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How Common Are Pulmonary and Hepatic Adverse Effects in Older Adults Prescribed Nitrofurantoin?

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Abstract

OBJECTIVES—To determine the frequency of serious pulmonary and hepatic adverse events in persons 65 and older who are prescribed nitrofurantoin.

DESIGN—Retrospective electronic medical records chart audit of nitrofurantoin prescriptions and associated adverse events.

SETTING—Urban Academic Medical Center

PARTICIPANTS—All inpatient and outpatients 65-years and older prescribed nitrofurantoin between 1/1/2010–12/31/2014.

MEASUREMENTS—Data acquisition by electronic health record (EHR) the number of nitrofurantoin prescriptions and pulmonary and hepatic adverse events associated with nitrofurantoin use. Age, dose, duration of use, estimated glomerular filtration rate were determined in those with suspected adverse events.

RESULTS—3400 patients at least 65-years old were prescribed nitrofurantoin during the study period. Of these, 641 were identified as possibly having one of five targeted symptoms/disease complications (pulmonary and hepatic) associated with nitrofurantoin. After a detailed chart audit, 89% were deemed to have no adverse reaction; 7% had a minor side effect or allergy; and 3.9% met criteria for suspicion of a nitrofurantoin-induced adverse events. Of the latter, five patients were rated as being highly suspicious for nitrofurantoin toxicity; four of the five were identified with pulmonary toxicity; and one with hepatotoxicity. Four out of five of these patients used nitrofurantoin chronically.

CONCLUSION—Nitrofurantoin was prescribed for 3400 patients 65 years or older during the five-year study period. Serious side effects appeared to be uncommon but chronic use appears to expose greater risk.

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Keywords

Nitrofurantoin; Beers criteria; adverse drug events; pulmonary toxicity; hepatotoxicity

INTRODUCTION

Nitrofurantoin use in older adults has been controversial. Nitrofurantoin prescriptions have dramatically risen since guideline changes by the Infectious Disease Society of America (IDSA) recommended nitrofurantoin as first choice treatment for acute uncomplicated cystitis and pyelonephritis in 2011.¹ These guidelines were limited to premenopausal women. Although the report noted that urinary tract infections (UTI) in postmenopausal women without urologic abnormalities or those with well controlled diabetes could be considered to have uncomplicated UTI, the committee specifically noted these patients were outside the scope of the IDSA guidelines. For premenopausal women the IDSA concluded that nitrofurantoin was the recommended choice due to minimal resistance and lower propensity for development of drug-resistant organisms and the drug's effectiveness, which is comparable to 3 days of trimethoprim-sulfamethoxazole.¹

Nitrofurantoin remains listed as a potentially inappropriate medication for older adults by the American Geriatrics Society Beers Criteria.² It was first added to the Beers list in 2002 when the panel of experts wrote "potential for renal impairment and safer alternatives available" and assigned a severity rating of "high."³ In a 2012 Beers update the rationale for listing included potential for pulmonary toxicity and lack of efficacy in patients with creatinine clearance < 60 mL/min due to inadequate drug concentration in urine.⁴ However, the evidence for lack of efficacy in patients with creatinine clearance below 60 mL/min has been questioned⁵ and the most recent 2015 Beers update has been modified to recommend avoidance when creatinine clearance is below 30 mL/min.² In addition, the committee's rationale for avoiding nitrofurantoin included pulmonary toxicity, hepatotoxicity, and peripheral neuropathy with particular unease about long-term use while safer alternatives are available.² The strength of the recommendation from the AGS Beers expert panel remained strong, but the quality of evidence was downgraded from moderate to low.

Two of the most serious nitrofurantoin-associated adverse reactions are pulmonary and hepatic.⁶⁻⁹ Because of limited published clinical reports we sought to determine how often pulmonary and hepatic adverse events occurred in patients 65 years and older prescribed nitrofurantoin in a large multidisciplinary academic health system. By doing so we hope to gain a better appreciation of how often nitrofurantoin resulted in serious adverse reactions and thereby inform physician decisions regarding the use and safety of nitrofurantoin in older adults.

METHODS

Study Design and Population

All patients aged 65 years or older prescribed nitrofurantoin at UT Southwestern Medical Center's clinics or hospitals (University Hospital or Zale-Lipshy Hospital) from Jan 1, 2010

to Dec 31, 2014 were identified from EHRs (Epic Systems Corporation, Verona, WI). Prescriptions are captured regardless of the site origination (hospital, clinic, home or other location) and irrespective of the location of the receiving pharmacy. Most prescriptions are e-prescribed but phone-in and printed prescriptions are also recorded in the electronic system.

