Urological Science 27 (2016) 193–198

Contents lists available at ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Review article

Risks of long-term use of nitrofurantoin for urinary tract prophylaxis in the older patient

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ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form
12 July 2016
Accepted 18 July 2016
Available online 23 November 2016

Keywords:
nitrofurantoin
older patients
urinary tract infections
urinary tract prophylaxis

ABSTRACT

Purpose: To review the current literature on reported pulmonary, liver, and nerve adverse reactions (ARs) of long-term Nitrofurantoin (NF) suppression in older patients treated for urinary tract infections (UTIs).
Materials and methods: An extensive literature search was performed on PubMed for the search terms "Nitrofurantoin," and "Nitrofurantoin and lung, pulmonary, liver, nerve or ARs". Relevant cited papers were also analyzed. Articles not in English, or related to children, or pregnant women were excluded.
Results: In 43 articles and other texts meeting the inclusion criteria from 1968 to 2014, rates of long-term NF-related pulmonary ARs compared to total NF prescriptions differed worldwide, but remained extremely small at 0.001% (USA) and 0.001% for pulmonary and hepatic ARs (France). Among all NF ARs, rates of pulmonary ARs differed across the literature from 2% (UK), 3% (Holland), 5% (Sweden), to 7% (Australia). Nerve ARs were reported as .0007% and liver ARs as .0003% of total prescriptions
Conclusions: Pulmonary, nerve, or liver ARs resulting from long-term NF prophylaxis in older patients treated for UTIs are potentially serious but extremely rare, and should not deter from the cautious use of NF in this population.

1. Introduction

The management of recurrent urinary tract infections in women tends to be challenging and can be influenced by age, renal function, the mode of recurrence—namely persistence (same bacteria) or reinfection (different bacteria), antibiotic allergies, and strain resistance to some antibiotics. Antibiotic resistance is a growing concern, especially for certain classes of antibiotics such as fluoroquinolones.

Nitrofurantoin (NF) has been the focus of much attention lately, in part due to the recommendations for its use outlined in the Beers criteria. In 2003, the first set of Beers criteria alerted the public to the dangers of NF in older adults because of the "potential for renal impairment" with a high level of severity rating.[1] In 2012, the Beers criteria update expert panel included NF on a list of drugs potentially inappropriate to use in older adults. This time the focus was on "potential for pulmonary toxicity," with a quality of evidence rated as moderate, and a strong strength of recommendation.[2] The 2012 Beers document emphasized three additional points: (1) avoid in patients with renal impairment (creatinine clearance < 60 mL/min); (2) safer alternatives are available; and (3) avoid for long-term suppression.[2]

For practitioners, these 2012 recommendations prompted additional justification to reassure concerned patients already on NF suppression. Health insurance providers also circulated notifications to physicians prescribing NF to encourage them to reconsider their decision and change to other therapies. Subsequently, the Beers 2015 recommendations were issued,[3] followed very recently by a special American Urological Association white paper on this matter to revisit the intended purpose of the Beers criteria.[4]

In this context, our goal was not to reconsider the well-established recommendations to avoid NF in older adults with renal impairment,[3] but instead to focus on the available literature data regarding NF adverse reactions (ARs), with a special emphasis on pulmonary, liver, and nerve toxicity in order to better communicate these risks to older women and to assist in their regular monitoring.

2. Materials and methods

An extensive literature search was performed on PubMed for the search terms "Nitrofurantoin," and "Nitrofurantoin and lung, pulmonary, liver, or nerves, or ARs." Relevant cited reviews were

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http://dx.doi.org/10.1016/j.urols.2016.07.004

also analyzed. Articles not in English, or related to children or pregnant women were excluded. Four datasets were queried: ARs versus prescriptions of NF, ARs alone, retrospective and prospective studies, and tallying of case study reports in older women. As a general comment, most datasets did not provide a separate analysis of sex involvement, and thus, although not always clearly established in reports, the majority of data reviewed were for women. To determine the impact of age on pulmonary ARs, a case study subanalysis was performed in affected women using age 65 years as a traditional cut-off for older adults.

3. Results

The following results were extracted from 43 articles and other texts meeting our inclusion criteria from 1968 to 2014.

3.1. Lung toxicity and avoidance of NF for long-term suppression

This result section includes data primarily on lung toxicity as it is the most commonly involved organ. The data are presented in four sections including: ARs, retrospective and prospective series, and case series (Appendix 1).

3.1.1. Spectrum of pulmonary adverse reactions

Pulmonary ARs are typically divided into acute and chronic reactions. The acute reactions are more common and the development of one does not appear to increase one's risk for the other reaction.[5,6] Acute pulmonary reactions appear within days of starting the medication.[7] Patients typically report respiratory and constitutional symptoms. Rash and eosinophilia are also common. If the drug is stopped complete resolution is the norm; however, if not, the reactions can become severe and progress to acute respiratory distress syndrome.[8] Rechallenge virtually always causes a relapse and is not recommended.

