EFFECT OF FREQUENCY OF INJECTION ON THE TOXIC ACTION OF FURFURAL

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Under certain conditions daily injection of furfural into albino mice and rats produces a lower mortality than injection of the same compound on alternate days, although the total dose of the poison was twice as great in the first case as in the second. Daily injection of furfural is accompanied by increased xanthine oxidase activity, whereas the activity of this enzyme is inhibited if furfural is injected on alternate days.

There is extensive evidence in the literature concerning the dependence of the toxic action of a poison on its dose and on the frequency of its administration. It has been shown, for instance, that small doses of naphthol yellow S, if given frequently, are more dangerous to the body than larges doses given at infrequent intervals [5]. Quantitative studies have involved determination of the coefficient of cumulation of poisons, i. e., the ratio between the total dose producing a certain effect when given subdivided into fractions and the dose producing the same effect if given all at once [3]. Also relevant to this problem is the investigation of D. S. Sarkisov et al. [1], who found that, following injection of a poison (CCl_4) into albino mice on alternate days, fewer animals died than if the same dose was given once every two weeks. Despite the fact that the total dose of CCl_4, when administered every other day, was about 6 times greater than when it was given once every two weeks, the mortality among the animals in the first case was less than in the second. This paradoxical result was explained by assuming that a certain rhythm of injection of the poison corresponds to a certain intensity of reparative regeneration, compensating for the harmful action of the chemical compound.

In the case of CCl_4, the less frequent injection of the poison induced a lower intensity of regeneration than its more frequent injection [2].

If this effect is not applicable only to the action of CCl_4, it can be postulated that the intensity of reparative regeneration and the increase in synthesis of protein and adaptive enzymes responsible for detoxication of a given poison are closely connected with the rhythm of that substance.

This problem has been investigated in experiments with the cyclic aldehyde furfural, which was injected at different frequencies. At the same time, estimations were made of the activity of xanthine oxidase, an enzyme responsible for conversion of aldehydes [4].

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on male albino mice weighing 18-22 g and male albino rats weighing 150-200 g. Furfural was injected subcutaneously into the albino mice at different times in a dose of 150 mg/kg, or approximately 0.7 LD_{50}. When determined by the probit analysis method, LD_{50} was 200 mg/kg. Furfural was injected intraperitoneally into the albino rats at different times in a dose of 70 mg/kg body weight, or about 0.6 LD_{50}. When determined by the probit analysis method, LD_{50} was 120 mg/kg.

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TABLE 1. Effect of Furfural on Mortality of Albino Rats and Mice in Relation to Frequency of Its Injection

Animals	Frequency of injection	Total dose per animal, mg	Number of animals		P
			total	dying	
Albino mice	Every other day	75,0	25	20	0,05
	Daily	150,0	25	14	
	Control	—	15	0	
Albino rats	Every other day	273,0	15	10	0,05
	Daily	546,0	15	4	
	Control	—	15	0	

TABLE 2. Effect of Furfural on Liver Xanthine Oxidase Activity of Albino Mice in Relation to Frequency of Its Injection

Frequency of Adminstration	No. of animals	Xanthine oxidase activity, mmoles xanthine/h/g liver	P (compared with control)
Control	7	19,30±0,27	
Twice a week	5	16,1±0,24	0,001
Every other day	5	15,30±1,4	0,03
Daily	5	20,3±0,2	0,015

Control animals received injections of distilled water. The mortality of the animals was recorded. The liver xanthine oxidase activity of some of the control and experimental albino mice was determined 20 days after the beginning of the experiment by Litwack's colorimetric method [6]. Injection of furfural into albino mice and rats in equal doses, but at different frequencies, showed that if the poison was injected daily the mortality was lower than if injected less frequently (every other day), despite the fact that the total dose of poison in the first case was twice as high as in the second (Table 1).

The experiments with furfural thus confirmed the observation [1, 2] that, with definite doses, an increase in frequency of administration may not only not increase, but actually reduce, the mortality among the animals.

For furfural in the doses selected, this effect was observed if the compound was injected daily. Evidently each substance has its own characteristic rhythm of action, at which the greatest degree of intensification of intracellular compensatory processes, minimizing the toxic effect, takes place.

Investigation of the liver xanthine oxidase activity of albino mice receiving furfural showed that daily injection of the poison increased the activity of this enzyme, which plays a role in aldehyde metabolism. During the less frequent injection of the poison (on alternate days), inhibition of xanthine oxidase activity was observed. The results of these experiments are given in Table 2.

These results suggest that the severity of the toxic effect of a poison, if administered repeatedly, depends not only on the dose and duration of administration, but also on the degree of intensification of reparative regeneration and of synthesis of protein and adaptive enzymes, which are connected to some degree with the rhythm of administration of the chemical stimulus. It is therefore possible to have conditions under which the intensity of regeneration and synthesis of adaptive enzymes will play a decisive role in the formation of the toxic effect, and in this way the paradoxical result that the larger dose of poison produces a smaller mortality can be obtained.

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