

AN EFFECT OF FOSFOMYCIN ON THE PHARMACOKINETICS OF AMIKACIN

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The effect on amikacin pharmacokinetics by fosfomycin previously or simultaneously administered *via* the intraperitoneal, intramuscular, or oral route was studied in the rats.

Absorption of amikacin from the peritoneal cavity was prolonged by co-administered fosfomycin. High serum fosfomycin levels prevented renal lysosomal accumulation of amikacin, possibly because of the interference of urinary fosfomycin with the endocytosis of proximal tubular cells. These characteristics may explain the effect of fosfomycin in protecting against amikacin nephrotoxicity.

In a previous study in rats, fosfomycin prolonged the absorption of amikacin from the peritoneal cavity and decreased the lysosomal accumulation of amikacin in the kidney¹⁾. The present study was intended to determine whether the decreased lysosomal accumulation is the result of the prolonged absorption or whether the two phenomena are independent.

Materials and Methods

Antibiotics

Amikacin (1-*N*-(*L*-(-)- γ -amino- α -hydroxybutyryl)kanamycin A) obtained from Banyu Pharmaceutical Co., and the sodium salt of fosfomycin (disodium-(-)-(1*R*,2*S*)-(1,2-epoxypropyl)phosphonate) obtained from Meiji Seika Kaisha, Ltd. were used in this study.

Animals

Male Wistar rats weighing approximately 200 g were used.

Groups

Group 1: 20 mg/kg of amikacin was injected intraperitoneally.

Group 2: Animals were forced to drink 1 g/kg of fosfomycin and 1 hour later 20 mg/kg of amikacin was injected intraperitoneally.

Group 3: 500 mg/kg of fosfomycin was injected intramuscularly and 15 minutes later 20 mg/kg of amikacin was injected intraperitoneally.

Group 4: 200 mg/kg of fosfomycin and 20 mg/kg of amikacin were injected simultaneously into the peritoneal cavity.

Each group consisted of 8 rats. Four rats were sacrificed 30 minutes after intraperitoneal injection of amikacin and the remaining rats were sacrificed 90 minutes thereafter. At the time of the sacrifice, blood was withdrawn from the aorta. Kidneys were irrigated from the puncture site with 0.3 M sucrose - 1 mM EDTA solution (pH 7.0) and removed, then homogenized with 4 volumes of the sucrose - EDTA solution. The supernatant fraction and sediment fraction (large organelle fraction containing lysosomes) were prepared by centrifugation as previously described²⁾.

Bioassay

Antibiotic activities were determined by bioassay. *Proteus* sp. MB-838 was used for fosfomycin assay and *Bacillus subtilis* ATCC 6633 was used for amikacin assay.

In Vitro Study

Pellets of the lysosome-containing fraction of rat kidneys were prepared. Amikacin was dissolved in the supernatant fractions containing 1,000 $\mu\text{g/ml}$ of fosfomycin to achieve final amikacin concentrations of 400, 300, 200, 100, 50, 25, 12.5 $\mu\text{g/ml}$ each. Pellets were then dissolved in these solutions and kept at 20°C for 30 minutes. Supernatants of these solutions were obtained by re-centrifugation for 3 minutes at $9,000 \times g$, the sediments were dissolved in the original volume and re-centrifuged at $9,000 \times g$ again. The pellets from this final centrifugation were again dissolved and used for assay.

Results

Serum levels are shown in Fig. 1. The oral administration of fosfomycin did not result high serum fosfomycin levels nor did it affect serum amikacin levels. Simultaneous intraperitoneal administration of fosfomycin lowered peak amikacin levels and prolonged amikacin levels (Group 4). Group 3 did not show any tendency toward prolonged amikacin levels, although higher serum fosfomycin levels were obtained than those of Group 4.

Fig. 2 shows observed kidney concentrations. Renal fosfomycin concentrations directly reflected serum fosfomycin concentration patterns. Renal amikacin concentrations were also related to serum levels.

In Fig. 3 concentrations of amikacin in the sediment (lysosome-containing) fraction are shown. Fosfomycin levels incorporated into this fraction were negligible. Amikacin levels in Groups 1 and 2 were high while in Groups 3 and 4 they were low. The latter groups had high serum fosfomycin levels, while the former groups had either no or very low fosfomycin serum levels.

Fig. 4 shows the ratios of amikacin in the sediment fraction to the total amikacin in the kidney.

Fig. 1. Serum levels of amikacin (AMK) following intraperitoneal administration (20 mg/kg) and fosfomycin (FOM).