Patients prescribed nitrofurantoin associated with international classification of diseases codes (ICD 9) for dyspnea (786.09), pulmonary fibrosis (515), cholestatic jaundice (782.4), chronic hepatitis (571.40), or hepatotoxicity (575.3) helped identify patients suspected of serious nitrofurantoin-induced adverse events and were selected for further direct chart audit. Study data electronically extracted included patient's age, sex, number of capsules (<30 or ≥30), number of individual prescriptions per patient, allergy to nitrofurantoin and estimated glomerular filtration rate (eGFR) less than or greater than 60.

Determination of Nitrofurantoin-Associated Adverse Events

The electronic records of patients prescribed nitrofurantoin and identified with one of the suspect diagnostic ICD-9 codes were manually audited by two medical students (KC and ES) utilizing a decision matrix to systematically grade the likelihood of a nitrofurantoin-associated adverse event to minimize subjectivity. An adverse event had to be temporally associated with nitrofurantoin use within 6 months after prescribing nitrofurantoin episodically or up to a year after cessation of prophylactic use.

The medical record was then inspected for the presence of acute or chronic problems that could explain the patient's symptoms and for any investigation or assessment of nitrofurantoin induced adverse effect. The reviews independently categorized the adverse event into seven categories (Table 1). If discordance occurred between reviewers, a third reviewer, a senior faculty physician (CDR), examined the chart and the category was assigned based on the majority.

Patients classified as "High Suspicion" were determined to have no other underlying condition or acute cause to explain their symptoms after the case was highly clinically investigated (e.g. patient chronically taking nitrofurantoin or developed pulmonary fibrosis, all other causes ruled out, symptoms improved after cessation of nitrofurantoin).

Possible "A" patients had an underlying condition to explain their symptoms (e.g. dyspnea attributed to chronic obstructive pulmonary disease (COPD), dyspnea worsened on nitrofurantoin but improved after cessation of nitrofurantoin) and the patient returned to previous baseline after nitrofurantoin cessation. Possible "B" cohort had no relevant underlying condition and no definitive evidence for an acute explanation of their symptoms (e.g. patient in hospital for dyspnea after taking nitrofurantoin with many possible etiologies for dyspnea; nitrofurantoin as a cause neither confirmed nor denied). Possible "C" cohort consisted of patients with no underlying conditions or acute cause to explain their symptoms and was not investigated clinically (e.g. patient called during short course of nitrofurantoin reporting transient symptoms and stopped nitrofurantoin).

Nitrofurantoin allergic reactions were noted when pruritus, rash, swelling, or anaphylaxis occurred. Minor adverse reactions were categorized for mild non-specific complaints such as nausea, diarrhea and headache. No adverse effects were reported if chart documentation revealed minimal exposure such as patient prescribed three doses or less as a suppressive treatment before a urologic procedure or lack of documentation of an adverse event.

For patients with suspected adverse reactions, age, sex, and kidney function (eGFR) were evaluated as contributing factors to nitrofurantoin-associated adverse events. In addition, dosage and maximum length of nitrofurantoin therapy were obtained by chart review.

Following the initial evaluation and the probability determination of a nitrofurantoin adverse event, those classified as High Suspicion or Possible Suspicion (A, B or C) for drug toxicity were assessed using the Naranjo adverse drug reaction probability scale score which was developed for use in controlled trials and registration studies of new medications but not for retrospective studies.¹⁰ Nonetheless the scoring was completed to assess some degree of consistency of our evaluation. Total scoring ranges from -4 to +13. Score from 1 to 4 are interpreted as possible drug reaction, 5 to 8 probable and above 9 as a definite drug reaction. Scores of zero or less indicate a doubtful adverse drug reaction.

Statistical Methods

This is a descriptive study. Age group and gender comparisons between the adverse event and non-adverse event patients were made with the Cochran-Armitage Trend Test and the Fisher's Exact Test, respectively.

