REVIEW PAPER

URINARY TRACT INFECTIONS

Nitroxoline: treatment and prevention of urinary tract infections from the urologist's perspective

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Introduction Nitroxoline is an old antimicrobial agent with a broad spectrum of pharmacological applications and a unique mechanism of action. However, its use in the treatment and prevention of urinary tract infections (UTIs) has not been popular in the recent past. Recently, nitroxoline is gaining interest, due to frequent drug-resistance in uropathogens. Unfortunately, there are few modern clinical trials assessing this antibiotic. Also, older researchers often do not meet current scientific standards. This review seeks to provide a comprehensive overview of nitroxoline as a viable option in treating uncomplicated lower UTIs.

Material and methods A comprehensive literature search regarding the use of nitroxoline in UTIs was conducted using Pubmed, Cochrane Library and Embase databases. A cross-reference search was also performed. Case reports, editorials and non-peer-reviewed literature were excluded from further analysis. As a result, 21 publications were included in this review.

Results The available literature on nitroxoline's mechanism of action, pharmacokinetics, minimum inhibitory concentrations, *in vitro* activity and resistance rates strongly suggests that nitroxoline is a potent broad-spectrum antimicrobial agent. Moreover, clinical efficacy of the drug was analyzed – 2 articles proved high eradication rates in women with uncomplicated lower UTIs and 1 reported unsuccessful treatment in geriatric patients with lower complicated and uncomplicated UTIs. Finally, the present data on adverse effects indicate that nitroxoline is well-tolerated.

Conclusions Nitroxoline is an obscure, yet potentially effective and safe antimicrobial agent in uncomplicated lower UTIs. Unfortunately, it is available only in a few countries. Nonetheless, nitroxoline can be useful in urological practice.

Key Words: Nitroxoline ‹› 5-nitro-8-hydroxyquinoline ‹› urinary tract infection ‹› cystitis

INTRODUCTION

Nitroxoline (5-nitro-8-hydroxyquinoline) is an old antimicrobial agent with a broad spectrum of pharmacological applications and a unique mechanism of action [1]. Even though it had been known as an effective uroantiseptic since the previous century, its use in the treatment and prevention of urinary tract infections (UTIs) has not been popular in the recent past. At the moment, nitroxoline is commercially available only in Germany, Poland, Croatia, Bulgaria, Romania, Bosnia-Herzegovina and Montenegro [2]. Nonetheless, in interdisciplinary German guidelines nitroxoline is recommended in uncomplicated lower UTIs [3].

As drug resistance in uropathogens is becoming more common, the search for alternative treatment options intensifies. That is why nitroxoline is quickly gaining interest. It is active against a variety of Gram-negative and -positive bacteria, mycoplasmas

and *Candida spp.*, while maintaining a reasonably low risk of adverse effects [4].
Unfortunately, there are only a few modern clinical trials assessing nitroxoline, due to its low popularity. Also, older researches often do not meet current scientific standards.
Nonetheless, in this review we examined nitroxoline's mechanism of action, pharmacokinetics, safety profile and efficacy against common uropathogens, considering their resistance mechanisms. Through a lens focused on the current urological practice, this review seeks to provide a comprehensive overview of nitroxoline as a viable option in treating active uncomplicated lower UTIs, as well as preventing recurrent infections.

MATERIAL AND METHODS

By employing the PICO framework, we have developed the following research question: "In adult patients with urinary tract infections (P), how does treatment with nitroxoline (I) compare to standard antibiotic treatment (C) in terms of effectiveness in treating UTIs, preventing recurrent UTIs, reducing side effects and minimising the development of antibiotic resistance (O)?". To answer this question, a literature search was conducted. Pubmed, Cochrane Library and Embase databases were searched using the following search string "("nitroxoline" OR 5-nitro-8-hydroxyquinoline) AND (urinary tract infection OR UTI)". A cross-reference search was also conducted. Case reports, editorials and non-peer-reviewed literature were excluded from further analysis. The PRISMA flowchart below illustrates the approach employed during the process of data extraction [Figure 1].

