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When the precautionary principle disrupts 3 years of antibiotic stewardship: nitrofurantoin in the treatment of urinary tract infections

C. Slekovec[1,2], J. Leroy[3], A. Huttner[4], O. Ruyer[5], D. Talon[1,2], D. Hocquet[1,2] and X. Bertrand[1,2]*

[1]Service d'Hygiène Hospitalière, Centre Hospitalier Universitaire Besançon, Besançon, France; [2]UMR 6249 Chrono-environnement, Université de Franche-Comté, Besançon, France; [3]Service de Maladies Infectieuses, Centre Hospitalier Universitaire Besançon, Besançon, France; [4]Service de Prévention et Contrôle de l'Infection, Hôpitaux Universitaires de Genève, Geneva, Switzerland; [5]Service de Maladies Infectieuses et Réanimation, Centre Hospitalier de Belfort-Montbéliard, Belfort, France

*Corresponding author. Service d'Hygiène Hospitalière, Centre Hospitalier Universitaire Besançon, Besançon, France. Tel: +33-3-81669053; Fax: +33-3-81668914; E-mail: xbertrand@chu-besancon.fr

Keywords: fluoroquinolones, fosfomycin, adverse effects

Sir,

In 2008, the alarming level of antibiotic resistance in France led us to release regional guidelines for the treatment of urinary tract infections (UTIs).[1] Briefly, we recommended (i) the avoidance of fluoroquinolones for uncomplicated UTIs and (ii) the use of fosfomycin (single 3 g dose) or nitrofurantoin (100 mg three times a day, 5 days) as first-line treatment. Accordingly, fosfomycin and nitrofurantoin prescriptions increased, while fluoroquinolone prescriptions declined.[2] In February 2011, the French Agency for the Safety of Medicine and Health Products (ANSM) published a drug monitoring alert concerning nitrofurantoin.[3] This letter reported new cases of severe hepatic and pulmonary toxicity after prolonged treatments with nitrofurantoin. National guidelines were suspended, while nitrofurantoin's use as prophylaxis for UTIs was strongly discouraged. One year later the ANSM issued its new guidelines, stating that: (i) nitrofurantoin is responsible for severe pulmonary and hepatic toxicity; (ii) nitrofurantoin should be used for documented cystitis due to susceptible microorganisms only when no other antimicrobial presenting a better benefit/risk ratio can be used orally; (iii) nitrofurantoin can nevertheless be considered for empirical treatment in cases of urgency or in the setting of a previous history of multidrug-resistant bacteria; and (iv) nitrofurantoin must not be used as prophylaxis.

We assessed the impact of the ANSM guidelines on drugs prescribed for UTIs in our region using antibiotic prescription data (nitrofurantoin, fosfomycin and fluoroquinolones with the exception of anti-pneumococcal fluoroquinolones) extracted from the region's health insurance agency (ambulatory care for women aged 15–65 years). Antibiotic consumption was measured from May 2007 to August 2012 via monthly totals of daily defined doses (DDDs) according to WHO recommendations.[4]

The publication of the drug monitoring alert led to a prompt and significant ($P<0.001$) decrease in nitrofurantoin use: the relative variation was −49.3% 16 months after the release (Figure 1). We also observed a significant increase in 3 day fluoroquinolone treatment packs (lomefloxacin), single-dose fluoroquinolone packs (ofloxacin or ciprofloxacin) and multi-dose ofloxacin packs. Throughout the entire study period, the consumption of fosfomycin increased, that of ciprofloxacin was stable and that of norfloxacin decreased, with no change in trend (Figure 1). Our dataset did not allow the tracing of indications for nitrofurantoin prescriptions (i.e. short-term use versus prophylaxis or intermittent use). However, a French global prescription survey suggests that ∼75% of nitrofurantoin is prescribed for short-term treatments.[5] It is thus very likely that the two-to-one reduction in nitrofurantoin use in our region is not only linked to the ban on nitrofurantoin for UTI prophylaxis but has also impacted short-term use. For the latter, prescribers largely replaced nitrofurantoin with fluoroquinolones.

