Use of gentamicin sulphate in ophthalmology

I. Absorption of gentamicin into the rabbit aqueous

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Gentamicin sulphate is an aminoglycoside antibiotic with broad-spectrum properties (Black, Calesnick, Williams, and Weinstein, 1963). It is especially useful in infections due to *Pseudomonas pyocyaneus*, an organism which may cause severe ocular infection. Knowledge of the absorption of gentamicin into the eye is thus important.

The purpose of this study was to assess the penetration and persistence of subconjunctivally administered gentamicin into both the primary and secondary aqueous humour of the rabbit eye.

The absorption of subconjunctivally administered gentamicin into the bloodstream was also studied and, as a corollary, the absorption of systemically administered gentamicin into the aqueous humour was assessed.

Material and methods

Adult Dutch rabbits were used. 0.05 per cent. of a 4 per cent. solution (*i.e.* 20 mg.) gentamicin sulphate injectable* was administered by an aseptic technique into the anaesthetized superior subconjunctival space.

Assays were performed at the South African Institute for Medical Research using a microplate diffusion technique, which is more accurate than methods previously used (Litwack, Petit, and Lamar-Johnson, 1969).

Dosage schedule and results

(1) TO ASSESS THE PENETRATION OF SUBCONJUNCTIVALLY ADMINISTERED GENTAMICIN INTO THE PRIMARY AQUEOUS HUMOUR

Group A Each of five rabbits received a subconjunctival injection of 20 mg. gentamicin into the right eye. Aqueous samples were withdrawn at $\frac{1}{2}$, 1, 3, 6, and 24 hrs from the right eye. The experiments were repeated six times except in the 3- and 24-hour specimens, which were done only twice, and the results were averaged.

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*Garamycin Injectable supplied by Scherag (Pty.) Limited, a South African subsidiary of Schering Corporation, U.S.A.

A maximum level of 12.6 μg . was found at $\frac{1}{2}$ hour, dropping to 3.6 μg . at 3 hrs and to nil at 24 hrs (Fig. 1).

Group B Each of five rabbits received a subconjunctival injection of 20 mg. gentamicin into the right eye. Aqueous samples were withdrawn at $\frac{1}{2}$, 1, 3, 6, and 24 hours from the left eye. The experiment was repeated six times except in the 3- and 24-hour specimens which were done only twice. The results were averaged.

After $\frac{1}{2}$ hour the drug had reached the aqueous of the left eye; it reached a maximum of 2.9 μg . at 1 hr and had virtually disappeared from the aqueous by 6 hrs (Fig. 2).

FIG. 1 Gentamicin levels in right eye after injection into right eye

FIG. 2 Gentamicin levels in left eye after injection into right eye

Group C Each of five rabbits was given a subconjunctival injection of 20 mg. gentamicin into the right eye. Serum was withdrawn at $\frac{1}{2}$, 1, 3, 6, and 24 hrs and the serum levels assayed. The experiment was repeated four times except at 3 and 24 hrs, when it was done twice. The results were averaged.

There was a loss of gentamicin from the aqueous humour into the systemic circulation. The serum level was highest within $\frac{1}{2}$ hour and by 6 hrs had virtually disappeared (Fig. 3).

Group D A placebo injection of gentamicin sulphate base was given into the right eye and gentamicin levels were assayed at 1 and 24 hrs in the right aqueous, left aqueous, and serum. None was detectable.

Group E 20 mg. gentamicin were administered twice daily by intravenous injection for 3 days. Aqueous and serum samples were withdrawn 1 hr after the last injection. The studies were repeated four times in the aqueous and twice in the serum, and averaged.

The results showed an aqueous level of 0.62 μg . after 1 hr (see lower aqueous level, Fig. 5).

FIG. 3 Gentamicin levels in circulation after injection into right eye

FIG. 4 Penetration of subconjunctivally injected gentamicin into the formed secondary aqueous

(2) TO ASSESS THE PENETRATION OF GENTAMICIN INTO THE SECONDARY AQUEOUS HUMOUR OF THE RABBIT EYE

Group A In order to produce a secondary aqueous humour, primary aqueous humour was aspirated from the eyes of five rabbits; gentamicin 20 mg. was then injected subconjunctivally immediately and again 12 hrs later. Aqueous was withdrawn at $\frac{1}{2}$, 1, 3, 6, and 24 hrs and the experiment was repeated four times.

The results show that there was rapid penetration of gentamicin into the secondary aqueous, reaching a peak of 15 μg . at 1 hr (Fig. 4).

Group B Gentamicin 20 mg. was administered intravenously twice daily for 3 days. The aqueous was then aspirated and discarded and 12 hrs later a further dose of 20 mg. gentamicin was given intravenously. The secondary aqueous and serum levels of gentamicin were assayed at 1 and 6 hrs after the last intravenous injection.

The results (see Fig. 5 – upper aqueous line) show that the disruption of the blood-aqueous barrier caused by producing a secondary aqueous humour permits the entrance of fairly large amounts of systemically circulating gentamicin—3.2 μg . at 1 hr.

The levels observed in the primary aqueous (Part 1—Group E) of 0.62 μg . at 1 hr confirm this (Fig. 5—lower aqueous line).

FIG. 5 Penetration of intravenously injected gentamicin into the primary and secondary aqueous

Discussion

These results confirm the rapid penetration of gentamicin into both the primary and secondary aqueous humour (Litwack and others, 1969; Furgiuele, 1967; Golden and Coppel, 1970). Levels produced in the secondary aqueous are much higher than those produced in the primary aqueous and almost double at the equivalent time periods. By 12 hrs minimal levels are present in the aqueous.

The efficacy of the blood-aqueous barrier was demonstrated. Interestingly, a certain amount of gentamicin in these experiments did pass into the primary aqueous of the contralateral eye. The data show that systemically administered gentamicin does not pass into the primary aqueous in appreciable quantities but does penetrate the secondary aqueous effectively.

No instances of untoward side-effects such as conjunctival necrosis, iritis, or corneal oedema were observed in the animals after the injections.

Summary

Gentamicin sulphate is rapidly absorbed into the primary aqueous humour. After interference with the blood-aqueous barrier, increased levels are found in the secondary aqueous humour. A dosage of 20 mg. subconjunctivally produced levels in the rabbit eye above the minimum inhibitory concentration for *Ps. pyocyaneus*. It is concluded that the subconjunctival administration of gentamicin sulphate is an effective method of achieving rapid and high levels of gentamicin and should control infection due to gentamicin-sensitive organisms.

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