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Erythromycin in the aqueous humour

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The presence of treponemes despite penicillin therapy has been demonstrated in lymph nodes of both man and animals by Collart (1964), Boncinelli, Vaccari, Pincelli, and Lancellotti (1966), and Del Carpio (1963). Furthermore, treponemes have been identified in the aqueous humour after treatment for syphilis by Smith and Israel (1967), Goldman and Girard (1967), Christman, Hamilton, Heaton, and Hoffmeyer (1968), and Jones (1968). Indeed, *Treponema pallidum* has now been shown to persist in both man and animals despite re-treatment with penicillin by the Venereal Disease Research Laboratory of the United States Public Health Service (Yobs, Clark, Mothershed, Bullard, and Artley, 1968).

The following study was made because penicillin, streptomycin, aureomycin, and terramycin are all known to penetrate the blood–aqueous barrier poorly (Struble and Bellows, 1944; Leopold and LaMotte, 1945; Leopold and Nichols, 1946; DeRoetth, 1949; Cannon, Nichols, and Leopold, 1952), and erythromycin is the accepted drug of choice in treating syphilis in the penicillin-sensitive individual (Montgomery and Knox, 1959). This is to our knowledge the first reported study of erythromycin levels in the aqueous humour after oral administration of the drug.

Material and methods

Erythromycin was provided as the lauryl sulphate of the proprionyl ester (Ilosone) through the courtesy of Dr. L. D. Bechtol of the Eli Lilly Company. The dry powder was taken from the 250 mg. commercially prepared capsules immediately before use and suspended in water. Healthy adult rabbits with non-inflamed eyes were used for this study. Each rabbit was weighed before use, and the erythromycin solution was administered as a single dose through an oral-gastric tube. Each dose was followed by 2 ml. water to make certain that all the solution reached the animal's stomach.

Two dose ranges were evaluated in this study. The first—44 mg./kg.—is the human paediatric recommended dose, and was selected to evaluate aqueous humour levels using the customary therapeutic range. The second—500 mg./kg.—was used to determine how high an aqueous humour level could be obtained with a 10-fold increase in dosage, to determine how long this would be maintained, and to compare the serum/aqueous ratio of this drug at two markedly different dose ranges.

Matched samples of serum and aqueous humour were taken at hourly intervals up to 8 hours. Each rabbit was used twice after a single dosage—for example, the right eye and right ear vein were used after 1 hour, and the left eye and ear after 2 hours. No rabbit was used more often than once a week. The anterior chamber paracenteses were carried out with disposable sterile tuberculin syringes with No. 27 gauge needles after

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topical anaesthesia with 0·5 per cent. proparacaine hydrochloride. Blood was obtained with sterile vacutainer tubes and then immediately centrifuged. The serum and aqueous humour samples were frozen, accumulated, packed in dry ice, and shipped *via* airmail special delivery to Lilly Research Laboratories were the drug levels were estimated. The Sarcina lutea disc-plate technique of bioassay was used at the Lilly Laboratory, and data were reported in μg./ml. In a previous study of sodium cephalothin by Dr. Robert R. Sexton, the Lilly Laboratory method of bioassay was found to give accurate and reproducible data when compared with simultaneous determinations in this department.

Results

This study consisted of 112 specimens (56 each of serum and matched aqueous humour from rabbits after oral erythromycin and four control specimens (2 each of serum and aqueous humour) from normal rabbits which had received no medication. No activity was found in the control specimens. Of the 112 posterythromycin specimens, 44 were taken after a dose of 44 mg./kg. and 68 after a dose of 500 mg./kg. The data for the smaller and larger doses are given in the Table and summarized in the Figure (opposite).