Mechanism of action

Nitroxoline has a unique molecular structure and does not belong to any typical class of antibiotics [1]. Moreover, it is arguably the only antimicrobial drug that uses chelation of metallic bivalent cations as the only mechanism of action [1, 4]. Chelation is a process in which metallic cations form covalent bonds with a polydentate ligand (in this case nitroxoline), thus eliminating these cations from microbes. What is crucial, bacteria and yeast use metal cations as cofactors for cellular proteins, which are essential for their survival [1].
Also, presence of Mg2+ cations favour the accumulation of nitroxoline in the cell wall of some bacteria (for example in *E. coli*). Even in low concentration of nitroxoline, this results in the increase of bacterial wall hydrophobicity and reduction of adherence to the catheter surface [5]. Therefore, subinhibitory concentrations of nitroxoline might lower adhesin expression and bacterial attachment [4].
Also, nitroxoline can reduce the biofilm formed by *Pseudomonas aeruginosa*, by chelation of iron and zinc. It enhances twitching motility in surface-attached cells, which stops microcolony formation [6].
Finally, nitroxoline and its derivatives act as metallo-beta-lactamase (MBL) inhibitors, by chelation of Zn^{2+} that is necessary for the enzyme activation. Combination of imipenem and nitroxoline derivative can overcome carbapenem resistance, including New Delhi MBL *K. pneumoniae* and Verona integron-encoded MBL *E. coli* [7].

Pharmacokinetics

In this review, pharmacokinetics (PK) of nitroxoline have been presented using the ADME approach: A – absorption, D – distribution, M – metabolism, E – excretion.
According to the available data, after oral administration, nitroxoline is quickly and almost completely absorbed in the gastrointestinal tract. Then, the drug is rapidly metabolised in the liver creating conjugated metabolites that most probably also exhibit antibacterial activity [8]. Around 60%

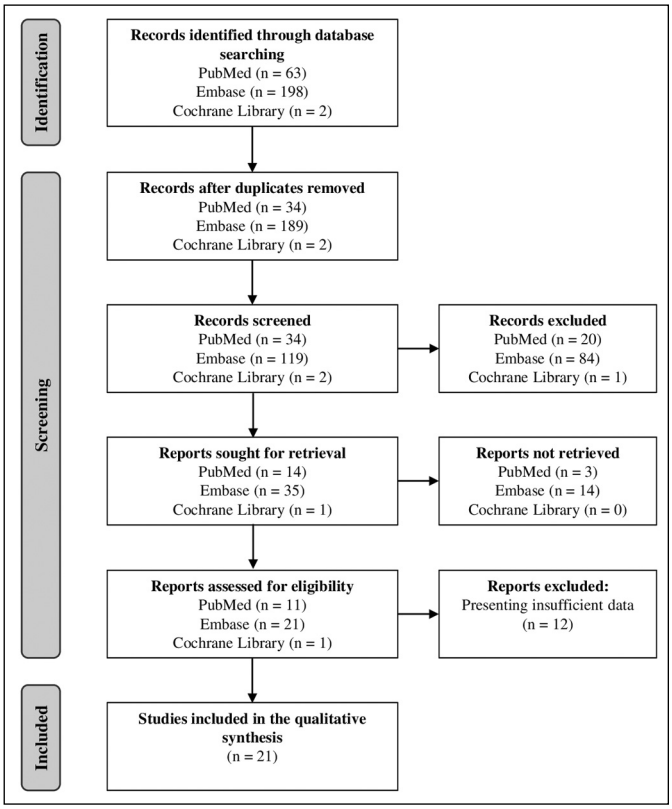

Figure 1. *Flow diagram of the study selection process.*

of the drug is excreted through the urine, almost only in a conjugated form. It is worth mentioning that a linear relationship between the dose and maximal concentration in urine can be observed. Moreover, nitroxoline reaches high concentrations in urine in just 1 hour after oral administration [8]. Due to the kidney-dependent elimination mechanism, renal insufficiency causes lower urinary concentrations of nitroxoline. However, the exact impact of renal function on PK of nitroxoline has not been well researched yet [8].

