Review of the pharmacokinetic properties of nitrofurantoin and nitroxoline

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ABSTRACT

Nitrofurantoin and nitroxoline are oral antibiotics for the treatment or prophylaxis of acute urinary tract infections. New interest in both drugs is increasing because of the emergence of resistance to other antibiotics, but knowledge of their pharmacokinetics (PK) is lacking since they were developed before the advent of standardized research for drug approval. The aims of this review were to (1) summarize the PK data reported in literature and (2) to identify PK knowledge gaps. The current body of PK knowledge of both drugs appears to be poor and mainly based on old studies. Nitrofurantoin PK values were obtained from studies using many variables, *e.g.*, formulations, crystal sizes and analytical methods, resulting in high inter-individual variability in PK parameters and no uniform PK profile. Clinical experience and PK data for nitroxoline are even more limited since the drug is registered in only Germany and a few (eastern European) countries. Clinical studies in relevant patient populations are needed with commercially available nitrofurantoin and nitroxoline formulations at approved dosing regimens to more fully characterize their PK profiles and to investigate the influence of patient characteristics on these profiles in order to optimize efficacy and avoid toxicity and emergence of resistance. Only with this updated knowledge and efficacy data from well-structured trials can both drugs maintain their antimicrobial activity against uropathogens.

INTRODUCTION

In an era of increasing multi-drug resistance, old antibiotics such as nitrofurantoin and nitroxoline are gaining renewed interest as oral therapeutic or prophylactic agents for acute urinary tract infections (UTI) (1–4). Nitrofurantoin was approved by the FDA in 1954 and has been in clinical use ever since in many countries.(5) It is currently recommended as first-line UTI therapy because of the emergence of resistance to other antibiotics such as cotrimoxazole, trimethoprim, the fluoroquinolones, and amoxicillin. (2, 6) Nitrofurantoin is mainly bacteriostatic, but can also have a bactericidal effect when present in high concentrations (≥2x MIC) (7, 8). Nitroxoline has been used since 1962 for the treatment and prophylaxis of acute and recurrent UTIs caused by *Escherichia coli* in children and adults (9, 10). It is recommended by some for catheter-related infections because of its anti-biofilm properties (11–13), but is available only in Eastern European countries as well as Germany, where resistance among *E. coli* still seems to be rare (12). This fact makes nitroxoline a promising candidate as an oral treatment option for UTIs in more countries worldwide. Where nitrofurantoin proved to be effective in the treatment and prophylaxis of UTIs, the clinical effectiveness of nitroxoline has not been convincingly demonstrated (14–16). Though several *in vitro* studies have demonstrated its activity against uropathogens and a meta-analysis of four clinical studies demonstrated comparable efficacy when nitroxoline was compared to cotrimoxazole or norfloxacine, well-structured randomized clinical trials to prove its early effectiveness in UTI are lacking (9, 11, 17).

In general, for old antibiotics such as nitrofurantoin and nitroxoline, crucial data on the pharmacokinetics (PK) in relevant matrices such as plasma and urine are sparse or even lacking (18). This is an important limitation since the consumption of nitrofurantoin and nitroxoline has increased and because optimizing PK improves patient outcomes and minimizes the risk of emergence of drug resistance (19, 20). Knowledge about the PK properties is also needed as input for *in vitro* pharmacodynamics (PD) models in order to investigate the effect of the antibiotic concentrations obtained in human subjects on a pathogen and thus to establish clinical breakpoints.

We aimed to map the size of this knowledge gap by giving an overview of the papers wherein PK data on both commercially available and unavailable formulations of nitrofurantoin and nitroxoline were mentioned. We selected digital as well as publications on paper in which PK parameters describing the absorption, distribution, metabolism and elimination of nitrofurantoin or nitroxoline were reported after oral administration in volunteers or in patients. The chemical and pharmacological properties of both nitrofurantoin and nitroxoline will be described, followed by the different analytical methods, which are used in the reviewed papers. The major part of this review will be devoted to nitrofurantoin; nitroxoline will be discussed in the last section.

CHEMISTRY, MECHANISM OF ACTION AND CURRENTLY USED DOSING REGIMENS

Nitrofurantoin (figure 1a) is a member of the nitrofuran family. The defining structural component is a furan ring (five-membered aromatic ring with four carbon (C) atoms and one oxygen (O)) directly connected to a nitro group (-NO_2). Nitrofurantoin is commercially available as capsules containing 50 mg or 100 mg of the macrocrystalline form of nitrofurantoin, which is also available as slow-release formulation and as a suspension (21–23). Microcrystalline nitrofurantoin is still available, but is not a first-line product because of its higher rate of gastrointestinal (GI) side effects. The standard dose of nitrofurantoin depends on the indication and on the geographical location: regimens of either 50-100 mg q6h (regular-release formulation) or 100 mg q12h or q8h (slow-release formulation) are prescribed for the treatment of acute UTI, while 50-100 mg q24h is prescribed for prophylactic use. Both nitrofurantoin and its metabolites have antibacterial activity, which is enhanced under acidic conditions (24–26). Metabolites are formed by reduction by bacterial enzymes, but the exact structure and antibacterial activity of each metabolite is still unclear (24, 27). The spectrum of activity includes (vancomycin-resistant) enterococci and ESBL-producing Enterobacteriaceae with the exception of *Pseudomonas aeruginosa* and several *Proteae* strains because they carry intrinsic resistance for nitrofurantoin (8, 28, 29). Resistance among *E. coli* and most other ESBL-producing Enterobacteriaceae to nitrofurantoin is still low, likely because nitrofurantoin has a different mode of action compared to other antibiotics and has multiple mechanisms of action (30)(14).

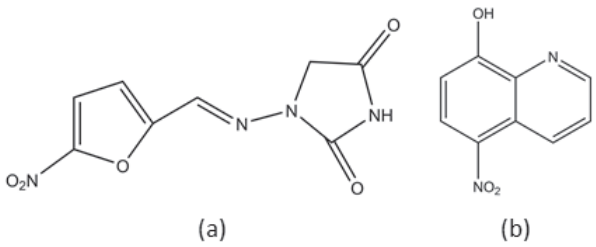

Figure 1: the chemical structures of nitrofurantoin **(a)** and nitroxoline **(b)**.

While its name may suggest the opposite, nitroxoline (8-hydroxy-5-nitroquinolin) is not a member of the nitrofurans. This hydroxychinolin derivate is considered structurally unrelated to any other drug class (figure 1b), and is available as soft capsules containing 250 mg nitroxoline. The standard dose is 250 mg q8h (12). Nitroxoline's mechanism of action is based on the chelation of cations resulting in the inhibition of bacterial adhesion to the bladder epithelial cells, which in turn results in a bacteriostatic effect

that is enhanced under acidic conditions (11, 31, 32). Its spectrum of activity includes *E. coli*, (multidrug resistant) *Staphylococcus aureus* and *Acinetobacter baumannii* strains (13). Resistance rates of *E. coli* to nitroxoline are still reported to be low, probably because of the drug's low prescription rates (12).

ANALYTICAL METHODS

Nitrofurantoin

Since nitrofurantoin is sensitive to photochemical degradation, it is important to take the analytical method together with the corresponding sample preparation method into account when interpreting the reported concentrations of nitrofurantoin (33).