RESULTS

3400 patients 65 or older (average age 76.5 years, range 65–103 years) were prescribed nitrofurantoin during the study period; 641 patients were initially identified as having one to five target ICD-9 codes associated with a nitrofurantoin-associated adverse event. After manual chart inspection of these 641 suspected cases, 89% were deemed to have no drug-related adverse event; 5.1% experienced a minor side effect; 1.9% were due to allergy; and 3.9% (25/641) were identified as possibly experiencing a pulmonary or hepatic-associated nitrofurantoin-induced adverse event. Five (0.8%) of the 25 possible serious adverse event cases were rated as “High Suspicion (HS)” for nitrofurantoin toxicity and 20 patients as Possible Suspicion (PS) for an adverse drug effect (3.1%) (Table 2). Of the HS cases, four were identified with pulmonary toxicity and one with hepatotoxicity; four of the five HS cases used nitrofurantoin chronically

In addition, four patients with existing interstitial lung disease (ILD) worsened when they were on nitrofurantoin. This accounts for 57% or four of the seven Possible A patients. Adverse events by age, sex, drug exposure and eGFR are shown in Figure 1. There were no differences among the three age groups listed ($p=0.34$) but a difference in gender among the 25 patients with possible adverse events was noted. Women were more likely to have a possible adverse event ($p=0.04$) although the number of men in this category was very low ($n=1$). The eGFR was only available for the 25 patients with suspicion for nitrofurantoin adverse events but the distribution above and below 60 mL/min appeared similar (Figure 1).

When evaluating chronicity of use, we found 80% (4/5) of HS patients took nitrofurantoin for at least one month while only 14% of Possible A, 40% of possible B and none of Possible C categorized patients received nitrofurantoin long-term.

When the Naranjo Adverse Drug Reaction Probability Scale was used, all HS patients scored a four and were considered to have a “possible” reaction. One PS “B” patient scored four; the other 19 PS cases scored three or less; none scored zero or less.

DISUSSION

Despite nitrofurantoin placement on the Beers list we found it commonly prescribed in patients age 65 years and older in a large multi-specialty academic health system. Among the 3400 patients prescribed nitrofurantoin we identified 25 over a five-year period with pulmonary or hepatic diagnoses possibly associated with nitrofurantoin, five of which were felt to be highly suspicious for a serious nitrofurantoin-induced adverse event. Overall we found that 0.7% (25/3400) of patients experienced possible serious pulmonary or hepatic adverse effects and 0.15% (5/3400) of patients were classified as highly suspicious of having a serious lung or liver reaction. The majority of HS cases used nitrofurantoin chronically; the most common reason as discerned by chart inspection were for neurogenic bladder and idiopathic recurrent UTI.

D’Arcy reported pulmonary and hepatic toxicity due to nitrofurantoin occurred in 0.001% and 0.0003%, respectively.¹¹ In a recent systematic review Huttner et al¹² found no pulmonary or hepatotoxic events related to nitrofurantoin among 4807 patients from 27 controlled trials. However, trials were of short-term use and predominantly among younger patients. Overall toxicity was 5%–16% in the 17 of 27 studies reporting toxicity and were mostly mild reversible gastrointestinal side effects. A recently published study by Santos et al¹³ did not reveal an overall greater risk of lung injury in individuals given nitrofurantoin than in those given other antimicrobials for cystitis. However, the group taking nitrofurantoin for at least 14 days had a higher risk than those taking it for a shorter duration.¹³

Our results may be skewed due to possible pre-exclusion of nitrofurantoin prescriptions to patients with a low GFR. However, despite recommendations during the time of the study to avoid use in older patients and in particular in those with creatinine clearance below 60 mL/min, nitrofurantoin use was common. The eGFR among the 25 patients with a possible adverse events were almost equally divided above and below 60 (Figure 1). We did not evaluate treatment failure which has been a concern with use of nitrofurantoin in older populations. Findings from a recent study in woman over 65 years treated with nitrofurantoin for UTIs found no difference in treatment response with mild or moderate reduction in eGFR.¹⁴

While peripheral neuropathy is another serious adverse event associated with nitrofurantoin use, we elected not to include ICD codes for peripheral neuropathy because of the potential difficulty assigning nitrofurantoin causation for this common problem in older adults as other confounders such as diabetes, alcohol consumption, or idiopathic neuropathy may also

have been present. Nonetheless by omitting this potential side effect we may be underreporting a common serious reaction to nitrofurantoin use. Within the 641 charts reviewed for possible pulmonary or hepatic complications we did not find evidence of drug-induced neuropathy.