Minimum inhibitory concentration

Minimum Inhibitory Concentration (MIC), is a key term in microbiology, particularly in the context of antibiotics like nitroxoline. It refers to the lowest concentration of an antibiotic that inhibits the visible growth of a bacterium after a specific period, usually 24 hours, in a controlled environment.
EUCAST set nitroxoline's MIC breakpoint for *E. coli* at 16 mg/L in uncomplicated UTI [9]. Nonetheless, according to multiple studies, various uropathogens were susceptible at a MIC of nitroxoline 1–8 mg/L [4]. These concentrations are reached by conjugated nitroxoline after oral administration of standard dose of 250 mg 3 times a day [4, 8].

In vitro activity

Recently, a variety of academic papers have been published on nitroxoline's *in vitro* antibacterial and antifungal activity. The consensus is that nitroxoline exhibits mainly bacteriostatic characteristics [4]. Nonetheless, bactericidal and fungicidal properties were also observed against some microbes (*i.e.*, *Mycoplasmas*, *Ureoplasma parvum*) [10, 11]. What is more, the drug is more effective in acidic urine [4]. Importantly, according to EUCAST rationale from 2016, *P. aeruginosa* is considered resistant [2].
In 2022 Wykowski, Fuentefria and de Andrade analysed 18 trials regarding nitroxoline's antibacterial, antifungal, antiparasitic and antiviral activity [10]. In the reports included in this review, nitroxoline presented a broad-spectrum activity against a number of pathogens, such as, *E. coli, Klebsiella spp., Enterobacteriaceae, Proteus mirabilis, N. gonorrhoeae, Citrobacter freundii, Bartonella henselae, Ureoplasma spp., Mycoplasma spp., S. aureus, Acinetobacter baumannii, Morganella morganii, P. aeruginosa, Candida spp., Saccharomyces cerevisiae*, diarrheagenic bacteria, Japanese Encephalitis Virus and others [10]. A variety of MIC values were reported depending on the study and the microbe. Moreover, nitroxoline was active against bacterial biofilms, multi-drug resistant (MDR) *E. coli, K. pneumoniae* and *P. mirabilis*, carbapenemase producing bacteria and penicillin-resistant *N. gonorrhoeae* [10]. Another meta-analysis confirmed a broad antibacterial spectrum of nitroxoline [4].
A study by Fuchs et al. from 2022, nitroxoline showed superior activity against carbapenem-resistant *Acinetobacter baumannii* isolated from urine samples [12] It is worth mentioning that the majority of the isolated bacteria were also resistant to ciprofloxacin and trimethoprim/sulfamethoxazole, which are commonly used in the treatment of UTI. Also, in higher concentration, nitroxoline was capable of *Acinetobacter* biofilm eradication [12].
Ahmadzada et al. found that nitroxoline was effective against *A. urinae* and *A. sanguinicola*, which have become popular uropathogens in recent years [13]. However, the authors noted that MICs for *A. sanguinicola* were significantly higher than for *A. urinae* (128 vs 2 mg/L respectively). Hence, *A. sanguinicola* would be considered resistant if the EUCAST breakpoint for *E. coli* (16 mg/L) was used [13].
Interestingly, nitroxoline showed an excellent activity against MDR *Mycobacterium Tuberculosis* Complex, with MIC90 of 4 mg/L [14].

Resistance rates

Resistance to nitroxoline is still uncommon, probably due to low prescription rates, unavailability in most countries and a unique mechanism of action. However, there are no European-wide, nor local Polish data regarding resistance to nitroxoline.
Stoltidis-Claus et al. published a large retrospective trial held in Germany in 2016-2021. The authors assessed the resistance of 162,268 urine cultures positive for Enterobacterales [15]. In addition, the study stratified antibiotic resistance based on urine collection method, which is relevant for urological practice. Unfortunately, the resistance for nitroxoline was not routinely tested, thus only 1,246 samples were evaluated, almost all of them from midstream urine [15]. Nonetheless the resistance for nitroxoline was 3.9% overall, 3.8% from midstream urine and 10% from catheter [15]. It is worth mentioning that nitroxoline had the lowest resistance rates out of all drugs in this research.
In another study, Plambeck et al. found that nitroxoline was highly effective against MDR Enterebacterales found in urine specimens, regardless of the bacterial strain or resistance mechanism [16]. What is important, only 2% out of 394 samples were resistant to nitroxoline [16].
A trial from 2021 found that only 3/600 susceptible *E. coli*, 0/88 MDR *E. coli*, 4/79 susceptible