The first method for nitrofurantoin detection in urine was reported by Bender, Nohle and Paul in 1956 (34). The paper describes the chromatographic separation followed by colorimetric or spectrophotometric detection. The majority of the papers included in this review, however, used the spectrophotometric method of Conklin and Hollifield, described in 1965 (35). This method is applicable for quantification of urinary concentrations, but no distinction was made between detecting different metabolites. The method uses a liquid-liquid extraction for preparation of the samples followed by spectrophotometric detection. An updated version of this method was developed by Mason *et al* (36). Nitrofurantoin was separated from the urine matrix with HPLC. From that moment on, more HPLC methods with UV detection were developed for nitrofurantoin alone or for the quantification of the amino and the cyano metabolite in both plasma and urine (37–39). All these methods took the photochemical degradation of nitrofurantoin into account. The only method for which the photochemical degradation was not mentioned specifically was the method of Arancibia *et al*. for the quantification of nitrofurantoin and its toxic metabolite in urine (40). The most recently developed method consists of HPLC with MS detection for nitrofurantoin in plasma; amber-colored vials are used in order to protect the nitrofurantoin content from light (41). It appears that concentrations can be well quantified using UV detection since most PK paper report concentrations using this detection method (tables 1 and 2) and concentrations in urine are relatively high. MS detection therefore does not seem to be specifically necessary to determine nitrofurantoin concentrations. However, MS detection may be of added value in the elucidation of nitrofurantoins metabolism pattern since these concentrations may fall out of the UV detection range.

Nitroxoline

When considering the nitroxoline concentrations, one should keep in mind that about 99% of the excreted nitroxoline is eliminated in the urine as (conjugated) metabolites

Table 1: The PK parameters of nitrofurantoin in **urine**.

Reference	Subjects	Drug information		Fasting status	PK parameters						Analytical method
		Crystal size	Formulation		C_{max}	T_{max}	Recovery		Max. excretion rate		
					(mg/l)	(h)	(%)	(h)		(h)	
Multiple dose: 4x50 mg (therapeutic use)											
Lippman (68)	9[a]	micro	tablet	nf	0-230	5-10	-		-		Chrom. + UV
Multiple dose: 4x100 mg (therapeutic use)											
Lippman (68)	6[a]	micro	tablet	nf	60-230	10-15	-		-		Chrom. + UV
Jawetz (61)	3[a]	micro	tablet	-	15-60[b]		-		-		Micro. [e]
Conklin (47)	10	micro	*capsule*	nf	-	4-8	42.7	24	14.1 mg/h	4-8	LLE + UV
						4-8	43.6	24	15.4 mg/h	4-8	
		macro	capsule	nf	-	12-24	37.9	24	10.5 mg/h	4-8	
						12-24	35,0	24	9.9 mg/h	4-8	
Single dose: 1x50 mg (prophylactic use)											
Meyer (54)	14	micro	tablet	f	-	-	15-39	12	1.3-3.3%/h	-	LLE + UV
Hoener (66)	6	micro	tablet	f	132	1,8	-		-		HPLC + UV
				nf[c]	50	2,8					
Gröning (58)	4	micro	tablet	f	-	-	34.5	8	-		Polarogr.
Meyer (62)	14	micro	4 tablets	f	-	-	34.3-42.1	23	13.4-17.9 %/h	1.4-2.3	HPLC + UV
Single dose: 1x100 mg (prophylactic use)											
Meyer (54)	14	micro	tablet	f	-	-	25-38	12	2.1-3.2%/h	-	LLE + UV
Meyer (62)	14	micro	3 tablets	f	-	-	31.6-33.7	23	11.1-11.7 %/h	2.0-2.6	HPLC + UV

Table 1: The PK parameters of nitrofurantoin in **urine**. (*continued*)

Reference	Subjects	Drug information		Fasting status	PK parameters						Analytical method
		Crystal size	Formulation		C_{max}	T_{max}	Recovery		Max. excretion rate		
					(mg/l)	(h)	(%)	(h)		(h)	
Paul (46)	15	micro	tablet	nf	151	3	36.1	24	10 %/h	3.6	Chrom. + UV
		macro	4 capsules		83-159	3.4-5.5	19.6-35.4	24	4.2-8.9 %/h	3.6-4.9	
Stoll (53)	4	micro	suspension	nf	-	-	14.8	24	-	3,6	Chrom. + UV
Albert (48)	10	micro	tablet	f	-	-	56.7	24	-		LLE + UV
		macro	capsule				59.2	24			
Bates (64)	4	micro	tablet	f	-	-	36.1	24	10.9 mg/h	2.6	Chrom. + UV
				nf			44.4	24	14.4 mg/h	4.5	
		macro	capsule	f	-	-	22.4	24	7.2 mg/h	2.3	
				nf			40.4	24	10.4 mg/h	3.5	
Rosenberg (65)	4	micro	3 tablets	f	-	-	4.3-36.1	24	-		LLE + UV
		micro	suspension				37.2	24			
		macro	capsule				22.4	24			
		micro	3 tablets	nf			21.45-44.4	24	-		
		micro	suspension				43.7	24			
		macro	capsule				40.4	24			
Mendes (55)	5	micro	tablet	nf	-	-	41.5	24	13.4 mg/h	2.4	LLE + UV
Naggar (57)	6	micro	tablet	f	-	-	22	12			LLE + UV
Ogunbona (67)	8	micro	tablet	f	-	-	33	24	10.2 mg/h	3.3	LLE + UV
				nf[c]			46.2	24	14.7 mg/h	2.5	

Table 1: The PK parameters of nitrofurantoin in **urine**. (*continued*)

Reference	Subjects	Drug information		Fasting status	PK parameters						Analytical method
		Crystal size	Formulation		C_{max}	T_{max}	Recovery		Max. excretion rate		
					(mg/l)	(h)	(%)	(h)		(h)	
Panayotis (59)	4	macro	capsule	fd	-	-	26.3	24	6.1 mg/h	-	LLE + UV
							27.6	24	5.3 mg/h		
							21.2	24	5.3 mg/h		
Mason (36)	24	macro	capsule	f	95	5	24.5	24	5.6 mg/h	4.7	LLE + UV
			3 slow-release		120-150	3-5	30.4-34.1	24	7.5-8.3 mg/h	3.7-4.2	
Slow release formulation: 2x100 mg (therapeutic use)											
Maier-Lenz (56)	6	-	slow-release	-	-	-	47.5	24	-		LLE + UV [e]
							33.7	24			
Mason (36)	24	macro	capsule	f	95	5	24.5	24	5.6 mg/h	4.7	LLE + UV
			3 slow-release		120-150	3-5	30.4-34.1	24	7.5-8.3 mg/h	3.7-4.2	

Abbreviations used: [nf = non-fasting] [f = fasting] [Photodeg. = photodegradation] [Chrom. = chromatography] [LLE = liquid-liquid extraction] [micro. = microbiologically] [Polarogr. = polarographical].
The '-' sign is used when data are missing.
[a] Patients with recurrent UTI
[b] After 14 days of treatment
[c] After high fat meal
[d] Administered with milk
[e] It was not specifically mentioned if the photochemical degradation of nitrofurantoin was taken into account for this method. All the other methods did took this into account.

