Pharmacokinetics and metabolism of fosmidomycin, a new phosphonic acid, in rats and dogs

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SUMMARY

The absorption, distribution, metabolism, and excretion of 3-(N-formylhydroxylamino) propylphosphonic acid monosodium salt (fosmidomycin), a new antibiotic, were investigated in rats and dogs after i.v. and oral dosing.

After i.v. administration of 10 mg/kg of body weight, [14C]-fosmidomycin was excreted mainly in the urine (about 90% of dose within 72 h); and only a little was excreted in the expired air (14CO2) and bile of rats (less than 1% of dose), which suggested the absence of enterohepatic circulation. After oral administration of 10 mg/kg of body weight to rats, 34% and 61% of dose were excreted in the urine and faeces, respectively, suggesting about 30% gastro-intestinal absorption. No metabolites were found by autoradiography of the urine after thin layer chromatography. Radioactivity levels in the serum essentially agreed with the unchanged fosmidomycin levels determined by reverse isotope dilution method. [14C]-fosmidomycin was rapidly distributed in the tissues of rats, and was maintained in high concentration in the liver, kidneys, and bone. The serum level data after i.v. administration closely fitted a 3-compartment open model with first order kinetics after nonlinear least squares regression by NONLIN. The half-lives of the serum level curves for the early, midway, and terminal phases were: 0.13, 0.51, and 17.3 h, respectively in rats; and 0.44, 0.75, and 2.0 h, respectively in dogs.

INTRODUCTION

Fosmidomycin (3-(N-formylhydroxylamino) propylphosphonic acid monosodium salt) is a new phosphonic acid antibiotic agent effective against most gram-negative bacterial infections in animals, such as Escheria coli, Pseudomonas aeruginos, Klebsiella pneumoniae, and Enterobacter (1, 2). The purpose of this study was to examine the absorption, distribution, metabolism, and excretion of [14C]-fosmidomycin in rats and dogs as a part of the preclinical trial.

MATERIALS AND METHODS

Chemicals

Fosmidomycin and [14C]-fosmidomycin were synthesized and supplied by the Department of Organic Chemistry, Research Laboratories, Fujisawa Pharmaceutical Co. Ltd. The [14C]-fosmidomycin (specific activity, 43.2 mCi/mmol) was labelled in the carbon of position 1 as indicated in the structural formula by the asterisk, and was diluted appropriately in the experiments. Radioactive purity by thin layer chromatography exceeded 98%.

Animal experiments

Male JCL:SD rats (CLEA Japan Inc., Tokyo), weighing about 230 g, and male beagle dogs (Japan E.D.M.), weighing 9.4 to 11.8 kg, were given 10 mg
of [14C]-fosmidomycin per kg of body weight after fasting overnight.

**Serum levels and tissue distribution in rats**

Rats were dosed i.v. through the femoral vein. The animals were anaesthetized with chloroform 5, 15, 30 min, 1, 2, 3, 4 or 6 h after dosing and blood samples were collected by cardiac puncture. The tissues were removed immediately, and homogenized in 9 volumes of water. Bone samples were dissolved in 9 volumes of 6 mol/l HCl at 60°C.

**Urinary, faecal and expiratory excretion in rats**

Three rats were dosed i.v. and 5 rats were dosed orally. The animals were housed individually in glass metabolism cages. The urine and faeces were collected separately in an ice-cold receivers 4, 8, 24, 48 and 72 h after dosing. The cages were washed with a small volume of water when the urine receiver was changed and the washings were combined with the collected urine. At the end of the experiment, the rats were killed with chloroform, their gastrointestinal tracts (including contents) were homogenized, and the carcasses were dissolved in 6 mol/l HCl by heat. Three different rats were dosed i.v. and housed individually in glass metabolism cages equipped with 14CO2 trap containing 100 ml of ethanolamine. The ethanolamine, urine and faeces were collected 24, 48, and 72 h after dosing. At each collection time the trap was washed with methylcellosolve and the cage was washed with a small volume of water and these washings were combined with ethanolamine and urine, respectively. At the end of the experiment, the gastrointestinal tracts were homogenized and carcasses were dissolved in 6 mol/l HCl by heat.

**Biliary excretion in rats**

Five rats were restricted in a supine position, and the bile duct was cannulated under ether anaesthesia. [14C]-fosmidomycin was given i.v. 30 min after recovery from anaesthesia followed immediately by 5 ml of water given orally. Water (5 ml orally) was then given 2 h after dosing, and in the morning and evening of the study. The bile and urine were collected in ice-cold tubes 2, 4, 8, 24, and 48 h after dosing.

**Serum levels, and urinary and faecal excretion in dogs**

Five dogs were dosed i.v. and were housed individually in metabolism cages. Blood samples were collected 5, 15, 30 min, 1, 3, 4, 6, and 8 h after dosing. Urine and faeces were collected 4, 8, 24, 48, and 72 h after dosing.

**Measurement of radioactivity**

Samples were dissolved in Protosol® (New England Nuclear Corp.) and mixed with toluene scintillation fluid. Radioactivity was measured with a Tri-Carb liquid scintillation spectrometer Model 3385 (Packard Inst.). Quenching was corrected by the external standard channels ratio method.

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**Fig. 1** : Serum levels of radioactivity and unchanged drug in rats after i.v. dosing with [14C]-fosmidomycin (10 mg/kg of body weight). Values are the mean of 5 rats for radioactivity (□□□□□) and unchanged drug (○○○○○) expressed as µg equivalents of fosmidomycin or µg/ml.