymphoid organs, whose importance has not yet been finally elucidated.

SUMMARY

Urethane does not cause protective effect in experimentally induced typhoid fever intoxication. Prolonged use of urethane in the doses of 20 mg per mouse, weighing 17-18 g; decreases the resistance of the animals to subsequent bacterial intoxication. Subcutaneous introduction of urethane in the dose of 0.5 mg per mouse during 3 or 4 days results in decrease of the weight of the thymus gland, while the dose of 10 to 15 mg causes reduction in the weight of the spleen. This effect is reached both in normal mice and in adrenalectomized ones.

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* In Russian.