Table 2: The PK parameters of nitrofurantoin in **plasma**.

Reference	Subjects	Drug information		Fasting status	PK parameters					Analytical method[c]
		Crystal size	Formulation		C_{max}	T_{max}	AUC		$T_{1/2}$	
					(mg/l)	(h)	(mg/l.h)	(h)	(h)	
Multiple dose: 4x100 mg (therapeutic use)										
Carroll (60)	2[a]	macro	capsule	f	1.11	> 48	-	-	-	Chrom . + UV
	10[a]	macro	capsule[b]	f	0.8-1.81					
Single dose: 1x50 mg (prophylactic use)										
Liedtke (51)	10	macro	tablet	f	0.26	2.1	1.5	-	1.7	HPLC+ polarogr.
Hoener (66)	6	micro	tablet	f	0.428	2,3	1.05	0-∞	-	HPLC + UV
				nf	0.427	2,6	1.13			
Single dose: 1x100 mg (prophylactic use)										
Felts (69)	11		-	nf	0.9-4.6	2-4	-	-	-	Chrom.+ color.
	6				0.75-3.7					
Albert (48)	10	micro	tablet	f	0.986	2	2,10	0-4	-	LLE + UV
		macro	capsule		1.47		3,28			
Adkison (70)	36	macro	capsule	f	0.88	2-2.3	2.21	0-∞	0.78	LC-UV or LC-MS/MS
					0.96		2.42		0.76	
					0.96		2.32		0.72	
Patel (41)	36	macro	capsule	nf	0.51	4.5	2.62	0-∞	1.66	LC-MS/MS
						4.7	2.56		1.55	

Abbreviations used: [nf = non-fasting] [f = fasting] [Chrom. = chromatography] [LLE = liquid-liquid extraction] [polarogr. = polarographical] [color. = colorimetric].

[a] UTI patients with loading dose of 100 mg.

[b] UTI patients with loading dose of 200 mg.

[c] All methods took the photochemical degradation of nitrofurantoin into account.

and only 1% as the unconjugated form (3, 10, 42). This factor seems to be less important when plasma concentrations are considered (43).

Three of the reported papers used an UV spectrophotometric method in order to quantify urinary levels or urinary and plasma levels of both unconjugated and conjugated nitroxoline (42–44). An electrochemical method for the quantification of unconjugated nitroxoline in plasma was used by Ghoneim *et al* (45). The first HPLC method for quantification on unconjugated and conjugated nitroxoline in plasma and urine was used by Bergogne-Berezin *et al* (10). Wagenlehner *et al*. and Forstner *et al*. reported urinary concentrations of unconjugated and conjugated nitroxoline measured by HPLC with MS detection (3, 16). Since nitroxoline concentrations of both unconjugated and conjugated nitroxoline vary (table 3), it is difficult to make a statement about the applicability of UV or MS detection. The high nitroxoline concentrations in urine and plasma seem to be enough to quantify with the less sensitive UV detection method, but the lower concentrations of the unconjugated nitroxoline form may need the more precise MS detection (3, 10, 16, 43–45). Especially if PK research is conducted in patient populations in whom lower nitroxoline concentrations can be expected, for example elderly patients with renal impairment (44). More clinical research is needed to establish in which order of magnitude the concentrations of unconjugated nitroxoline in urine can be expected to determine whether UV or MS detection is preferred.

PHARMACOKINETIC PROPERTIES OF NITROFURANTOIN

The current knowledge of nitrofurantoins PK profile is poor and mainly based on old studies from the fifties. The majority of the publications report data obtained in a phase of product development during which pharmaceutical companies attempted to maximize bioavailability and minimize toxicity. Therefore, nitrofurantoin was administrated in different crystal sizes (46–48), formulations (36, 49–59), dosages (60–62), fasting states (63–67) and/or populations (68–70). The influence of these different parameters on nitrofurantoins PK is discussed in the following sections. A summary of the literature search results is found in the supplementary tables S1 (urine PK) and S2 (plasma PK).

Effect of crystal size on the pharmacokinetics

It is important to keep in mind the crystal sizes of nitrofurantoin in the commercially available products when interpreting PK results. Nowadays, the macrocrystalline formulations have almost completely replaced microcrystalline formulations because microcrystals were more associated with unwanted side effects due to their rapid absorption (46, 64, 71).

Table 3: The PK parameters of nitroxoline in urine and plasma.

Reference	Subjects	Dose	Fasting status	Metabolite	PK parameters						Analytical method
					C_{max}	T_{max}	Recovery		Max. excretion rate	Time to max. excretion rate	
		(mg)			(mg/l)	(h)	(%)	(h)	(%/h)	(h)	
URINE											
Mrhar (42)	8	400	f	Uncj.	17	4	1.8	24	-		UV
				Conj.			60.0	24			
	8	200	f	Uncj.	9	2	1.5	24	-		
				Conj.			50.0	24			
Makhailova (43)[a]	8	200[b]	nf	Uncj.	380	2-4	53.0	24	10.8	4	UV
				Uncj.	400	0-2	63.0	24	9	2	
Mikhailova (44)[c]	7	200	nf	Uncj.	160	6	50	24	6.6	3.5	UV
	6	200			120	6	39	24	4.5	5	
	7	200			30	6	21	24	2.1	6.5	
Wagenlehner (3)	6	250	nf	Uncj.	0.5	0-4	0.2	24	-		HPLC-MS
				Conj.	27.8	0-4	11.7	24			
Forstner (16)[c]	30	3x250	nf	Uncj.	5.4		-		-		HPLC-MS
				Conj.	210.6						

Table 3: The PK parameters of nitroxoline in urine and plasma. (*continued*)

Reference	Subjects	Dose	Fasting status	Metabolite	PK parameters						Analytical method
					C_{max}	T_{max}	Recovery		Max. excretion rate	Time to max. excretion rate	
		(mg)			(mg/l)	(h)	(%)	(h)	(%/h)	(h)	
PLASMA											
Makhailova (43)	8	200[b]	nf	Uncj.	9.5	1.5	-		-		UV
				Uncj.	8.5	1.5					
Mikhailova (44)	7	200	nf	Uncj.	7	2.5	-		-		UV
	6	200			5.5	4.5					
	7	200			5	7					
Bergogne (10)[d]	8	200	-	Uncj.	5.50	1.75	-		-		HPLC
		3x200									
Ghoneim (45)	2	100	f	-	5.4	1.75	-		-		Voltammetric

The abbreviations for non-fasting (nf) and fasting (f) are used in the fasting column. The '-' sign is used when data are missing.

