Nitrofurantoin

Resistance reduces therapeutic options for urinary tract infections.

The multidrug resistance problem has arrived in the community setting, where multidrug resistant Escherichia coli are recognised as important causes of hard-to-treat community-acquired urinary tract infections (UTI). The Europe-wide increase of E. coli resistance to all major antimicrobial classes, as detected by the European resistance surveillance system EARS-Net and the ECO-SENS study, is a disturbing development with potentially serious consequences for patients. The speed with which fluoroquinolones as first-line drugs lose their activity against E. coli, the most common pathogen in UTI is without precedent. Not only fluoroquinolone resistance, but also combined resistance to all first-line drugs, is a frequently observed phenomenon that limits therapeutic options and may require parenteral therapy in infections otherwise treatable outside the hospital. These disturbing situations raise questions regarding the routine use of the most widely used antibacterial classes (fluoroquinolones, aminopenicillins, cephalosporins, sulfamethoxazole/trimethoprim) as first-line agents for acute uncomplicated UTIs in the community. Resistance threatens the future of currently standard medical treatment.

No other choice – Relying on old antibiotics.

Development of novel antibiotics with activity against relevant multidrug-resistant bacteria causing UTIs is not on the horizon. In situations such as this, physicians increasingly resort to old and “forgotten” antibacterial drugs as these drugs may have retained their activity after many years of rarely being used. However, these old antibiotics have never been characterized using a structured drug assessment process and approval issues now considered essential have not been applied. Hence, vital questions such as identification of appropriate dosage regimens to maximize activity while minimizing toxic effects and resistance development, as well as comparison with other therapeutic options, remain open.

AIDA studies old drugs to optimize current usage.

In recognition of the vital nature of these issues, the European Commission has included the characterization of old off-patent antibiotics in their funding scheme for the 7th Framework Program (FP7). One of the work packages of project AIDA (Preserving old antibiotics for the future) aims to examine the clinical effectiveness of nitrofurantoin vs fosfomycin-trometamol as well as to identify optimal dosing regimens and treatment duration based on sound PK/PD studies. Despite of 60 years of clinical usage, basic knowledge such as this has been either lost or has never been generated for nitrofurantoin. Resorting to the old antibiotic nitrofurantoin needs to be supported by new studies that are based on scientific principles and modern techniques.

Nitrofurantoin – a revived antibiotic

Nitrofurantoin is the best known compound in the class of nitrofurans. This synthetic compound has been available for clinical use since 1953. Due to several reports of severe adverse effects, (primarily pulmonary reactions) during the 1970’s, the prescribing of nitrofurantoin decreased. During this time nitrofurantoin had been used for long-term prophylaxis of UTIs. Long-term low-dose usage as well as acute high dose usage or extreme high systemic concentrations due to renal insufficiency are risk factors for adverse events. Nowadays, nitrofurantoin has been revived for short-term treatment of community-acquired uncomplicated UTIs in patients with normal kidney function due to the untenable resistance crisis. Even in countries with rather low resistance rates, such as Sweden, medical societies recommend nitrofurantoin as a first-line quinolone-sparing treatment to ease the selection pressure that would otherwise trigger co-
resistance and, thus, lead to multi-drug resistance with limited or no remaining therapeutic options.

Nitrofurantoin in various formulations with differing pharmacokinetic properties

Numerous manufacturers of generic nitrofurantoin produce the solid oral form of nitrofurantoin in three different formulations:

- A macrocrystallized form
- Nitrofurantoin monohydrate
- A mixture of macrocrystals (75%) and the monohydrate (25%) contained in a delayed-release gel matrix

The formulations differ in their absorption properties as the macrocrystallized form shows a slower dissolution and absorption in comparison to the monohydrate. The crystal mixture is a delayed release formulation with an even slower release over time, thus supporting an extended dosing interval according to very old clinical studies.

In Europe, all three formulations are used while in some Eastern European countries only furazidin, another nitrofuran derivative, is available.

Clinical usage of nitrofurantoin

Nitrofurantoin is considered a specialised UTI drug. Due to nitrofurantoin's short half life and distribution pattern, concentrations in serum and tissue fluids are not high enough for treating systemic infections. Nitrofurantoin is eliminated by biliary metabolism and renal elimination, thus providing sufficient concentrations in the urine and renal medulla to cover the major community-acquired pathogens of uncomplicated UTIs especially E. coli, staphylococci, and E. faecalis. However, Pseudomonas and Proteus are not affected by clinically achievable nitrofurantoin concentrations. Nitrofurantoin has remained effective after 60 years of worldwide usage with little or no resistance. Several surveillance studies show this unchanged susceptibility even in high multidrug resistance environments. Due to the unique mode of action co-resistance with other drug classes is not expected. Several molecular targets in the bacterial cell delay the development of resistance as multiple mutations in parallel are needed to survive nitrofurantoin's action. These characteristics make nitrofurantoin a suitable candidate for new and improved studies to gain more knowledge in support of its effective and safe usage in community-acquired uncomplicated UTI.

Safety

The toxic effects of nitrofurantoin are well known. Though rare, some of the reactions are severe including allergic, pulmonary (acute and chronic), hepatic, gastrointestinal, hematological, and neurological (peripheral neuropathy) events. Acute toxicity is concentration dependent and excessive doses as well as therapy in renally impaired patients must be avoided. Long term use of nitrofurantoin is a known risk factor for chronic adverse events. Studying the dosage/toxicity relationship while considering single and cumulative doses, as well as other risk factors should improve the safe prescribing of the old but now revived antibiotic nitrofurantoin.

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