The alert was the consequence of a survey of nitrofurantoin's adverse effects: the French Committee on Drug Monitoring reported severe adverse effects, mainly pulmonary or hepatic, with a frequency of 12.7 per year (1 per 20551 nitrofurantoin prescriptions).[5] This frequency increased with treatment duration: from 1 case per 24800 short-term prescriptions (<1 month) to 1 case per 7666 long-term prescriptions (>1 month). In addition, the context of this alert must be taken into account. It was issued shortly after the French medical community had been rocked by the Mediator scandal, which appeared to some to expose the French pharmaceutical oversight apparatus as relatively permissive, if not lax.[6]

To our knowledge, no other European country has released similar recommendations, while most of them use more nitrofurantoin than France, including for recurrent UTIs.[7] According to

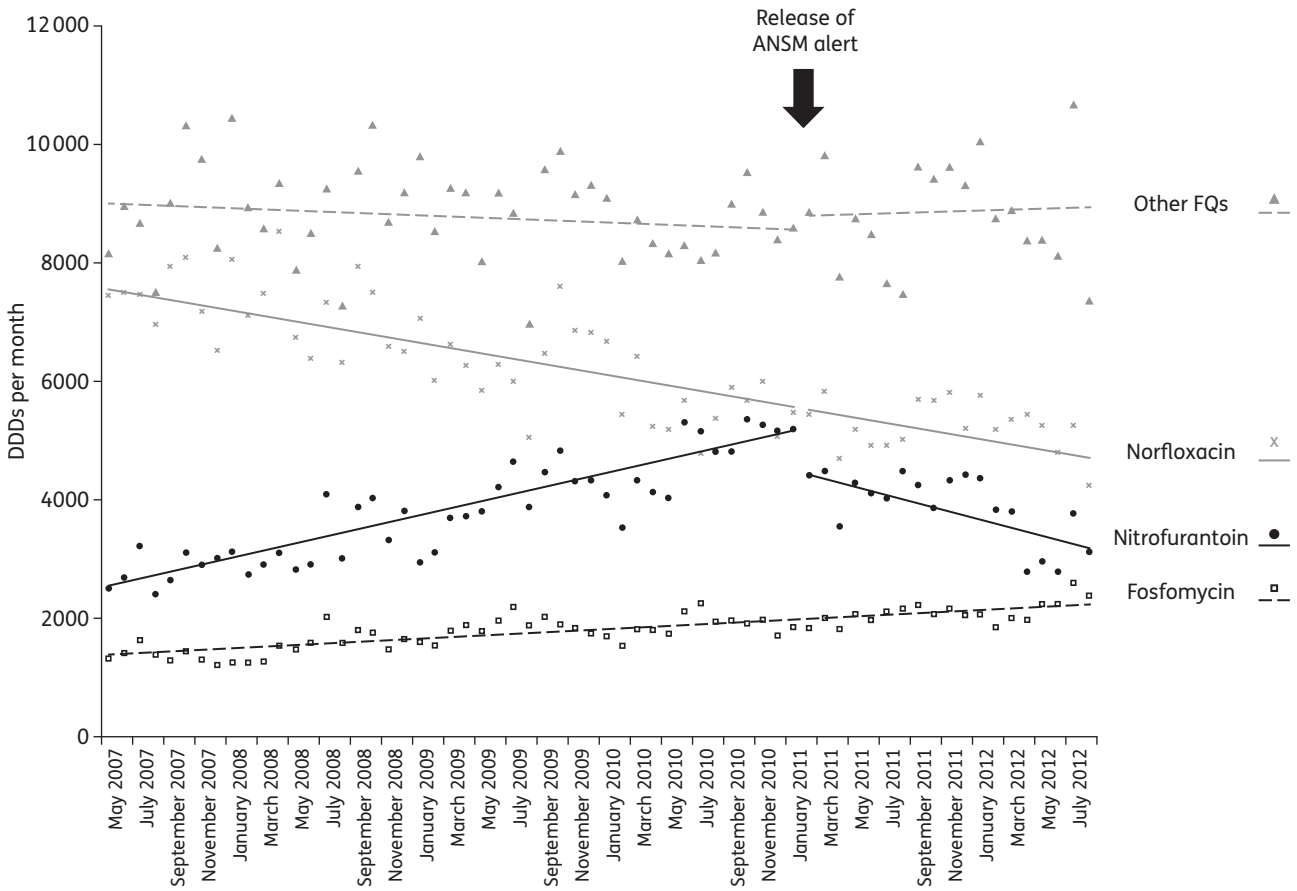

Figure 1. Graphical representation of the segmented regression modification of antibiotic use before and after the release of the ANSM alert. FQs, fluoroquinolones.

most European experts' analyses, there is no strong scientific evidence to limit the use of nitrofurantoin for both incident and recurrent short-term UTI treatment, and its use is now recommended in numerous guidelines worldwide.[8] The incidence of serious adverse events due to antibiotic classes deserves scrutiny. A survey led by the CDC estimated nearly identical incidence rates in emergency department visits triggered by nitrofurantoin and quinolone use (9.8 versus 9.2 visits per 10 000 outpatient prescriptions, respectively); the study aggregated data for short- and long-term nitrofurantoin therapy.[9]