[a] two different nitroxoline products were administered

[b] dose based on bodyweight (3 mg/kg). one subject received 250 mg

[c] PK parameters obtained in kidney failure patients (Mikhailova) or elderly patients at steady-state (Forstner)

[d] mean of 1x200 mg and 3x200 mg dose

The effect of different nitrofurantoin crystal sizes on the absorption and excretion profile of nitrofurantoin was clearly demonstrated by Conklin *et al* (47). Figure 2 demonstrates their findings. More inter-individual variability in recovery values is observed when macrocrystalline nitrofurantoin is administered compared to microcrystalline nitrofurantoin. Urinary excretion was monitored for 24 hours on the first day and on the last day after administration of 100 mg q6h microcrystals or macrocrystals for 7 days. On days 1 and 7, 42.7% and 43.6% was excreted in the microcrystal group, respectively, and 37.9% and 35.0% in the macrocrystal group. An overall higher percentage was found for the microcrystals because more microcrystalline nitrofurantoin was excreted in the first 12 hours compared to the percentage of macrocrystalline nitrofurantoin. Yet from 12 to 24 hours, the opposite was observed, reflecting a slower rate of absorption of the macrocrystal form (not shown in figure 2). In daily clinical practice, this slow absorption property of the macrocrystal form is overcome by administering the drug with food which prolongs the residence time in the GI tract and therefore the time in which the drug can be absorbed (21–23, 64, 65).

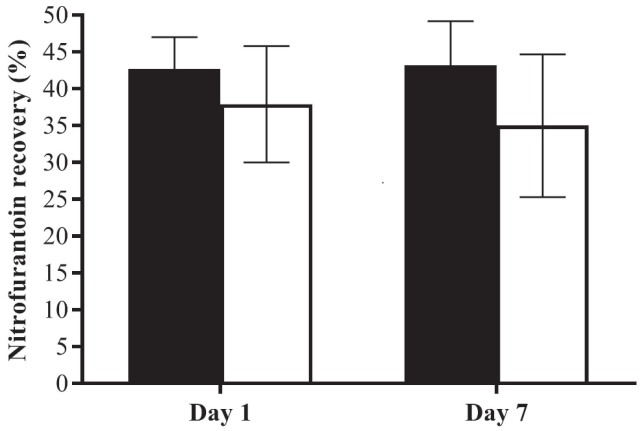

Figure 2: Recovery of nitrofurantoin (%) on the first day and on the seventh day of the treatment with microcrystals (black) or macrocrystals (white). Brackets represent the standard deviation of the mean recovery.

Effect of product formulation on pharmacokinetics

The slow-release formulation was investigated only by Maier-Lenz *et al.*; recovery values ranged from 33.7% to 47.7% over 24 hours (56). Total excretion (%) as well as excretion rates over 24 hours for slow-release products were found to be higher compared to a normal macrocrystal capsule (36). When the absorption of the regular-release formulation was defined as 100%, the absorption of the slow-release products were 129.8%, 130.2% and 145.3%. This indicates that prolongation of the residence

time in the GI tract results in a higher amount of nitrofurantoin absorption and therefore higher amounts excreted in urine.

Effect of food on pharmacokinetics

The presence of food in the GI tract increases the gastric emptying time and therefore increases residence time so that more nitrofurantoin can be dissolved in the gastric fluids before passing to the duodenum, where absorption of nitrofurantoin is maximal (72). The influence of food is stronger when macrocrystalline nitrofurantoin is administered compared to microcrystalline nitrofurantoin, suggesting that the critical, time-dependent step in the absorption of nitrofurantoin is its dissolution in GI fluids rather than its residence time in the GI tract (73). This results in a smaller absorption rate compared to the excretion rate, which is also known as 'flip-flop kinetics'(74). The hypothesis of dissolution time is supported by the results of Naggar *et al.*, who showed that absorption was increased when nitrofurantoins solubility was increased by the addition of $Mg_2O_8Si_3$ (57). The occurrence of side effects is increased with smaller nitrofurantoin crystal size (75). To counter these side effects, manufacturers suggested administering nitrofurantoin with food. It was then demonstrated that food increases the bioavailability of nitrofurantoin, reflected by increased urinary recovery (64, 65). Thus the administration of the macrocrystalline nitrofurantoin formulation with food both increases the drug's exposure to uropathogens and minimizes its side effects.

General discussion: urinary pharmacokinetics

An overview of the urinary PK data after administration of a clinically relevant dose in a commercially available formulation is given in table 1. The following PK data were considered clinically relevant: all data after a multiple dose of 50 mg q6h or 100 mg q6h; data after a single dose of 50 mg or 100 mg; data after administration of the slow-release formulation in a dose of 100 mg q12h or 100 mg q24h (up to 12 hours). The following PK parameters were investigated in urine: maximum concentration (C_{max}), time to maximum concentration (T_{max}), recovery, maximum excretion rate and maximum absorption rate. The recovery represents the cumulative excretion and is expressed as a percentage of the total administered dose. The maximum excretion rate was reported as percentage per time or as amount per time, based on what was reported in the reference paper. C_{max} or excretion rates were reported as a range instead of one value if the reference reported values of different subjects separately instead of one mean value. If the crystal size of the product under investigation was not specifically mentioned, tablets were considered to contain microcrystals and capsules contained macrocrystals based on the product information (21–23).

Only one study investigated PK after the standard dose of 50 mg q6h: this dose was administered to nine patients with recurrent UTI when nitrofurantoin was given

as a prolonged administration from 1 month to 3 years (68). A high inter-individual variability in maximum urinary concentrations was found in this population with concentrations of 0-140 mg/l; 20-230 mg/l; 5-160 mg/l; and 40-210 mg/l after one to four administrations, respectively. The researchers concluded that in the group with normal renal function, concentrations usually exceeded 50 mg/l throughout the day. The maximum concentration after administration of 100 mg q6h was lower in the first time interval compared to the 50 mg q6h dose, but remained higher for a longer time (120 mg/l after the fourth administration compared to 90 mg/l after 50 mg q6h) (68). This is remarkable and points to the hypothesis that the PK pattern of nitrofurantoin is not linear, but may be dose-dependent. Preliminary data from a PK study in healthy volunteers in which nitrofurantoin concentrations in plasma and urine after a dose of 50 mg q6h or 100 mg q8h were compared confirms the pattern in urine found by Lippman *et al.*, but also reveals that plasma concentrations change in proportion to the dose received (76). More research is needed to fully understand the absorption and excretion pattern of nitrofurantoin.

The mean recovery over 24 hours after administration of 100 mg q6h of the microcrystalline form could be calculated based on the values reported in several papers (36, 46, 48, 53, 55, 59, 64, 65, 67). The recovery was not found to be different between the microcrystalline and macrocrystalline forms (32.9 ± 13.9% versus 32.1 ± 11.6%). Recovery after a single dose of 100 mg was also found to be comparable with that after 200 mg, so the dose seems not to influence the total recovery over 24 hours.(56) The maximum excretion rate of the microcrystalline formulation was 50% higher (≈15 mg/h) compared to the macrocrystalline formulation (≈10 mg/h) so absorption of nitrofurantoin can be increased by using macrocrystalline nitrofurantoin and administering the drug with food.

General discussion: plasma pharmacokinetics

The AUC, the elimination half-life ($T_{1/2}$) and the elimination constant (K_{el}) were investigated as specific plasma parameters together with the PK parameters which were also investigated for describing the urine PK. A complete overview of these parameters is presented in table S2. An overview of the plasma PK data after administration of a clinically relevant dose in a commercially available formulation is given in table 2.

