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In vitro activity of nitroxoline against uropathogens other than *Escherichia coli* and impact of pH

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Introduction and Purpose

Urinary tract infections are one of the most common infectious diseases in humans, with approximately 150 million cases yearly worldwide (1). Against the background of rising antimicrobial resistance in *Escherichia coli* and other uropathogens, nitroxoline (5-nitro-8-hydoxyquinoline; NTX) has become an attractive drug for the treatment of acute and recurrent urinary tract infections (2). NTX is active against Gram-positive and Gram-negative bacteria and acts by chelating divalent cations **(Figure)** (3). In a previous study, NTX showed uniform in vitro activity against a German collection of *E. coli* urine isolates, irrespective of the resistance profile as well as patients' gender and age (4).

The objectives of the present study were i) to evaluate the in vitro activity of NTX in comparison to nitrofurantoin (NIT) against a panel of uropathogens other than *E. coli* and ii) to define the relationship between pH and the in vitro activity of NTX.

Methods

Susceptibility of 211 isolates (*Proteus mirabilis* n=101, *Klebsiella pneumoniae* n=30, *Morganella morganii* n=30, *P. vulgaris* n=20, and *Staphylococcus saprophyticus* n=30) to NTX and NIT was determined by the broth microdilution method according to the standard ISO 20776-1 (5). In addition, MICs of both drugs were determined against 27 selected strains (including *E. coli*) at pH values of 5.5, 7.4 (standard) and 8.0.

Results

$MIC_{50/90}$ values (mg/L) of NTX and NIT for *K. pneumoniae, M. morganii, P. mirabilis, P. vulgaris,* and *S. saprophyticus* were 4/8 and 64/128, 4/8 and 32/32, 8/8 and 128/128, 4/4 and 64/64, and 8/8 and ≤16/≤16, respectively **(Table 1)**. The highest observed MICs were 8 mg/L for NTX and 512 mg/L for NIT.

Data on the activity of NTX and NIT against the 27 selected bacteria determined at the three pH values are given in **Table 2**. MICs were generally lower at the acidic pH and largely unchanged at the alkaline pH compared to MICs at pH 7.4, but the magnitude of difference in activity varied between species.

MICs of both drugs for *E. coli* and *Klebsiella* spp. were no more than four-fold lower at pH 5.5 compared to standard pH (data not shown), but MICs of NTX for *P. mirabilis* and staphylococci decreased up to 32-fold at the acidic pH **(Table 3)**. In contrast, MICs of both drugs at pH 8.0 were either alike or one 2-fold dilution higher than at pH 7.4 for all bacterial strains tested.

Figure: **Chemical structure of NTX in the unchelated (A) and chelated form (B) with metal ion (3)**

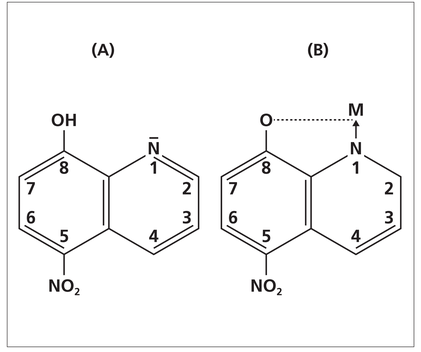

Table 1: **In vitro activity of NTX and NIT against 211 bacterial isolates**

Isolates (no. tested)	Drug	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Gram-negative isolates (n=181)				
Klebsiella pneumoniae (n=30)	Nitroxoline	2–8	4	8
	Nitrofurantoin	≤16–128	64	128
Morganella morganii (n=30)	Nitroxoline	2–8	4	8
	Nitrofurantoin	8–32	32	32
Proteus mirabilis (n=101)	Nitroxoline	4–8	8	8
	Nitrofurantoin	32–512	128	128
Proteus vulgaris (n=20)	Nitroxoline	4	4	4
	Nitrofurantoin	32–64	64	64
Gram-positive isolates (n=30)				
Staphylococcus saprophyticus (n=30)	Nitroxoline	8	8	8
	Nitrofurantoin	≤16	≤16	≤16

Abbreviations: NTX, nitroxoline; NIT, nitrofurantoin

Conclusions

- **Nitroxoline showed almost identical in vitro activity and was up to 16-fold more active than nitrofurantoin against the five uropathogens tested.**
- **Nitroxoline exhibited optimal antibacterial activity at acidic pH.**

References

1. Moriel DG and Schembri MA. 2014. Curr Pharm Biotechnol 14:967-74
2. Meier S et al. 2011. Infection 39:333-40
3. Pelletier C, Prognon P, Bourlioux P. 1995. Antimicrob Agents Chemother 39:707–713
4. Kresken M and Körber-Irrgang B. 2013. 23rd ECCMID, Berlin, Germany, 27-30 April, O311
5. Deutsches Institut für Normung (DIN). 2006. ISO/FDIS 20776-1:2006
6. Wagenlehner FM et al. 2014. Antimicrob Agents Chemother 58:713-21

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Table 2: **MICs of NTX and NIT against 27 bacterial strains at pH 5.5, 7.4 and 8.0**

Isolates (no. tested)	MIC (mg/L) of NTX at pH						MIC (mg/L) of NIT at pH					
	5.5		7.4		8.0		5.5		7.4		8.0	
	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median
Escherichia coli (n=9)	0.5–4	2	2–8	2	2–8	4	16–128	16	16–256	16	16–256	32
Klebsiella pneumoniae (n=9)	2–32	4	2–32	8	2–32	8	16–512	64	16–512	64	32–512	64
Klebsiella oxytoca (n=1)	4	n.a.	8	n.a.	16	n.a.	32	n.a.	32	n.a.	64	n.a.
Proteus mirabilis (n=3)	0.25–0.5	n.a.	8	n.a.	8–16	n.a.	32–64	n.a.	128	n.a.	256	n.a.
Staphylococcus aureus (n=2)	0.5–2	n.a.	2–8	n.a.	8	n.a.	16	n.a.	16	n.a.	32	n.a.
Staphylococcus saprophyticus (n=3)	1–4	n.a.	8–16	n.a.	16–32	n.a.	16	n.a.	16	n.a.	16	n.a.

Abbreviations: NTX, nitroxoline; NIT, nitrofurantoin; n.a., not applicable

Table 3: **In vitro activity of NTX and NIT against *Proteus mirabilis* and staphylococci at pH 5.5, 7.4 and 8.0**

Strain no.	MIC (mg/L) of NTX at pH			MIC (mg/L) of NIT at pH		
	5.5	7.4	8.0	5.5	7.4	8.0
Proteus mirabilis (n=3)						
PEG-10-37-7	0.5	8	8	32	128	256
PEG-10-71-80	0.25	8	8	32	128	256
1057[a)]	0.5	8	16	64	128	256
Staphylococcus aureus (n=2)						
ATCC 29213 (MSSA)	0.5	2	8	16	16	32
UR 2351/09 (MRSA)[b)]	2	8	8	16	16	32
Staphylococcus saprophyticus (n=3)						
721-1-10	4	8	16	16	16	16
721-1-18	4	8	16	16	16	16
Ho94[a)]	1	16	32	16	16	16

Abbreviations: NTX, nitroxoline; NIT, nitrofurantoin;
[a)] Provided by Prof. Dr. Holger Blenk, EuromedClinic, Fürth, Germany (see also Ref. 6). [b)] Provided by Prof. Dr. Wolfgang Pfister, University of Jena, Institute for Medical Microbiology, Jena, Germany.