There are several limitations to this study. This retrospective review of EHRs was dependent on the documentation of complaints and coding, medication adherence, and follow-up. This could lead to inaccurate reporting of adverse events if the former are not properly reported. If patients developed side-effects and did not return to our health system, their events would not have been captured. In addition, we did not confirm medication adherence by pill count or other measures but relied solely on prescribing information. Furthermore, the retrospective analysis did not allow for patient interviews or prospectively evaluate data, which would be particularly helpful to assess adverse drug events and likewise retrospective analysis did not provide the medical reasoning for nitrofurantoin selection. We tried to minimize subjectivity by using multiple chart reviewers and utilizing a decision matrix, our interpretation of adverse events could be a source of incidence under or over reporting. Lastly, limited demographic information may make application of our findings to individual practitioners difficult.

The 0.8–4% adverse event incidence reported here is of concern but should not prohibit nitrofurantoin prescriptions in older patients. Overall our findings support the recently updated Beers Criteria guideline² which advocates avoiding chronic use in older adults and in those with creatinine clearance less than 30 cc mL/min. However, since we did not include patients younger than 65 years in our study, we could not determine if there are age-related differences in hepatic and pulmonary complications. Since the initial listing of nitrofurantoin on the Beers List was at least partially based on the lack of efficacy with age-related decline in renal function, it is possible that this drugs placement on the Beers list may no longer be justified.

In summary our findings suggest avoidance of nitrofurantoin in patients with chronic lung disease (e.g. interstitial lung disease, pulmonary fibrosis) and to use particular caution when prescribing long-term utilization. However, we found little evidence to prohibit short-term use of nitrofurantoin. While caution should be exercised with all medications, we hope this analysis will stimulate improved reporting and risk assessment of nitrofurantoin use as well as provide more tangible data to inform providers and clarify the risk of adverse events associated with nitrofurantoin in older patients.

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Author Contributions:

Claussen: data acquisition, analysis and interpretation, preparation of manuscript

Stocks: data acquisition, analysis and interpretation, preparation of manuscript. Bhat: data acquisition, preparation of manuscript. Fish: study design, data acquisition, analysis and interpretation, preparation of manuscript. Rubin: study concept and design, data acquisition, analysis and interpretation, preparation of manuscript.

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Figure 1.
Rates of Nitrofurantoin-Induced Adverse Events by age, sex, exposure and eGFR.

Table 1

Nitrofurantoin-Induced Adverse Event (AE) Categories

AE Category	Description
High Suspicion	No relevant underlying conditions, no other cause, highly investigated clinically
Possible A	Possible exacerbation of underlying condition due to nitrofurantoin
Possible B	No relevant underlying conditions, no other causes, evidence not definitive
Possible C	No relevant underlying condition, no other cause, not investigated clinically
Allergy	Rash, pruritus, swelling, and anaphylaxis
Minor Side Effect	Nausea, diarrhea, and headache
No AE	Nothing in patient's chart indicative of an AE

Table 2**Summary of Nitrofurantoin-Induced Adverse Event Cases**

AE	Case No.	Age*	Sex	Dose**	Length of Use***	eGFR****
High Suspicion	1	73	F	100	6 years	23
High Suspicion	2	82	F	200	6 days	>60
High Suspicion	3	82	F	50	1 year	38
High Suspicion	4	69	F	100	30 years	30
High Suspicion	5	72	F	200	2 years	>60
Possible A	6	77	F	200	3 short courses	>60
Possible A	7	73	F	200	2 short courses	48
Possible A	8	74	F	200	3 short courses	78
Possible A	9	86	F	200	1 short course	16
Possible A	10	75	F	200	7 short courses, 3 month long.	40
Possible A	11	94	M	200	2 short courses	>60
Possible A	12	69	F	Not listed	23 years	>60
Possible B	13	86	F	50	3 years	48
Possible B	14	87	F	50	1 year	58
Possible B	15	85	F	200	1 short course	>60
Possible B	16	77	F	100	5 months	>60
Possible B	17	68	F	200	2 short courses	>60
Possible B	18	76	F	400	12 short courses	52
Possible B	19	83	F	100	6-one month courses	>60
Possible B	20	82	F	50	Unable to document	46
Possible B	21	69	F	100	Unable to document	-
Possible B	22	75	F	50	4 years	25
Possible C	23	73	F	200	2 short courses	>60
Possible C	24	68	F	200	Short courses	>60
Possible C	25	85	F	200	Short courses	>60

* Age at time of adverse event

** Daily dose in mg

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Short course defined as less than 30 tablets
Closest glomerular filtration rate in relation to nitrofurantoin adverse event.