No plasma PK values after administration of the clinically relevant dosing regimen were reported. In general, less research has been conducted on the PK properties of nitrofurantoin in plasma versus urine. This is not surprising since nitrofurantoin needs to be active in the bladder and is known to have minimal and transient plasma concentrations. Nonetheless, an idea of the PK pattern in plasma can be derived from the PK pattern in urine since urinary excretion reflects the time course of drug in the blood (71). Concentrations in plasma never exceed 2 mg/l under fasting conditions regardless of

the dose, the formulation and the time after dose. Concentrations of macrocrystalline nitrofurantoin are higher (up to 1.8 mg/l) compared to those of the microcrystalline form (maximum of 0.99 mg/l). When administered with food, nitrofurantoin concentrations were even higher: maximum 4.6 mg/l compared to non-fasting conditions (69).

Four papers report the plasma concentration-time profiles of individual subjects after administration of macrocrystalline nitrofurantoin under fasting conditions (48, 51, 60, 70). These values are presented in figure 3. A high inter-individual variability in nitrofurantoin PK, which was already observed in the urine PK, is also present in plasma. The wide distribution of plasma concentrations is probably a result of administration of different nitrofurantoin dosages, but even when only the 100 mg dose is considered, the high variability remains (figure 3b) (48, 60, 70). Differences in drug levels may be explained by different nitrofurantoin formulations since no details of the administered nitrofurantoin capsule were given (60). Also, differences in analytical methods may be responsible for the high variability in concentrations. For example, it was not clear whether the analytical method used by Carroll *et al*. takes into account the degradation of nitrofurantoin in daylight.

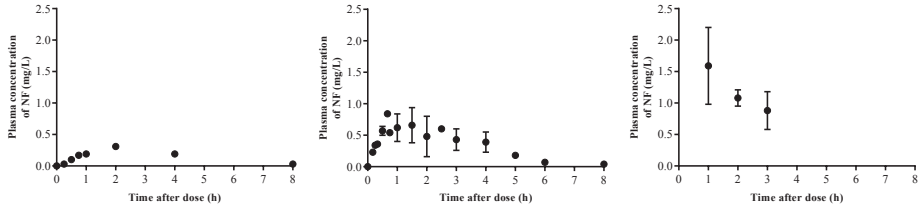

Figure 3: Plasma concentrations after administration of clinically relevant dosages of a single dose of 50 mg (a), 100 mg (b) or 200 mg (c) of macrocrystalline nitrofurantoin (NF) under fasting conditions. The concentrations in figure a are reported by Liedtke (mean of 10 subjects per value). Since several concentrations were reported for the 100 mg and the 200 mg dose for the majority of the time points, the concentrations in figure b and c are demonstrated as means and standard deviations, based on data from Adkison (n=12), Albert (n=10) and Carroll (n=2) for figure b and based on data from Carroll (n=10 for T1, n=6 for T2 and n=4 for T3) for figure c.

Pharmacokinetics in patients with renal dysfunction

Both treatment failures and high plasma levels have been observed in UTI patients with impaired renal function (69, 77, 78). Plasma levels can increase up to 5-6 mg/l and are associated with potential toxicity (78). Dose adjustments in order to avoid toxic plasma levels in these patients might only lead to subtherapeutic urine levels, so exploring the relationship between renal function and plasma and urine levels of nitrofurantoin is necessary. Several papers included subjects with impaired renal function; a linear relationship between creatinine clearance and urinary nitrofurantoin concentrations or urinary nitrofurantoin recovery was found (69, 77, 78).

Lippmann *et al*. administered the standard nitrofurantoin dose of 50 mg q12h to eight UTI patients with low creatinine clearance in the microcrystalline form as prolonged administrations over several months (68). The urinary C_{max} in nine UTI patients with normal renal clearance ranged from 70 mg/l to 110 mg/l during 24 hours after administration when nitrofurantoin concentrations were measured in five-hour interval urine portions. Concentrations were 10-20 mg/l in the patients with poor renal function. The excretion of nitrofurantoin was minimal in patients with creatinine clearances <20 mL/min, so its use should be avoided in these patients (79). However, some official guidelines recommend avoiding nitrofurantoin in patients with moderate renal insufficiency (creatinine clearance <60 mL/min) because of probable reduced efficacy (78). New guidelines have increased this limit to <30 mL/min, but the quality of evidence for either recommendation remains low (80). A recent study demonstrated that nitrofurantoin can be used safely in patients with mildly to moderately reduced renal function (81).

Pharmacokinetics in children

Nitrofurantoin is approved for the treatment and prophylaxis of UTI in children ≥12 years old (21–23). The only PK data are from a case report of Jawetz *et al*. describing a 9-year-old girl with recurrent UTI (61). A daily dose of 100 mg was administered for 14 days; a maximum urinary nitrofurantoin level of 240 mg/l was found. Karpman *et al*. reviewed the literature regarding the safety and toxicity of nitrofurantoin and two other drugs (82). They concluded that nitrofurantoin is safe in children for long-term prophylactic use, but no PK parameters were reported.

Effect of genotype

The only known gene associated with the PK of nitrofurantoin is the breast cancer resistance protein (BCRP) gene. Several *in vitro* studies have demonstrated that nitrofurantoin is a substrate of this transporter (83–85). Nitrofurantoin may thus be suitable as clinical probe substrate for BCRP activity, polymorphisms of which can reduce the absorption and/or increase the elimination of drugs. Urinary and plasma concentrations of nitrofurantoin were quantified in 36 Chinese male subjects with different BCRP polymorphisms, but there was no significant effect on plasma and urine concentrations in these subjects (70). Thus there is currently no evidence that different BCRP genotypes influence nitrofurantoins PK.

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS OF NITROFURANTOIN

In past years, a considerable amount of research has been conducted on nitrofurantoins PD properties. Yet the PK/PD index that best correlates with the drug's antibacterial effect is still unknown. The EUCAST does not mention a PK/PD index for nitrofurantoin, but does mention 64 mg/l as cut-off value (ECOFF) for susceptibility for *E. coli*, *S. saprophyticus*, *Enterococcus* spp and *Streptococcus agalactiae* (86). There are not enough PK/PD data available to set breakpoints in urine, the clinically relevant matrix for UTI.

It is therefore difficult to associate the nitrofurantoin concentrations with a therapeutic effect. Fransen *et al*. demonstrated bactericidal effect at ≥2x MIC against several *E. cloacae* after 4-8 hours, against *K. pneumoniae* after 8-10 hours and against *E. coli* (ESBL+ and ESBL-) species after 12-16 hours in an *in vitro* time-kill assay.(8) This effect was not uniform among the Enterobacteriaceae family: a concentration-dependent pattern was observed for *E. cloacae* and a time-dependent pattern was demonstrated for *E. coli* (as well as for *K. pneumoniae*). These findings are in line with the study of Lindgren *et al.*, where no behavioral differences between ESBL-producing and non-ESBL-producing species were found (7).

