LEADING ARTICLE

FOSFOMYCIN

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SING MED J. 1988; 29:91–92

Fosfomycin is a non beta-lactam, low molecular weight antibiotic which inhibits cell wall synthesis in gram-positive and gram-negative bacteria. It inhibits an early stage of muramic acid synthesis which is needed for the building of the bacterial cell wall. This action is dependent upon a glucose-6-phosphate-induced transport system which enhances penetration of the drug into bacterial cells. Mutants which lack this transport system are resistant to fosfomycin(1). This bactericidal drug has no cross-resistance with other antibiotics as it bears no chemical relationship to any of them.

It is active in vitro against staphylococci, gonococci, *Haemophilus influenzae, Escherichia coli, Proteus mirabilis,* salmonellae and shigellae particularly in the presence of glucose-6-phosphate in the medium. The loss of this transport system either in vitro by the presence of high concentrations of phosphate or glucose in the growth medium or in vivo, abolishes the action of fosfomycin(2). It is moderately active against streptococci, *Serratia marcescens* and *Pseudomonas aeruginosa.* Many strains of *Morganella morganii, Klebsiella pneumoniae* and *Enterobacter species* are resistant. The authors in this journal who tested the in vitro activity of fosfomycin had more or less the same results. It is inactive against all species of *Bacteroides.* Activity in vitro is very dependent on the culture, inoculum medim and method of testing(3).

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Fosfomycin is therefore a wide spectrum antibiotic. It has good tissue penetration and is well tolerated but is little used to date though it has been used in Europe for treating mainly meningitis and osteomyelitis cases with promising results (4,5). It would seem a good alternative for bacterial infections in patients allergic to the penicillins and cephalosporins though it is not advisable to use it as monotherapy in severe or life threatening infections(3). One interesting aspect of fosfomycin is that it exerts good in vitro activity against methicillin — resistant strains of *Staphylococcus aureus* (MRSA)(10). MRSA strains are a therapeutic problem being multiresistant and in our local strains generally sensitive only to vancomycin, fusidic acid, clindamycin and variable to cotrimoxazole.

Recent studies on the mechanism of MRSA resistance which is a form of intrinsic resistance to beta-lactam antibiotics, have concentrated on penicillin-binding proteins (PBPs) in *Staphylococcus aureus* strains(7). PBPs are cytoplasmic membrane proteins which specifically bind penicillin and other beta-lactam antibiotics and are involved in cell wall biosynthesis. Intrinsic resistance to methicillin in *Staphylococcus aureus* is caused by the production of a new low-affinity PBP 2' which can act as a murein transpeptidase for cell wall biosynthesis despite the presence of beta-lactam antibiotics(6). Experiments done in Japan have shown that PBP 2' were scarcely detectable in MRSA strains grown in the presence of fosfomycin and that the combined administration of cefmetazole, a beta-lactam antibiotic, with fosfomycin at a ratio of 1:1 against systemic MRSA infections in mice showed an excellent therapeutic efficacy as compared with the administration of either antibiotic alone(8). Other in vitro studies have shown synergistic killing against clinical isolates of *Staphylococcus aureus* (MRSA and MSSA) with the combination of fosfomycin-imipenem(9), fosfomycin-cefamandole (66%) and fosfomycin-methicillin (46%)(10).

In conclusion, fosfomycin in combination therapy is therefore a promising antibiotic to use for MRSA infections and warrants clinical trials in our local MRSA patients.

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