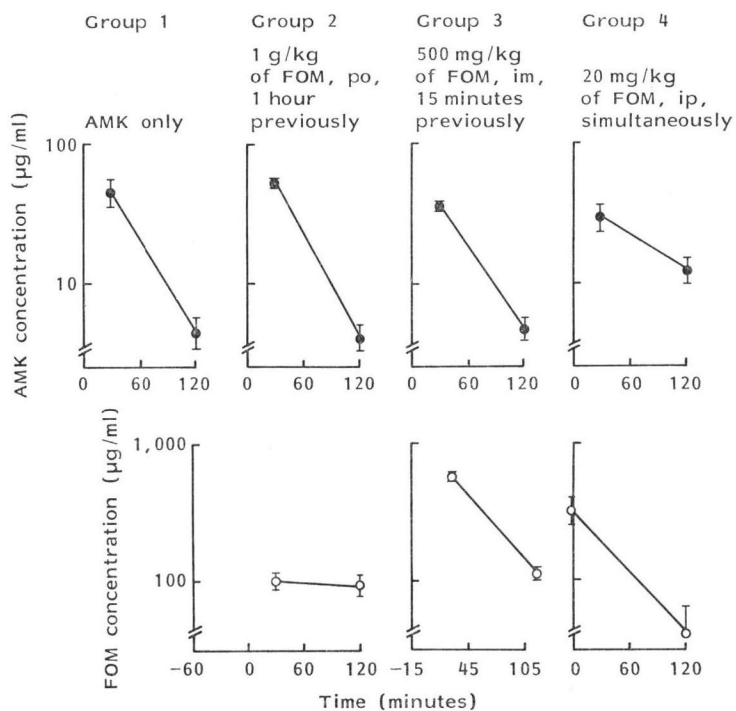


Fig. 2. Kidney concentrations of amikacin and fosfomycin.

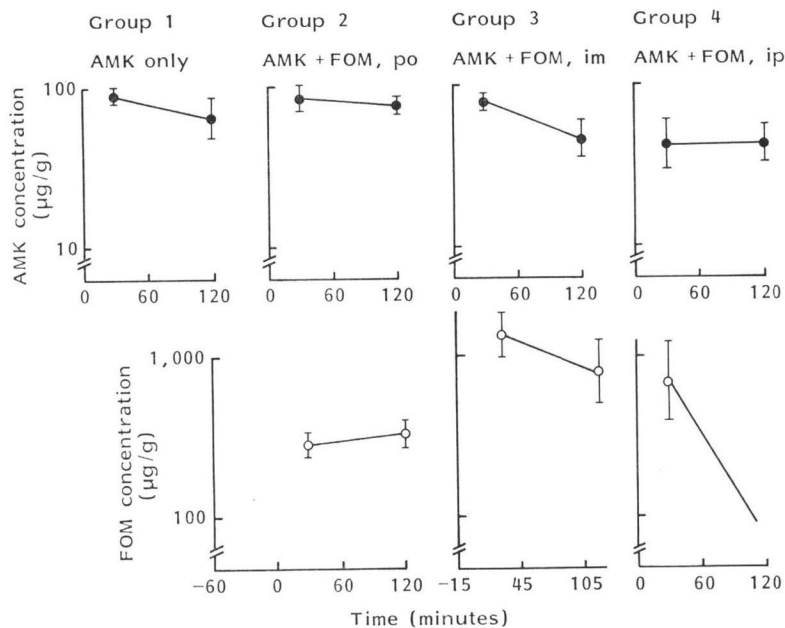
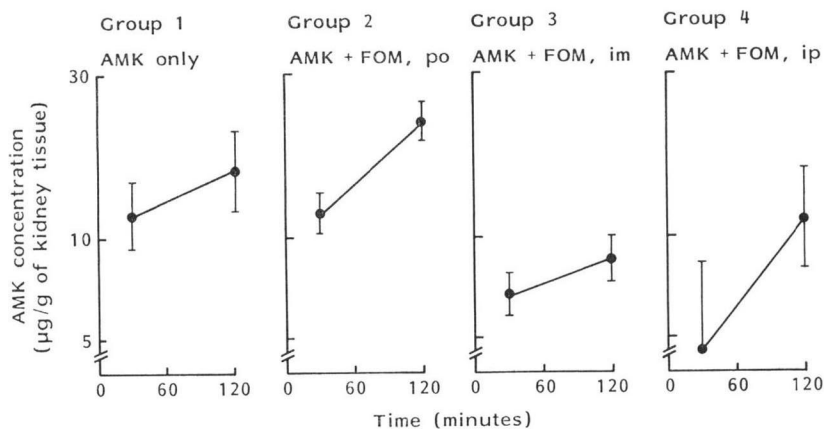


Fig. 3. Amikacin concentrations in the lysosome-containing fraction.



Ratios increased with time in all groups. Higher ratios were observed in Groups 1 and 2, than in Groups 3 and 4.