In contrast, the chronic ARs appear months to years after drug initiation. Persistent cough and dyspnea are the primary symptoms.[9] A large variety of interstitial lung disease patterns have been reported including nonspecific interstitial pneumonia, desquamative interstitial pneumonia, organizing pneumonia, and eosinophilic pneumonia.[10] Drug cessation is necessary for all and corticosteroids may be of value for severe disease or disease that progresses despite removal of the NF. Residual disease is common despite the above measures.

3.1.2. AR reporting compared to total NF prescriptions

Two large scale studies compared the number of reported chronic ARs of NF to the total number of prescriptions of NF. The first large dataset (1953–1984) was reported by D'Arcy[11] based on adverse reports to the drug manufacturer, Norwich Eaton Pharmaceuticals, Norwich, New York, USA, in which the rates of reported ARs in a study encompassing 121,430,000 courses of treatment were tallied.[10] Pulmonary reactions were reported in 0.0002% courses of treatment, liver reactions in 0.0003% of courses, neuropathy in 0.0007% of courses, and blood dyscrasias in 0.0004% of courses, totaling 0.001% in chronic, severe complications.[11] Notably, of all the chronic side effects, pulmonary reactions were the least frequent, despite being the reason stated in the Beers 2012 criteria for warning against NF. Another study analyzing NF prescriptions in France in 2010 compiled 261,000 prescriptions of NF, with an estimated 1500–2500 prescriptions for treatment > 4 months.[12] They estimated that chronic pulmonary or hepatic reactions occur in one out of every 517–862 prescriptions, or 2.9 cases/y. Meanwhile, the French Committee on Drug Monitoring reported "severe ARs," mainly pulmonary or hepatic for NF, with a frequency of 1/20,551 NF prescriptions (0.0049%).[13] This frequency increased with treatment duration: from 1 case/24,800 for short-term prescriptions (1 month) to 1 case/7666 for long-term prescriptions (>1 month). These two studies indicated that reactions to chronic NF remained very low when compared with the amount of prescriptions of NF.

3.1.3. AR reporting

In 1982, Penn and Griffin[14] compared ARs between the UK (reported from the Committee on Safety of Medicines), Sweden (from Holmberg et al[5]), and Holland (from the Netherlands Drug Registration Authority), noting that AR reporting varied between countries as seen in Table 1. From those data, pulmonary chronic effects of NF ranged from 2.0% to 5.3% of adverse reports. Furthermore, even within a country, AR reporting varied between years. For instance, from 1964 to 1980 in the UK, AR reporting declined from 1.77% to 0.11%, but increased from 1.5% in 1965–1969 to 7.9% in 1970–1974 in Sweden. In this same Swedish study from 1966 to 1976, Holmberg et al[5] analyzed 921 patients with ARs, 42 of which were on therapy for >1 year. Of those 42 patients (mean age 68 years), 23 experienced a pulmonary AR to NF. They also noted that risk of ARs increased with age, and that women were more at risk compared with men.

Two other studies focused solely on pulmonary ARs. The first study was performed by Holmberg and Boman[6] from 1966 to 1976 in Sweden, in which reports to the Swedish Adverse Drug Reaction Committee were analyzed. Out of 447 pulmonary AR reports, 49 were due to chronic NF intake, 41 of whom were on therapy for 10 months to >65 months. Approximately three quarters of the patients required hospitalization because of an adverse pulmonary reaction. The median age of the women on long-term therapy was 58 years, suggesting that younger women are equally susceptible to the chronic side effects of NF as older women are.

The second study from Australia focused on adverse outcome reporting without comparison to the amount of prescriptions. By 2004, the Australian Adverse Drug Reactions Advisory Committee received a total of 576 adverse reports.[15] Of these 142 were pulmonary ARs, 40 of which were chronic NF-induced pulmonary AR reports. Older women (median > 70 years) were the predominantly affected demographic group.[15] These authors and others have postulated this may reflect usage of NF.[15,16] Time of onset of the AR ranged from 8 months to 16 years. Of the 40 patients with chronic pulmonary toxicity, 12 patients recovered and two patients died. The remainder had persistent lung damage. This study illustrated the unpredictable onset and rarity of pulmonary damage.

3.1.4. Retrospective studies

Two large retrospective studies focused on pulmonary ARs. In the first retrospective study from 1989, Jick et al[17] identified 742 long-time users and 16,101 patients with first courses of treatment of NF, and compared their hospitalization rates. In the group of long-time users, only one man aged 65 years was hospitalized for dyspnea (one women aged 89 years was hospitalized for possible

Table 1
Percent of reported adverse reactions across the UK, Sweden, and Holland (total adverse reports).

Reaction	UK (155)	Sweden (921)	Holland (unknown)
Pulmonary reaction (%)	2	5.30	3.40
Liver damage (%)	3.90	Not available	9.10
Peripheral neuropathy (%)	14.10	2.20	9.10

Note. From "Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland," by Penn and Griffin, 1982, *British Medical Journal (Clinical Research Edition)*, 284, p. 1440–2. Copyright 1982, *BMJ Publishing Group Ltd.* Adapted with permission.