THE HYPERSENSITIVITY OF RABBITS TO THE TETRACYCLINES

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By comparison with animals showing normal sensitivity to antibiotics, the guinea pig is known to be hypersensitive to penicillin and to the tetracyclines [4-8]. This animal dies from very small doses of these antibiotics when given repeatedly or only once.

There are various theories to account for the mechanism of the toxic action of penicillin and the tetracyclines on guinea pigs. Some authors [5, 7, 8] explain it by the appearance of Escherichia coli, which is not present in animals not receiving antibiotics, in the intestine of the guinea pigs after these antibiotics have been given. Other workers [4, 6] explain the hypersensitivity of guinea pigs by the absence of any penicillin-inactivating substance from the central nervous system of these animals, by allergy to penicillin and so on.

In experiments on guinea pigs (35 animals) weighing from 200 to 400 g, we showed that after the oral administration of antibiotics of the tetracycline group in doses of 10 mg/kg for 2-5 days, Esch. coli and Bacillus proteus were isolated from the intestinal contents of the animals, but were not found in the guinea pigs of the control group.

The guinea pigs which received antibiotics in these doses rapidly lost weight and died in the course of 5-12 days.

The findings of other authors in relation to changes in the intestinal flora of guinea pigs under the influence of the tetracyclines and to the high sensitivity of the animals to these antibiotics were thus confirmed.

Besides the extensive literature on the hypersensitivity of guinea pigs to certain antibiotics, in articles on the treatment of candidomycosis in rabbits, Ambrosioni and Masoni[2, 3] in 1955 noted the high sensitivity of these animals to chlortetracycline. A. M. Kharitonova [1] described the pathological-anatomical changes in rabbits after taking repeated doses of tetracycline.

Since the subject of the sensitivity of rabbits has been inadequately discussed in the literature and is of great importance in the elucidation of the mechanism of the side-effects of the tetracycline antibiotics on the body, we carried out a special investigation in this direction.

EXPERIMENTAL METHOD

Experiments were carried out on 87 rabbits weighing from 1500 to 4100 g. Fifty rabbits were given chlortetracycline, 19-tetracycline and 18-oxytetracycline. The antibiotics were taken by mouth in doses of 5, 25 and 50 mg/kg daily. We used crystalline hydrochlorides of chlortetracycline, tetracycline and oxytetracycline of Soviet manufacture. The animals were weighed daily, and observations were made on their condition. In order to study the changes taking place in the rabbits, periodic investigations were made of their blood, their fecal microflora and, in some cases, their intestinal microflora. Postmortem examination was carried out on 36 rabbits.

Survival of Rabbits After Treatment With Tetracyclines

Dose of drug given (in mg/kg)	Dry chlortetracycline: total number of experimental animals	Dry chlortetracycline: number which died	Dry chlortetracycline: time of death (in days)	Dry chlortetracycline: loss of weight (in g)	Dry tetracycline: total number of experimental animals	Dry tetracycline: number which died	Dry tetracycline: time of death (in days)	Dry tetracycline: loss of weight (in g)	Dry oxytetracycline: total number of experimental animals	Dry oxytetracycline: number which died	Dry oxytetracycline: time of death (in days)	Dry oxytetracycline: loss of weight (in g)
	number of animals				number of animals				number of animals			
5	22	22	2—9	50—500	10	10	2—10	100—400	8	8	1—11	50—750
25	4	4	2—5	60—300	5	4 *	2—5	110—370	2	2	8—9	350—380
50	24	23 **	2—31	150—1 000	4	4	2—23	300—1 510	8	8	3—15	100—900

*One rabbit was sacrificed after receiving the drug for 25 days without any signs of toxic effects.

**One rabbit was sacrificed after 33 days in a similar condition.

EXPERIMENTAL RESULTS

Nearly all the experimental animals (83 of 87) receiving the above doses of antibiotics died in the course of two weeks from the beginning of administration of the tetracyclines (see table) with signs of increasing sluggishness, anorexia, loss of weight and profuse diarrhea, with excretion of a large quantity of mucus. Two rabbits died with the same manifestations 15-31 days from the start of administration of the drug. In some rabbits the toxicosis was severe, but there were no intestinal manifestations. Besides the doses indicated in the table, 4 rabbits received chlortetracycline at the rate of 1 and 2 mg/kg, and one rabbit received tetracycline in a dose of 2 mg/kg. All these animals also died, with the signs mentioned above, after 3 to 15 days. It must be pointed out that the trend of the loss of weight in the experimental animals was roughly the same, and depended to a considerable degree on the duration of their survival.

We were unable to establish any essential difference in the clinical picture and the time of death of the animals in relation to the drug and dose given.

The high sensitivity of rabbits to the tetracyclines was thus established with reasonable certainty.