CLINICAL USE OF NITROFURANTOIN

The clinical efficacy and toxicity of nitrofurantoin when used as treatment of lower UTIs or as prophylaxis have been recently described in two meta-analyses based on controlled trials (14, 15). Twenty-seven controlled trials including 4807 patients were assessed to investigate nitrofurantoin as treatment for UTIs; nitrofurantoin was found to be clinical and microbiologically effective with clinical cure rates ranging from 79%-92% and microbiological eradication rates of 80%-92%. Treatment for 7 days was not found to be more effective compared to the standard treatment of 5 days, but its clinical efficacy was diminished (61%-70%) when given for only 3 days. Toxicity was found in 5% to 16% of the cases and was mild, reversible and mainly limited to GI related side effects. Twenty-six controlled trials including 3052 patients were assessed to determine nitrofurantoins efficacy and safety as prophylaxis against UTI; the drug is effective in the prevention of UTIs, and side effects were noted again to be mild, with the risk of (severe) toxicity increasing with the duration of the prophylactic use (14, 15, 87). Not only crystal size, but also (high) plasma levels are associated with toxicity (21). It would therefore be interesting to compare plasma concentrations of patients who do experience side effects to those who experience no side effects.

NITROXOLINE

The nitroxoline papers in which PK data are mentioned are older and more limited than those reporting nitrofurantoin data (3, 10, 16, 42–45). The results of the literature search are demonstrated in table 3.

Urine and plasma pharmacokinetics

Absorption, distribution and metabolism

The C_{max} of both unconjugated and conjugated forms obtained in the first time interval in all studies indicate rapid absorption from the GI tract and rapid conjugation in the liver. Mrhar *et al*. demonstrated complete and rapid absorption even when a high dose of 400 mg was administered (42). When comparing urine concentrations after a dose of 400 versus 200 mg, higher concentrations with a longer time period >6 mg/l were observed, indicating a linear relationship between dose and C_{max} in urine (42).

Almost all absorbed nitroxoline is metabolized in the liver and subsequently excreted in the urine (10, 42). There seems to be inter-individual variability in the metabolism pattern since varying concentrations of the conjugated metabolite were found, but this could also be a result of differences in excretion patterns between subjects, since no data are available on plasma concentrations of the conjugated form (10). Metabolism occurs soon after absorption, based on early levels of conjugated nitroxoline (10). The consensus seems to be that while the unconjugated form of nitroxoline exhibits antibacterial activity, its metabolites may also significantly contribute to its antibacterial effect (3, 9, 12). This would appear plausible, as it seems unlikely that the almost negligible amount of unconjugated nitroxoline would be fully responsible for the drug's total antibacterial effect. However, the relative contribution of these metabolites remains unclear; more research is clearly needed.

Excretion

The majority of the papers reported that approximately 60% of the total administered dose is eliminated in the urine, from which only ~1% in the unconjugated form (3, 10, 11, 42). The only study investigating nitroxoline PK after administration of the clinically relevant dose of 250 mg found a recovery of the unconjugated form of approximately 1.7% versus 98.3% for the conjugated sulfate form over 24 hours (3). Recovery levels after a registered dose of 250 mg q8h were not reported (16). The ratio between recovery of the conjugated and the unconjugated form was consistent with data from other studies.

Urinary elimination of both unconjugated and conjugated nitroxoline occurs rapidly: high urine concentrations of both forms are found already one hour after

administration (10). Two Bulgarian studies indicate that the majority is excreted within 10 hours after administration; the process is delayed in patients with renal insufficiency (43, 44). Impaired renal function not only influences recovery but also C_{max} levels of the unconjugated nitroxoline form in urine.(44) Urinary C_{max} levels of the unconjugated nitroxoline form decreased from 160 to 30 mg/l when creatinine clearance decreased from 40-90 mL/min to less than 20 mL/min. This decrease in urinary concentrations points to the hypotheses that either more nitroxoline is conjugated in the liver (due to decreased excretion of unconjugated nitroxoline in the urine, in turn resulting in a longer residence time in the central circulation, during which metabolism will occur) and/or less nitroxoline is excreted in the urine. An increase in nitroxoline metabolism would be reflected in high plasma levels of the conjugated nitroxoline form and/or in low unconjugated nitroxoline plasma levels, but these low plasma levels were not observed in patients with renal impairment (7 versus 5 mg/l) (44). This hypothesis may therefore not be valid. What is striking, however, is that the C_{max} in plasma is found much later when renal function decreases (2.5 versus 7 hours), which is was not observed in urine (C_{max} after 6 hours) (44). This again points to the hypothesis that a higher fraction of nitroxoline is metabolized when renal function decreases due to a longer residence time in the central circulation. The mechanism behind this observation is unclear; more research on conjugated nitroxoline concentrations is needed in order to clarify the influence of the renal function on the metabolism and excretion of nitroxoline. This is important information because the extent to which the antibacterial active form of nitroxoline is metabolized to (in)active metabolites would presumably influence the overall antibacterial activity of the administered therapy. It should be noted that the validity of the two Bulgarian studies is questionable since their reported concentrations are high and not in line with those reported by others (table 3). They also did not distinguish between the conjugated and the unconjugated nitroxoline forms. Nonetheless, though the values for absolute concentrations may be unreliable, the relationship between creatinine clearance and C_{max} seems valid and consistent with expectations, since renal excretion is the primary route of nitroxoline removal from the body (42). Forstner *et al*. confirm this relationship between urinary concentrations and creatinine clearance (16).

Pharmacokinetic-pharmacodynamic relationships

EUCAST and the German National Antibiotic Susceptibility Committee describe 16 mg/l as the clinical breakpoint for *E. coli* susceptibility for nitroxoline when treating uncomplicated UTI (17). This breakpoint was used in an *in vitro* study in which the activity of nitroxoline against clinical *E. coli* isolates was tested (12). Nitroxoline was efficacious in all 499 tested isolates, regardless of their baseline susceptibility for nitroxoline. Based on this breakpoint and in theory, effective urinary concentrations of

the conjugated sulfate form of nitroxoline can be reached in volunteers after a single dose of 250 mg measured over 24 hours (C_{max} 0.3-27.8 mg/l) and in patients after the registered dose of 250 mg q8h at steady-state (C_{max} 0.8-210.6 mg/l) (3, 16). No effective concentrations of the unconjugated form were reached in either of the groups. This is also true when the breakpoint of 6 mg/l for the unconjugated form, which has an *in vitro* antimicrobial effect in urine at a concentration of 6 mg/l, is considered (42).

No PK/PD index has been reported; there are yet few clinical data available for its determination. More research is needed in order to investigate the PK/PD index and the corresponding breakpoint. Only with this knowledge can treatment with nitroxoline be carried out in an effective and safe manner (18, 20).

Nitroxoline's activity is mainly bacteriostatic and seems to be dependent on urinary pH (3). The highest reciprocal inhibitory titers were found for *E. coli* ATCC 25922 with a relatively low MIC of 2 mg/l for nitroxoline. No *E. coli* strains with higher MICs were tested, but a *Proteus* and a *S. saprophyticus* strain with a MIC of 8 mg/l were tested, which both showed lower inhibitory titers (mostly 0) compared to the *E. coli* ATCC strain. These results support the hypothesis that nitroxolines activity is also dependent on the species and less dependent on the MIC.