Fig. 5 shows the result of the *in vitro* study in which the effect of added fosfomycin on the distribution of amikacin in kidney fractions was measured. Similar amikacin distribution was obtained in both kidney supernatants and sediments regardless of the presence or absence of fosfomycin.

Discussion

Simultaneous intraperitoneal injection of fosfomycin suppresses peak serum levels of amikacin, but maintains their levels for a longer time. This finding was not observed when fosfomycin was given by other routes of administration. Coexisting fosfomycin in the peritoneal cavity probably interfered with

Fig. 4. Ratios of the incorporated amikacin to whole amikacin in the kidney.

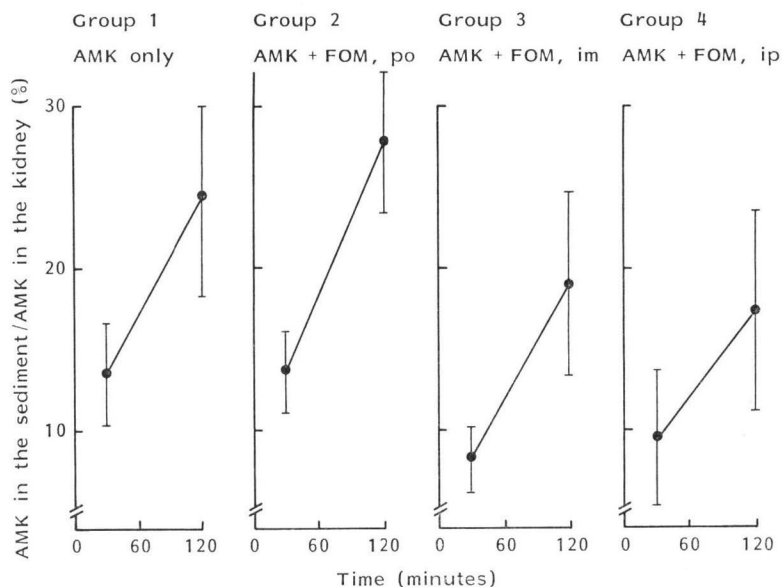
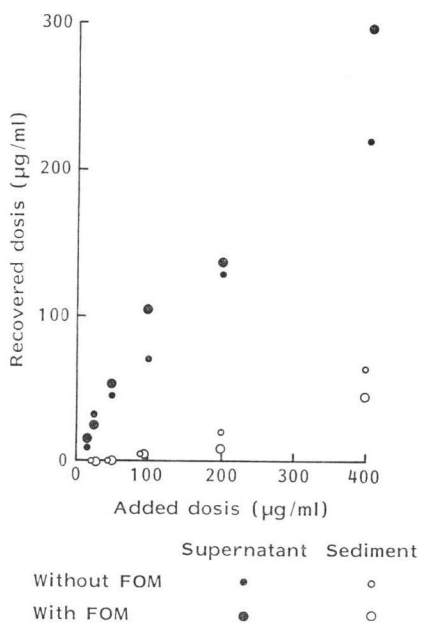


Fig. 5. Effect of fosfomycin on the intracellular distribution of amikacin added.



and prolonged the absorption of amikacin. Since incorporation into the sediment fraction increases with time, at least a part of the reduced lysosomal uptake in Group 4 may be explained by the prolonged absorption of amikacin.

The high serum fosfomycin levels following intramuscular administration did not affect the serum amikacin level pattern. This finding suggests that fosfomycin does not interfere with glomerular filtration of amikacin. The high fosfomycin levels, regardless of the administration route, did suppress lysosomal incorporation of amikacin (Fig. 3).

MORIN and associates³⁾ reported the stabilizing effect of fosfomycin against the disruption of lysosomal membranes caused by aminoglycosides. In our *in vitro* study, fosfomycin failed to block lysosomal incorporation of amikacin. Although this result does not contradict the stabilizing effect reported by MORIN³⁾, the inhibition of lysosomal amikacin uptake by fosfomycin cannot be explained from this *in vitro* study.

The endocytic process of aminoglycosides has been demonstrated by JUST *et al.*⁴⁾ and SILVERBLATT

*et al.*⁵⁾. Aminoglycoside trapped in endocytes may be a small portion of the total aminoglycoside filtered through the glomerulus. It may, however, be sufficient to disturb tubular function. The process is intimately related to the lysosomal system⁶⁾. High serum fosfomycin concentration results in high fosfomycin concentration in urine. Interference of urinary fosfomycin with this process thereby decreases the amount of aminoglycoside in lysosome.

The preventive effect of fosfomycin is not noted when it is administered after aminoglycoside injec-

tion⁷⁾. It is another proof for the preventive mechanism that the coexisting fosfomycin might directly interfere with aminoglycosides in their nephrotoxic process.

References

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