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SERUM CONCENTRATIONS OF TOBRAMYCIN® AFTER INTRAARTICULAR ADMINISTRATION

An Experimental Study in the Rabbit

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Serum concentration of the aminoglycoside tobramycin was followed for 120 min after intraarticular injection of 20 mg tobramycin in six rabbit knee joints. Highest concentration was observed after 15–30 min, and compared with the values after intramuscular injection the serum half life was equal. No pathological changes were observed by histological examination of the synovial membrane and articular cartilage.

It was concluded that no damage of the joint has been demonstrated after intraarticular injection of tobramycin, but the serum concentration must be monitored due to the rapid transport from the joint cavity.

Key words: animal experiment; septic arthritis; tobramycin

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Effective treatment of suppurative arthritis depends on whether the concentration of antibiotics in the synovial fluid reaches levels at or above the minimal inhibitory concentrations of the infecting organisms. Systemic treatment with penicillins or cephalosporins usually results in such concentrations in the synovial fluid (Nelson 1971, Parker & Schmid 1971) especially if high doses are given. Aminoglycosides, however, do not seem to pass the synovial membrane as readily as the betalactam antibiotics (Chow et al. 1971). Increasing the dose of aminoglycosides is hazardous due to their oto- and nephro-toxic potential. Intraarticular administration of antibiotics for suppurative arthritis is controversial and not without complications (Argen et al. 1966), but in arthritis caused by such pathogens as *Pseudomonas aeruginosa* (Chow et al. 1971, Gifford et al. 1975), the need for local antibiotic treatment might become more pertinent. While there is some information available about diffusion of antibiotics into joints after systemic treatment (Parker & Schmid 1971), there is very little about the uptake of antibiotics in the blood after intraarticular administration (Rummelkamp & Keefer 1943).

The purpose of the present study was to investigate the pharmacokinetic behaviour of an aminoglycoside, e.g. tobramycin, in serum after intraarticular injection of the drug, as well as to study whether any toxic action of the drug on the synovial membrane or the articular cartilage could be demonstrated.

MATERIAL AND METHODS

Tobramycin is an antibiotic drug of the aminoglycoside group and effective against most Gram negative organisms. The molecular weight is 467, and the drug is highly soluble in water. Practically no protein binding occurs, and the drug is removed from the blood by glomerular filtration. The side effects are the same as for other aminoglycosides (e.g. gentamicin).

Three to six months old rabbits weighing 3000–4000 g were used for the study. After anaesthetizing the rabbits with mebumal or Combelen®, 20 mg tobramycin diluted in 1 ml sterile saline was injected with a 26-gauge cannula in one of the knee joints. Blood samples were obtained from an ear vein 5, 10, 15, 30, 45, 60 and 120 min after tobramycin administration. The experiment was repeated using the contralateral knee 1–7 weeks later; thus six experiments were included in the study. One of the rabbits received an intramuscular injection with the same dose of tobramycin, and blood samples were then obtained as above.

The animals were sacrificed 1–2 weeks after the last injection, and both knees were examined for any macroscopical changes and the joints were prapared for histological examination. Specimens of the synovial membrane were obtained from both the medial and lateral compartment of the joint, fixed in 10 per cent buffered formalin phosphate, embedded in paraffin and sections 6 μm thick were stained with hematoxylin and eosin. Samples from the patella and the femoral condyles were fixed in 10 per cent buffered formalin phosphate, decalcified in 22 per cent formic acid with 10 per cent sodium citrate, and double-embedded in celloidin-paraffin. Sections 6 μm thick were stained with hematoxylin and eosin and with Safranin O.

Serum concentrations of tobramycin were determined by a disc diffusion method using *Klebsiella pneumoniae* as test strain. Standard concentration curves were generated from pooled rabbit serum. All serum samples were measured in quadruplets. Serum elimination half lives were calculated from the formula: $t_{\frac{1}{2}} = \ln 2/B$, where B is the slope of the elimination curve in a semilogarithmic plot.

RESULTS

The serum concentrations of tobramycin after intraarticular injection and after intramuscular administration are illustrated in Figure 1. The peak concentration occurred 15–30 min after tobramycin administration. Intraarticular administration of tobramycin resulted in serum concentration profiles identical to those obtained after intramuscular injection. Serum elimination half life after intramuscular administration was 54.6 min^{-1} and after intraarticular administration 63.1 ± 11.6 min^{-1} (mean ± S.D.). These results are similar to those reported for tobramycin in rabbits in other studies (Carbon et al. 1978) and indicate that tobramycin diffuses quite freely over the synovial membrane in the rabbit knee joint when injected intraarticularly.