Clinical use

In vitro data suggest that nitroxoline would be effective in the treatment of uncomplicated UTI's (11, 17). A meta-analysis of four unpublished, controlled trials examined the outcomes of 234 female UTI patients treated with 250 mg q8h nitroxoline versus 232 women treated with cotrimoxazole or norfloxacin (9), results suggested comparable toxicity and microbiologic efficacy, defined as a reduction of bacteriuria from $\geq 10^5$ to $<10^4$ cfu/mL, 7-13 days after end of therapy; this reduction was observed in over 90% of the patients after five (acute UTI) or 10 (recurrent UTI) days of treatment. Clinical efficacy was defined as symptom improvement and was found to be similar between the treatment groups (9). Additionally, Wagenlehner *et al.* concluded that urinary steady-state concentrations after a dose of 250 mg q8h in healthy volunteers had an *in vitro* bacteriostatic activity during 24 hours (3).

The opposite conclusion, however, was drawn in a prospective study in which nitroxoline was administered at the registered dose for 7 days to 30 hospitalized geriatric patients with lower UTIs (16). Only 17 patients were treated as planned, so conclusions were limited. Microbiological success, defined as a urine culture taken on day 12 showing reduction of bacteriuria from $\geq 10^5$ to $<10^4$ cfu/mL, was limited especially in elderly patients with either comorbidities (*e.g.*, diabetes) or those with catheter-associated or otherwise complicated UTIs. Clinical symptoms were still observed in 23.5% of the patients at day 7. The study was terminated early because of disappointing microbiological and response results. Since urinary concentrations of the

unconjugated form and the conjugated form were comparable with those of healthy volunteers, it is unlikely that the difference in microbiological success was due to a difference in exposure. The static effect of nitroxoline may therefore not be sufficient to successfully treat UTIs in this specific patient population, about half of which had complicated (catheter-associated) UTI (3). Antibiotics with a bactericidal effect may be needed in order to treat this group of patients. On the contrary, this static effect of nitroxoline was enough to successfully treat 90% of the patients with uncomplicated UTIs as shown in a meta-analysis (9).

Overall, there is currently only modest evidence for early microbiological and clinical success with nitroxoline as therapy for UTI. However, a distinction must be made between different patient groups if treatment with nitroxoline is considered. In primary care, where in general young and relatively healthy women are treated for UTI, nitroxoline could be a possible oral treatment option. When older, more comorbid patients are considered, nitroxoline appears to be microbiologically inferior. Randomized clinical trials with longer follow-up and clearly defined clinical outcomes are needed to assess the drug's true efficacy. Additional research is needed in order to investigate the antibacterial activity of its metabolites; in the meantime, its use should be considered carefully.

CONCLUSIONS

Pharmacokinetic data on both nitrofurantoin and nitroxoline are sparse and have been obtained largely via outdated analytical methods. High inter-individual variability was found for the PK profile of nitrofurantoin, which can (partly) be explained by inconsistencies in crystal size, product formulation and/or dose. New PK studies using commercially available nitrofurantoin products at approved dosages and current analytical methods are needed. More knowledge of these two drugs' metabolism, including the activity and toxicity of their metabolites, will help to optimize their use. Nitroxoline's potential as a therapeutic agent for uncomplicated UTI was demonstrated in a non-inferiority study in relative healthy patients, but its short-term effect and its effect in patients with comorbidities remain unknown. In an age of reduced oral options for UTI, pharmacokinetic results from much needed randomized clinical trials would help to optimize therapy and minimize emergence of resistance.

Transparency declarations

The authors declare that there are no conflicts of interest.

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Table S1: Complete overview of the PK parameters of nitrofurantoin in urine.

Reference	Subjects	Drug information			Fasting status	PK parameters						Analytical method
		Dose (mg)	Crystal size	Formulation		C_{max} (mg/l)		T_{max} (h)	Recovery (%)	(h)	Max. excretion rate (time. h)	
Carroll 1955	9	200 + 4x100	macro	Furadantin (capsule)	f	-		-	10,6 29,0 34,2	3 12 24	-	Chrom. + UV
Richards 1955	1	4x200	-	-	f	-	500	0-1	-		-	Micro.
		2x200			nf		450	2-3				
Jawetz 1957	1 child	4x50	micro	tablet	-	Day 14:	240	-	-		-	Micro.[d]
	1	4x75				Day 14:	15					
	3	4x100				Day 14-15:	15-60					
	1	4x125				Day 15:	60-120					
	5	4x150				Day 14-19:	60-240					
Lippman 1958 [a]	4	4x25	micro	tablet	nf + normal weight		80-70	5-10	-		-	Chrom. + UV
	3	4x25			nf + low weight		70-200	10-15				
	9	4x50			nf + normal GFR		40-230	5-10				
	8	4x50			nf + renal imp.		0-50	0-5				
	6	4x100			nf		60-230	10-15				
Henry Paul 1967	15	100	micro	tablet	nf		151	3	36,1	24	10 %/h	3,6	Chrom. + UV
			macro	4 capsules			83-159	3,4-5,5	19,6-35,4		4,2-8,9 %/h	3,6-4,9	
Stoffels 1968	10	200	micro	tablet	nf		-	-	62,5	12	7,3 %/h	0-4	Colorimetric
				coated dragee					64,9		11,4 %/h		
	16[b]			tablet					33,6		3,6 %/h		
				coated dragee					43,8		5,4 %/h		

Table S1: Complete overview of the PK parameters of nitrofurantoin in urine. (*continued*)

Reference	Subjects	Drug information			Fasting status	PK parameters					Analytical method
		Dose (mg)	Crystal size	Formulation		C_{max} (mg/l)	T_{max} (h)	Recovery (%)	(h)	Max. excretion rate (time. h)	
Conklin 1969	10	4x100[c]	micro	capsule	nf	Day 1: 56,5 mg	4-8	42,7	24	14,1 mg/h	4-8h	LLE + UV
						Day 7: 61,7 mg		43,6		15,4 mg/h	
			macro			Day 1: 60,4 mg		37,9		10,5 mg/h	
						Day 7: 49,4 mg	12-24	35,0		9,9 mg/h	
Felts 1971	11	100	-	-	nf + normal GFR	1,1-104	2-4	-		-		Chrom. + colorimetric
	6				nf + renal imp.	1,7-27,6					
Schwartländer 1972	5	150	macro	capsule	-	195,7	2-4	38,3	8	-		Colorimetric
		150	macro	capsule		273,5	0-2	35,1				
		150	micro	tablet		225	0-2	22,5				
		150	micro	tablet		295,1	2-4	34,8				
		3x50	macro	capsule		124,9	0-2	39,4	12			
		3x50	micro	tablet		94,3	0-2	30	12	-		
		75	-	Slow release tablet		166,4	2-4	26,5	10			
Stoll 1973	4	100	micro	suspension	nf	-	-	14,8	24	-	3,6h	Chrom. + UV
Albert 1974	10	100	micro	tablet	f + 4h	-	-	56,7	24	-		LLE + UV
			macro	capsule				59,2				

Table S1: Complete overview of the PK parameters of nitrofurantoin in urine. (*continued*)