From our point of view, the unfortunate phrasing of new French guidelines left virtually no room for nitrofurantoin in UTIs, given that cultures are not routinely collected and thus true infection is rarely documented in women presenting with symptoms of UTI. In conclusion, while long-term, prophylactic nitrofurantoin should be restricted, we believe that nitrofurantoin should retain its place in the therapeutic armamentarium for UTIs, especially in the face of rising multidrug-resistant Enterobacteriaceae. The tremendous impact of increased fluoroquinolone consumption on antimicrobial resistance has been well documented.[10] In the setting of rapidly increasing antimicrobial resistance and an alarming paucity of novel therapeutic options, it is imperative that policy makers avoid reactionary measures and take instead the long view.

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Urolithiasis associated with atazanavir may mask a metabolic 'channelling' bias

Giovanni Guaraldi[1]*, Giovanni Dolci[1] and Antonio Bellasi[2]

[1]Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [2]UOC Nefrologia e Dialisi, Azienda Ospedaliera Sant'Anna, Como, Italy

*Corresponding author. Tel: +39-059-4225318; Fax: +39 059-4223710; E-mail: giovanni.guaraldi@unimore.it

Keywords: metabolic syndrome, protease inhibitors, chronic kidney disease

Sir,

Chronic kidney disease (CKD) is an emerging clinical issue in HIV, particularly in ageing infected patients. Nephrotoxicity is a major issue and a frequent cause of drug switching owing to glomerular or tubular damage and the fear of progressive CKD.[1,2] However, the incidence and impact of urolithiasis as an independent contributor to CKD are not known in HIV-infected patients.

Historically, antiretroviral-induced urolithiasis has been common in patients treated with indinavir, probably due to drug crystallization and precipitation in the kidneys.[3]

At present, with regards to the risk of urolithiasis, the use of boosted or unboosted atazanavir as preferred protease inhibitor (PI) is of concern. In a large retrospective study of 1240 HIV-infected individuals, Hamada *et al*.[4] reported a urolithiasis incidence of 23.7 cases per 1000 patient-years among atazanavir-treated patients. Notably, the authors postulated that atazanavir/ritonavir can promote kidney stones via similar mechanisms to indinavir-induced urolithiasis.[4] This single-centre study,[4] as the authors pointed out, had several limitations owing to its observational and retrospective nature and because of the absence of renal stone composition analyses. In particular, the hypothesized pathogenetic mechanism – atazanavir-supersaturated urine inducing crystalluria – is difficult to test in consideration of the lack of association between serum bilirubin levels, surrogate markers of plasma atazanavir concentration and the risk of kidney stones.

By contrast, baseline data showed significantly higher uric acid concentrations in patients treated with atazanavir/ritonavir compared with patients treated with other PIs. Even though uric acid levels did not affect the Cox proportional hazard regression model results, and atazanavir/ritonavir exposure was associated with a 10-fold increased risk for kidney stones, these results may have been distorted by a 'channelling' bias. Atazanavir/ritonavir is preferentially prescribed to patients with higher metabolic risk profiles (European AIDS Clinical Society; Version 6.1; November 2012; http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41).

An expanding body of evidence supports the notion that kidney stones are not always a separate entity but in some instances represent an epiphenomenon of a systemic metabolic disorder, being associated with insulin resistance and metabolic syndrome.[5,6] In keeping with the study by Hamada *et al*.,[4] it is plausible that at least some of the reported effects of atazanavir/ritonavir could be confounded by physician prescription.

Interestingly, the prevalence of nephrolithiasis seems higher among HIV-infected individuals than the general population (0.8%).[2] Raheem *et al*.[7] described 46 cases of nephrolithiasis in a cohort of 436 HIV-positive subjects, corresponding to an overall 11% prevalence: similar to what is expected in the general population. Unfortunately, stone analysis was only available in seven subjects and documented four cases of calcium oxalate monohydrate crystals and only one case each of cystine, uric acid and atazanavir crystals. A similar prevalence of kidney stones was described in the Castle study, the largest randomized clinical trial on atazanavir/ritonavir ever performed in naive patients.[3]

Though evidence in HIV-infected individuals is far from being conclusive, the study by Hamada *et al*.[4] suggests a thorough metabolic evaluation for nephrolithiasis in HIV-infected patients with recurrent episodes of kidney stones, a family history of nephrolithiasis or evidence of multiple kidney stones at imaging.

However, we suggest caution in interpreting the epidemiological data linking atazanavir exposure and kidney stones owing to a potential 'channelling' bias. Indeed, an excess number of patients