P. mirabilis, 0/11 MDR *P. mirabilis*, 5/94 susceptible *K. pneumoniae* and 16/50 MDR *K. pneumoniae* expressed resistance to nitroxoline [17]. What is more, the authors pointed out that cotrimoxazole is often inactive against MDR bacteria. Thus, they suggested that nitroxoline may be used instead of cotrimoxazole in uncomplicated UTI [17].
Finally, a large meta-analysis of 4 prospective and partially randomised clinical studies from 1992 and 1993 showed a resistance of 1.6% to nitroxoline in a variety of uropathogenic bacteria [4].

Clinical efficacy

A meta-analysis by Naber et al. assessed clinical response to nitroxoline in a group of 466 females with uncomplicated lower UTIs. Patients were treated with 250 mg of nitroxoline three times a day for 5 days in acute and 10 days in recurrent cystitis. Even though a variety of uropathogens were detected, nitroxoline's eradication rates (CFU$<10^4$ CFU/ml) were above 90% and were not inferior to cotrimoxazole or norfloxacin [4]. Moreover, nitroxoline allowed for a reduction of UTI symptoms [4].
Recently, Wagenlehner et al. published a study recruiting 316 women with uncomplicated cystitis. Only 53.5% of patients received a documented treatment of 250 mg of nitroxoline 3 times a day for 5 days. Despite that, therapeutic success (defined as a reduction of ailments on day 12–16) was achieved in over 80% of the patients [18]. Also, in the course of treatment leukocyte and erythrocyte counts decreased [18].
On the other hand, in an observational study, Forstner et al. claim that treatment with nitroxoline did not succeed in geriatric patients with lower UTIs [19]. This prospective observational study used a 7-day course of 250 mg of nitroxoline 3 times a day in 30 hospitalised patients over 60 years old. However, 56.7% of included patients had a complicated UTI, due to various reasons [19].

Adverse effects

Generally, nitroxoline is considered safe and the risk of adverse effects associated with the drug is low. Mild gastrointestinal symptoms constitute the majority of side effects. What is worth emphasising, treatment with the antibiotic has no effect on faecal flora [20].
A meta-analysis of controlled trials stated that 9.8% of patients reported adverse effects during the treatment. The main complaints were: nausea, diarrhoea, abdominal pain and headache. Crucially, only 3 (1.3%) patients discontinued the treatment, due to adverse effects, compared to 2 (0.9%) patients in control group (treated with cotrimoxazole or norfloxacin) [4].
In a large German trial 96% of the patients assessed nitroxoline tolerance as "good" or "very good". Even though 12.9% reported side effects, only few stopped the treatment [18]. Once again, the majority of symptoms were nausea, headache, stomach problems and diarrhoea [18].
Finally, none of the 6 patients from another study reported any side effects of nitroxoline [21].
Other extremely rare adverse effects noted in the analysed trials were: increased bowel movements, constipation, regurgitation, anorexia, allergy, itching, urticaria, eyelid swelling, fatigue, fever, incontinence, urine staining, polyuria, heart palpitations, colpitis, vaginal fungus and short-term hair-yellowing [4, 18].

CONCLUSIONS

Nitroxoline is an obscure, yet potentially effective and safe antimicrobial agent in uncomplicated lower UTIs. Unfortunately, the drug is available only in a few countries, however, years of use in Germany did not cause frequent resistance, which is an undeniable advantage. Nonetheless, nitroxoline can be useful in urological practice.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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