Reference	Subjects	Drug information			Fasting status	PK parameters					Analytical method
		Dose (mg)	Crystal size	Formulation		C_{max} (mg/l)	T_{max} (h)	Recovery (%)	(h)	Max. excretion rate (time. h)	
Bates 1974	4	100	micro	tablet	f	-	-	36,1	24	10,9 mg/h 2,6h	Chrom. + UV
					nf			44,4		14,4 mg/h 4,5h	
			macro	capsule	f			22,4		7,2 mg/h 2,3h	
					nf			40,4		10,4 mg/h 3,5h	
Meyer 1974	14	50	micro	tablet	f +4h	-	-	36	12	3,0%/h	LLE + UV
		50	micro	tablet				33		2,8%/h	
		50	micro	tablet				37		3,1%/h	
		50	micro	tablet				39		3,3%/h	
		50	macro	capsule				24		2,0%/h	
		50	micro	tablet				18		1,5%/h	
		50	micro	tablet				15		1,3%h	
		100	micro	tablet				30		2,5%/h	
		100	micro	tablet				32,5		2,7%/h	
		100	micro	tablet				38		3,2%/h	
		100	micro	tablet				33,5		2,8%/h	
		100	macro	capsule				25		2,1%/h	
		100	micro	tablet				30		2,5%/h	
		250	micro	tablet				31,5		2,6%/h	

Table S1: Complete overview of the PK parameters of nitrofurantoin in urine. (*continued*)

Reference	Subjects	Drug information			Fasting status	PK parameters					Analytical method
		Dose (mg)	Crystal size	Formulation		C_{max} (mg/l)	T_{max} (h)	Recovery (%)	(h)	Max. excretion rate (time. h)	
Rosenberg 1976	4	100	micro	3 tablets	f	-	-	4,3-36,1	24	-	LLE + UV
			micro	suspension				37,2			
			macro	capsule				22,4			
			micro	3 tablets	nf			21,45-44,4			
			micro	suspension				43,7			
			macro	capsule				40,4			
Mendes 1978	5	100	micro	2 chewable tablets	nf	-	-	40,7	24	13,6 mg/h 1,6h	LLE + UV
				2 swallow tablets				32,0		10,0 mg/h 2,6h	
				2 hard gelatin capsules				39,5		15,9 mg/h 2h	
				tablet				41,5		13,4 mg/h 2,4h	
Maier-Lenz 1979	6	200	micro	tablet	-	-	-	35,3	24	-	LLE + UV[d]
			-	Slow release tablet				47,5			
								33,7			
Naggar 1979	6	100	micro	tablet	f	-	-	22	12	-	LLE + UV
Hoener 1981	6	50	micro	tablet	f	132	1,8	-		-	HPLC + UV
					nf [e]	50	2,8				
Gröning 1981	4	50	micro	tablet	f +4h	-	-	34,5	8	-	Polarogr.
Ogunbona 1986	8	100	micro	tablet	f	-	-	33	24	10,2 mg/h 3,3h	LLE + UV
					nf [e]			46,2		14,7 mg/h 2,5h	
Panayotis 1986	4	100	macro	capsule	f + 100 mL milk	-	-	26,3	24	6,1 mg/h	LLE + UV
					f + 200 mL milk			27,6		5,3 mg/h -	
					f + 400 mL milk			21,2		5,3 mg/h	

Table S1: Complete overview of the PK parameters of nitrofurantoin in urine. (*continued*)

Reference	Subjects	Drug information			Fasting status	PK parameters					Analytical method
		Dose (mg)	Crystal size	Formulation		C_{max} (mg/l)	T_{max} (h)	Recovery (%)	(h)	Max. excretion rate	(time. h)	
Mason 1987	24	100	macro	Macrodantin	f +1h	95	5	24,5	24	5,6 mg/h	4,7h	LLE + UV
				3 slow release forms		120-150	3-5	30,4-34,1		7,5-8,3 mg/h	3,7-4,2h	
Meyer 1989	14	50	micro	4 tablets	f +4h	-	-	34,3-42,1	23	13,4-17,9 %/h	1,4-2,3h	HPLC + UV
		100		3 tablets				31,6-33,7		11,1-11,7 %/h	2,0-2,6h	
Ertan 1994	6	50	micro	pure NF in hard capsule	f +1h	14,3 mg	0-2	55,0	12	7,2 mg/h	0-2	TLC
				hard gelatin capsule		10,4 mg	2-4	47,9		5,2 mg/h	2-4	
				tableted capsule		12,5 mg	2-4	49,2		6,3 mg/h	2-4	
Adkison 2008	36	100	macro	capsule	f + CC genotype	-	-	43,1	30	-		LC-UV or LC-MS/MS
					f + CA genotype			44,3				
					f + AA genotype			38,8				

Abbreviations used: [nf = non-fasting] [f = fasting] [Photodeg. = photodegradation] [Chrom. = chromatography] [LLE = liquid-liquid extraction] [micro. = microbiologically] [Polarogr. = polarographical] [TLC] Thin layer chromatography.
[TLC] Thin layer chromatography
The '-' sign is used when data are missing.
[a] Patients with recurrent UTI
[b] UTI patient with a gastric resection
[c] Treated for 7 days
[d] It was not specifically mentioned if the photochemical degradation of NF was taken into account for this method. All the other methods did took this into account.
[e] After high fat meal

Table S2: Complete overview of the PK parameters of nitrofurantoin in plasma.

Reference	Subjects	Drug information				Cmax	T_{max}	AUC		T1/2	Analytical method[b]
		Dose (mg)	Crystal size	Formulation	Fasting status	(mg/l)	(h)	(mg/l .h)	(h)	(h)	
Carroll 1955	2[a]	100 + 4x100	macro	Furadantin (capsule)	f	1.11	> 48	-		-	Chrom. + UV
	10[a]	200 + 4x100				0.8-1.81					
Felts 1971	11	100	-	-	nf + normal GFR	0.9-4.6	2-4	-		-	Chrom. + color.
	6				nf + renal imp.	0.75-3.7					
Albert 1974	10	100	micro	Furadantin (tablet)	f +4h	0.986	2	2,10	0-4	-	LLE + UV
			macro	capsule		1.47		3,28			
Maier-Lenz 1979	6	200	micro	tablet	-	0.75	1.5	3885,00			LLE + UV[c]
			-	Slow release tablet		1,00	4	2896,00	0-∞	-	
						0.8	3	2419,00			
Liedtke 1980	10	50 mg	macro	sugar coated tablet	f	0.26	2.1	1.5		1.7	HPLC + polargr.
	7	150 mg				0.59	1.9	3.1	-	1.2	
	10			capsule[d]		0.71	2.6	3.6		1.2	
Hoener 1981	6	50	micro	tablet	f	0.428	2,3	1.05	0-∞	-	HPLC + UV
					nf	0.427	2,6	1.13			
Adkison 2008	36	100	macro	capsule	f + CC genotype	0.875	2-2.3	2.21	0-∞	0.78	LC-UV or LC-MS/MS
					f + CA genotype	0.961		2.42		0.76	
					f + AA genotype	0.963		2.32		0.72	
Patel 2013	36	100	macro	capsule	nf	0.513	4.5	2.62	0-∞	1.66	LC-MS/MS
						0.51	4.7	2.56		1.55	

Abbreviations used: [nf = non-fasting] [f = fasting] [Chrom. = chromatography] [LLE = liquid-liquid extraction] [polarogr. = polarographical] [color. = colorimetric].

[a] UTI patients with loading dose of 100 mg.

[b] All methods took the photochemical degradation of NF into account.

[c] It was not specifically mentioned if the photochemical degradation of NF was taken into account for this method. All the other methods did took this into account.

[d] Capsule with three different granulations.