

THE EFFECT OF SINGLE AND REPEATED DOSES OF TETRACYCLINES ON THE PHAGOCYTTIC FUNCTION OF THE RETICULO-ENDOTHELIAL SYSTEM

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We have previously shown [3] that a single dose of chlortetracycline or oxytetracycline, when given to mice, leads in some cases to stimulation of the phagocytic function of the reticulo-endothelial system (RES), depending on the size of the dose employed. In clinical practice it is unusual to give only a single dose of the tetracyclines, so that it is important to know whether they retain their stimulating effect on the RES when given in repeated doses.

We have studied the effect of single and repeated doses of chlortetracycline, tetracycline, and oxytetracycline on the phagocytic function of the RES in mice.

EXPERIMENTAL METHOD

The state of the phagocytic function of the RES after administration of the tetracyclines was determined by the microbiological method described earlier [1, 2].

Albino mice weighing 18-20 g were given a single dose of the tetracycline preparations by mouth, consisting of 0.2, 0.5, 1.0, and 2.0 mg per animal (0.5, 1.0, and 2.0 mg in the case of tetracycline). The antibiotics were given repeatedly for a period of 7 days in doses stimulating the RES when given singly, or in smaller doses. Thirty minutes after administration of the tetracyclines (in the case of repeated administration, on the 7th day) the mice received an intravenous injection of a suspension of *Staphylococcus aureus* (strain No. 209), and 5 min later blood was taken from the animals by decapitation for culture. A measured volume of blood was seeded on to Petri dishes containing a solid agar medium, and the colonies of staphylococci were counted after 36 h. The animals of the control groups received no antibiotics. To ensure standardization of the experimental conditions, each batch of mice was divided into experimental and control groups. Each group consisted of 15-36 animals.

The results were evaluated statistically. The arithmetical mean, standard error, and confidence limits were calculated.

EXPERIMENTAL RESULTS

Administration of a single dose of 0.5, 1.0, or 2.0 mg of chlortetracycline to mice stimulated the phagocytic function of the RES [1]. Administration of a single dose of 0.2 mg of the antibiotic to the animals had no effect on the state of the RES.

Repeated administration of chlortetracycline in a dose of 2.0 mg led to depression of the RES, but if doses of 0.5 and 0.2 mg were given, on the 7th day the state of the phagocytic function of the RES was indistinguishable from that found in the control group of animals (Table 1).

Administration of a single dose of 2.0 mg of tetracycline to the mice stimulated the phagocytic function of the RES; in doses of 0.5 and 1.0 mg, the drug had practically no effect on this system. After repeated administration of tetracycline in doses of 0.5, 1.0, and 2.0 mg, the indices of the state of the RES obtained at the end of the experiment were indistinguishable from the controls (Table 2).

Administration of a single dose of 1.0 and 2.0 mg of oxytetracycline had a stimulating effect on the RES.

TABLE 1. Effect of Administration of Single and Repeated Doses of Chlor-tetracycline on the Phagocytic Function of the RES in Mice

Dose (in mg) and conditions of administration of drug	No. of colonies (from 0.01 ml blood)
1,0 once	74±10,1 (54,3÷93,7)
2,0 "	48± 5,7 (36,9÷59,1)
control	105± 6,3 (92,1÷117,9)
0,5 once	27± 4,6 (17,2÷36,8)
0,5 repeatedly	37± 5,8 (25,7÷48,3)
2,0 "	64±10,4 (43,7÷84,3)
control	41± 7,1 (26,5÷55,5)
0,2 once	47±12,1 (21,2÷72,8)
0,2 repeatedly	40± 8,5 (18,2÷53,8)
control	41±10,0 (18,7÷63,3)

TABLE 2. Effect of Administration of Single and Repeated Doses of Tetracycline on the Phagocytic Function of the RES in Mice

Dose (in mg) and conditions of administration of drug	No. of colonies (from 0.01 ml blood)
1,0 once	134±16,7 (99,5÷168,5)
2,0 "	88±13,8 (59,5÷116,5)
control	115±20,5 (72,6÷157,4)
0,5 once	79±13,0 (49,6÷108,4)
0,5 repeatedly	88±18,5 (49,2÷126,8)
1,0 "	81±18,0 (43,1÷118,9)
2,0 "	89±13,2 (61,1÷116,9)
control	78±12,2 (52,2÷103,8)

Single doses of 0.2 and 0.5 mg of the antibiotic had no effect on the state of the phagocytic function of the RES of the mice. Repeated administration of oxytetracycline in every case gave results indistinguishable from the controls (Table 3).