Gross inspection of the knee joints revealed no visible changes of the synovial membrane or the articular cartilage.

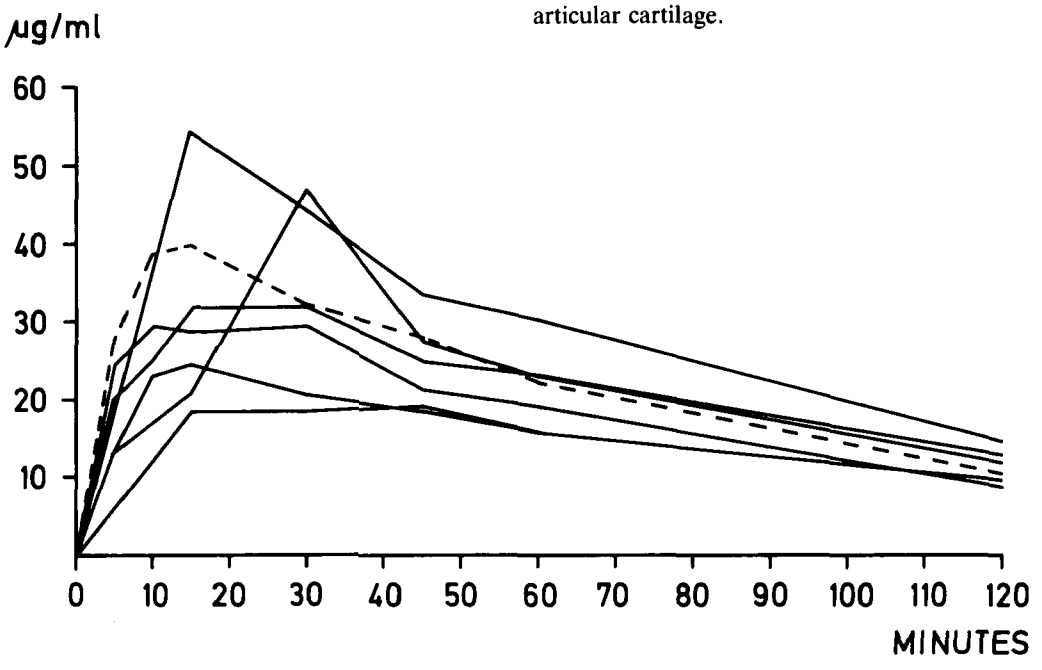

Figure 1. The serum concentration of tobramycin in six rabbits following intraarticular injection (full line) and intramuscular injection (dotted line) of 20 mg tobramycin.

Histological examination of the synovial membrane showed no signs of inflammatory changes and thus no hypertrophy of lining cells and no inflammation with lymphocytes, plasma cells or polymorphonuclear leukocytes. No signs of vascular changes – apart from one biopsy – were observed either. The articular cartilages of the patellae and the femoral condyles were in all cases normal. Thus all the cartilages were morphologically normal with an intact surface. The sections stained with Safranin O revealed no signs of depletion of glycosaminoclycans.

DISCUSSION

The main purpose of our study was to investigate if tobramycin appeared in appreciable concentrations in serum after intraarticular injection in the knee joint of rabbits. To our knowledge such a study has not been performed with any antibiotics.

After injection in the knee joint the aminoglycoside serum concentration was similar to that obtained after intramuscular injection of equal dose. A source of error could be that the injection missed the joint and the drug was actually deposited intramuscularly or subcutaneously. However, this is unlikely as the injections were performed at the medial border of the patella where no muscles are present. Furthermore the tip of the cannula could be felt inside the joint cavity touching the condyles, and a swelling of the suprapatellar bursa was observed during the injection.

The high intraarticular dose of tobramycin was also applied to investigate whether any toxic action of the drug could be demonstrated in the synovial membrane or the articular cartilage. The knee joints in this study were investigated 2–9 weeks after injection of tobramycin, and no signs of inflammation or cartilage damage were observed. It has been reported that penicillin may produce extensive synovitis after intraarticular injection, which is one of the main arguments for not administering antibiotics by this route (Argen et al. 1966).

The present study was performed on normal joints. However, as diffusion of drugs into the synovial fluid improves with inflammation of the joints (Nelson 1971, Parker & Schmid 1971), even higher tobramycin concentrations might be found in serum after injection into an inflamed joint.

In conclusion, the results showed that tobramycin injected into normal knee joints of rabbits produced no macroscopical or histological alterations of the synovial membrane or articular cartilage. These results should stimulate further research with other drugs with an even greater potential for toxic side effects such as steroids.

Care should be taken to monitor the serum concentration of the drug after intraarticular administration, especially in cases with impaired renal function.

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