Table *Passage of erythromycin across the blood–aqueous barrier in the rabbit (dosage 44 mg./kg.)*

Dosage (mg./kg.)	*Time (hrs)*	*No. of rabbits tested*	*Serum level (μg./ml.)*		*Aqueous humour level (μg./ml.)*		*Aqueous/Serum ratio*
			Range	*Mean*	*Range*	*Mean*	
44	1	2	0	0	0	0	—
	2	3	0 –0·54	0·20	0 –0·06	0·20	0·10
	3	3	0·21–1·67	**0·81**	0·09–0·43	**0·22**	0·27
	4	3	0·05–1·20	**0·52**	0·04–0·60	**0·24**	0·47
	5	3	0·08–0·33	0·17	0·02–0·04	0·03	0·16
	6	3	0·01–0·10	0·05	0 –0·06	0·03	0·53
	7	3	0 –0·16	0·09	0 –0·06	0·03	0·35
	8	2	0 –0·13	0·06	0 –0·05	0·02	0·38
500	1	5	0·45–4·40	1·78	0·03–0·11	0·07	0·04
	2	5	0·76–4·50	1·92	0·06–1·05	0·36	0·19
	3	4	0·33–3·60	2·06	0·16–0·55	0·35	0·17
	4	4	1·20–4·90	**3·03**	0·22–0·86	0·45	0·15
	5	4	1·85–4·10	**2·71**	0·30–1·05	0·52	0·19
	6	4	1·76–3·60	2·54	0·39–1·10	**0·69**	0·27
	7	4	1·67–3·90	2·84	0·30–1 62	**0·89**	0·31
	8	4	1·59–4·40	2·55	0·33–0·89	0·61	0·24

Mean peak levels shown in bold type

Discussion

The data obtained reveal that after the oral administration of erythromycin in the rabbit, the drug appears promptly in the serum, the peak level being reached 3 to 4 hours later. The drug enters the aqueous humour more slowly than the blood stream, as is not unexpected, the peak levels being reached 4 hours after the smaller dose and 7 hours after the larger dose.

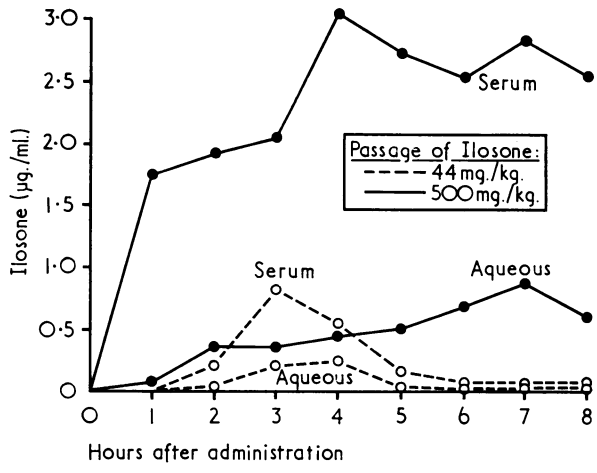

FIGURE *Passage of erythromycin across the blood–aqueous barrier in the rabbit*

The absolute serum level of erythromycin obtained in an individual rabbit will vary at a given time with intestinal absorption of the drug. This is influenced by such factors as eating and activity, and thus both minimum and maximum levels obtained at each time period are cited in the Table. However, consideration of the aqueous/serum ratios obtained reveals certain points of interest and gives information concerning the passage of this drug across the blood–aqueous barrier. The average aqueous/serum ratio for the smaller dose was 24 per cent. and for the larger dose 18 per cent. Again it is not unexpected that, with a larger dose, the blood–aqueous barrier would allow a smaller amount of drug to enter the eye than the serum. However, it is seen that approximately one-fifth of the serum levels of erythromycin were found in the aqueous humour. This appeared to represent a fairly good penetration of the drug into the aqueous, particularly in white and quiet eyes which were free from inflammation. Finally, it should be noted that other investigators have studied the penetration of erythromycin into the eye (Querengesser and Ormsby, 1955; Lee and Froman, 1961), but that their studies were done after topical or parenteral administration of the drug, rather than administration by mouth which is the route commonly employed in clinical practice today.

Summary

This is to our knowledge the first reported study of the penetration of erythromycin (Ilosone) into the aqueous humour of the normal rabbit eye after oral administration. The drug is rapidly absorbed, and peak serum levels were obtained after 3 to 4 hours. Erythromycin enters the aqueous humour at levels averaging about 20 per cent. of the serum levels. Aqueous humour levels were highest 4 to 7 hours after administration. The drug should therefore be given every 6 hours to maintain optimal aqueous humour levels.

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