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Commentary

Mecillinam – Reversion of Resistance and How to Test It

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Mecillinam (amdinocillin) is a penicillin produced by the Leo Pharmaceutical Company and marketed in 1976 (Lund & Tybring, 1972). It is available both in an i.v. and oral form, pivmecillinam. This antibiotic is an almost ideal antibiotic for treatment of urinary tract infections: It has a narrow spectrum being active against Gram-negative bacteria only, and notably so against *Escherichia coli*, *Proteus mirabilis*, Klebsiella spp., Salmonella and Shigella. Mecillinam shows 4–8 times lower MIC values than ampicillin. It is stable against a broad range of beta-lactamases including many ESBL-enzymes, however not against ampCs or carbapenemases. Mecillinam has excellent pharmacokinetic properties with high drug concentrations in urine (Ferry et al., 2007; Jansåker et al., 2014), but also shows good effect against bacterial diarrhea (Kabir et al., 1984). On top of this, in spite of more than 40 years of use as standard treatment for UTI in Denmark, Norway and, Sweden it has remained very active with around 90–95% of *E. coli* still being susceptible to the drug. One of the reasons for this beneficial activity of mecillinam is explained by the report from Thulin et al. in this issue of *EBioMedicine* (Thulin et al., 2017). Mutants resistant towards mecillinam do evolve quite easily during treatment, but most of them succumb due to increased fitness-cost (Thulin et al., 2015). The most important of the surviving mutants show a mutation in the *cysB* gene encoding for the CysB protein, the major positive regulator of the cysteine biosynthesis pathway and turning this pathway off confers mecillinam resistance, but only in growth media low in cysteine. Interestingly Thulin and co-workers show, that presence of cysteine in the medium reverts the resistance towards mecillinam, and cysteine is almost always present in urine (Thulin et al., 2017). Further, susceptibility towards mecillinam increases with decreasing osmolality, why dilution of the medium, e.g. as in urine after increased intake of fluid, enhances the activity of mecillinam. These findings further add to the reputation of this old beta-lactam antibiotic which deserves to have a broader use; it is only marketed in a few countries outside Scandinavia.

Thulin et al. also report (Thulin et al., 2017), that the reversion of mecillinam resistance was only found, when urine was used as test media or in MHB supplemented with cysteine. This leads the authors to open up for an old discussion on antibiotic susceptibility testing: Should we always test pathogens in environments similar to those of the infection in vivo? The basic principle for a susceptibility test is to detect resistance mechanisms in the infecting pathogen in order to guide the clinician in choosing the correct treatment for the patients. For testing by broth - or disc diffusion the idea is to provide optimal growth of the bacteria, expose them to the antibiotic in question in its most active form i.e. without binding to proteins but with presence of necessary constituents for their activity, e.g. magnesium ions for aminoglycosides, glucose-6-phosphate for fosfomycin etc., and then to detect the concentration of antibiotic needed for inhibiting growth or killing the bacteria. This inhibitory concentration (~MIC) is then related to the antibiotic concentrations achievable at the site of infection on doses, which ideally have been formulated according to the optimal pharmacodynamics properties for that (type of) antibiotic. This relationship between antibiotic, dose, MIC and infection needs to be validated in clinical studies; this is the principle for providing breakpoints in the EUCAST system: As long as theoretical breakpoints have not been clinically validated, the breakpoints are not "released" (www.eucast.com). If mecillinam was only tested in urine, the cysB mechanism would not be detected and there would be a risk, that the antibiotic might be used for treating infections, where cysteine was not present e.g. bacterial diarrhea. Ideally, the compound should be tested in such a manner, that resistance mechanisms are always detected. Thereafter, the drug can be tested for its possible activity under the conditions, where it is going to be used, for mecillinam either in urine or with cysteine supplement. This two-step method is used for many antibiotics, for example screening *Staphylococcus aureus* for methicillin-resistance with cefoxitin, and thereafter detection of the *mecA* gene with PCR; similar for vancomycin resistance in enterococci, carbapenem resistance in Enterobacteriaceae etc. Direct detection for resistance genes is increasingly being used in microbiology laboratories (e.g. *vanA* gene screening in rectal cultures), but this demands that there is a clear cut relation between the genotype and the phenotype. For the *mecA* gene it is a problem that it can also reside in coagulase-negative staphylococci, which are often present in clinical samples as contaminants. Antibiotic susceptibility testing is a research area in constant progress, not the least due to the ever increasing new resistance mechanisms appearing, and the report by Thulin et al. (Thulin et al., 2017) is a timely addition to our quest to continue understanding and acting on the crucial effort to provide optimal treatment of our patients.

Disclosure

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