Blood was examined from animals receiving all the above doses of the tetracyclines. The blood analyses were made on fasting animals, at intervals of 2-3 days. The red cells and leucocytes were counted, the hemoglobin level and ESR determined and the leucocyte formula calculated.

Irrespective of the drug they received and the dose, all the rabbits showed a leucocytosis (from 20,000 to 75,000 leucocytes as compared with a normal count of 7,000-10,000) on the 3rd-6th day. The changes in the leucocyte formula consisted of a fall in the number of lymphocytes to 20-30% (normal 50-60%) and an increase in the number of segmented neutrophils to 80% (normal 30-40%). In some animals, on the 2nd-3rd day before death, the ESR was raised to 50-60 mm in 1 hour. The red cell count and hemoglobin concentration were unchanged.

The fecal microflora were investigated in 25 rabbits, receiving tetracyclines in doses of 5, 25 and 50 mg/kg.

The number of E. coli, B. proteus and anaerobic bacteria were counted before the experiment and on the 2nd, 4th, 6th and 8th day (if the rabbits survived so long). In all the experimental animals, irrespective of the drug and the dose given, changes occurred in the number of E. coli and B. proteus.

There was a significant increase in the number of B. proteus. Before the experiment, no B. proteus was found in the feces of the majority of rabbits; in 2 of 25 rabbits a very

small number of these microorganisms was isolated. Starting on the second day of administration of tetracyclines to the rabbits, the number of B. proteus in the feces increased intensively, to reach 10^5-10^9 bacterial cells per g moist feces. At the same time the number of E. coli fell from 10^8-10^9 (before administration of the drug) to 10^3 -10^5 at the end of the experiment; in 2 of 25 rabbits, with intensive growth of B. proteus, only solitary colonies of E. coli were observed. The total number of aerobic bacteria in the majority of animals was increased on account of an increase in the number of B. proteus, but in a few animals it was unchanged. Investigation of the intestinal flora in 8 rabbits gave the same results as investigation of the microflora of the feces. The sharp increase in the number of B. proteus led us to examine the blood for the number of this microorganism contained in it, which might be the cause of death of the animals. Numerous blood cultures from the rabbits at various times were sterile, however.

At postmortem examination of the rabbits dying at different times from the beginning of administration of the drug, a similar pattern of lesions was found. The most marked postmortem changes were seen in the gastrointestinal tract. The stomach was atonic, and in some cases the mucous membrane was ulcerated. In places the loops of small intestine were distended, and elsewhere in spastic contraction. The usual contents of the intestine were not present, but its lumen, especially in the proximal segments, contained a large quantity of thick transparent mucus. In the distended portions, mainly in the distal segments of the intestine, an accumulation of a large quantity of frothy fluid was observed. Congestion of the vessels of the mesentery and serous membrane, mainly of the proximal segments of the intestine, was often noted. The grossest changes were found in the large intestine, especially in the ascending part and the cecum. These portions, especially the cecum, were grossly distended and contained usually a large quantity of flocculent, brownish, frothy fluid. A frequent abnormality was marked congestion of the vessels of the mesentery and serous membrane. In the greater part of the rabbits, the cecum and sometimes the ascending part of the colon showed numerous small, and in some places confluent, hemorrhages beneath the serous membrane. Continuous areas of hemorrhage were also observed beneath the serous membrane of almost the whole extent of the cecum. The mucous membrane of the large intestine remained unchanged macroscopically. Among other changes frequently found may be mentioned considerable congestion of the vessels of the pia mater and liver, less often, congestion of the lungs, and also dystrophic changes of the heart, liver and kidneys.

The changes in the gastrointestinal tract were thus characterized by atony of the stomach, dystonia and catarrhal inflammation of the small intestine, and gross circulatory and functional disturbances of the large intestine. These clinical and morphological changes are the main and most characteristic signs of toxicosis in rabbits developing after administration of antibiotics of the tetracycline group to these animals. The intensity of the morphological changes, from our observations, differed in different animals, but was independent of the type and dose of the drug.

It may be accepted that important factors in the pathogenesis of the changes described in the rabbits are changes in the intestinal microflora and also the direct toxic action of the tetracyclines on the body, and mainly on the gastrointestinal tract.

SUMMARY

It has been established that rabbits possess an increased sensitivity to antibiotics of the tetracycline group. On administering chlortetracycline, tetracycline, or oxytetracycline to rabbits per os in doses of from 5 to 50 mg/kg per day the majority of the animals died within 2 weeks after initiation of the treatment, with phenomena of increasing apathy, anorexia, weight reduction and profuse diarrhea.

Large numbers of B. proteus appeared in the intestinal contents of rabbits which received tetracyclines.

Leukocytosis was noted in the blood due to the increase in the number of polymorphonuclear segmented neutrophils and relative lymphocytopenia was also present.

The most pronounced pathological-anatomical changes resulting from tetracycline administration to rabbits were observed in the gastrointestinal tract

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