Hence, after repeated administration of tetracyclines, by contrast to our findings after a single dose, we never observed a stimulating effect of the antibiotics on the phagocytic function of the RES. The repeated administration of chlortetracycline in a dose of 2.0 mg, a highly potent therapeutic dose, ultimately led to a statistically significant increase in the number of staphylococcal cultures in the experimental series by comparison with the controls. Stimulation of the phagocytic function of the RES observed in some cases after a single dose of tetracyclines apparently gave way quickly to the depression of this function or to the absence of perceptible action upon it after repeated administration of the antibiotics. It is interesting to note that the repeated administration of tetracyclines to mice in low doses, not affecting the RES if given once only (in the case of chlortetracycline 0.2 mg, tetracycline 0.5 and 1.0 g, and oxytetracycline 0.2 and 0.5 mg), also failed to stimulate the phagocytic activity of this system.

By means of these results, the tetracyclines can also be compared by the degree of their effect on the RES. The greater the difference between the number of colonies of staphylococci grown from the experimental and control animals, the more intensively the antibiotic stimulates or depresses the RES.

If from this point of view we compare the degree of the stimulating effect of the tetracyclines on the RES, we find that it was most marked in the case of chlortetracycline: it appeared after administration of 3 doses (0.5, 1.0, and 2.0 mg); the ratio between the number of colonies in the control and experimental series was 1.5, 1.4, and 2.2, respectively. Two doses of oxytetracycline were found to have a stimulating effect (1.0 and 2.0 mg); the ratio between the number of colonies in the control and experimental series was 1.4 and 1.6, respectively. The action of tetracycline was the least marked: it was found with only one dose (2.0 mg); the ratio between the control and experimental indices was 1.3.

TABLE 3. Effect of Administration of Single and Repeated Doses of Oxytetracycline on the Phagocytic Function of the RES in Mice

Dose (in mg) and conditions of administration of drug	No. of colonies (from 0.01 ml blood)
1,0 once	205±44,4 (114,0÷296,0)
2,0 "	185±35,6 (112,1÷257,9)
control	298±43,7 (207,2÷388,8)
2,0 repeatedly.	75±12,3 (50,9÷99,1)
control	72±11,0 (49,2÷94,8)
0,2 once	55±12,0 (29,5÷80,5)
0,2 repeatedly	66± 9,5 (45,9÷86,1)
0,5 once	64±11,3 (43,9÷88,1)
0,5 repeatedly.	64± 7,1 (49,1÷78,9)
control	43± 6,0 (40,5÷55,5)

With doses of the tetracyclines as used in these experiments, only chlortetracycline had a depressing effect on the RES. Absence of effect on the RES was noted in 3 cases for chlortetracycline and in 5 cases for tetracycline and oxytetracycline.

Hence chlortetracycline had the most marked effect on the phagocytic function of the RES, followed by oxytetracycline and, lastly, by tetracycline. Since, according to our findings the repeated administration of tetracyclines leads to depression of the phagocytic function of the RES, or at best leaves it unaffected, there are good grounds for the clinical use of tetracycline.

SUMMARY

As distinct from single administration of antibiotics belonging to the tetracycline group, repeated doses of these antibiotics did not stimulate the phagocytic function of the reticuloendothelial system; the latter was depressed or not affected. The most intensive action on the reticuloendothelial system is produced by chlortetracycline, then by oxytetracycline, and the least by tetracycline.

The results were assessed by recording the number of colonies of Staphylococcus aureus cultivated from the blood of mice into which this microorganism was injected intravenously.

LITERATURE CITED

1. N. A. Kalinina. Antibiotiki, 4, 88 (1959).
2. N. A. Kalinina. Byull. éksper. biol., 2, 60 (1963).
3. G. Ya. Kivman, and N. A. Kalinina. Byull. éksper. biol., 6, 46 (1962).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.