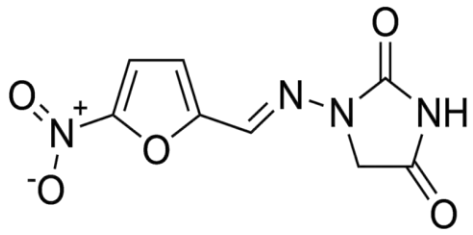


Nitrofurantoin

One of the old revived antibiotics

Anouk Muller
Clinical Microbiologist, MCHaaglanden, The Netherlands

History

- Developed in the 1940s
- Approved in 1953 by the FDA

Wikimedia.org

- Traditional uses:
  - Gram-negative cystitis/catheter-associated bacteriuria
  - Asymptomatic bacteriuria (in pregnancy)
  - Enterococcal cystitis

Cunha, p1089,2006

The use over time

From presentation of A. Huttner, AIDA meeting 2012

- Used from 1953
- Decreased use due to toxicity issues in the 1970s
- Increase use due to resistance problems to the alternative antibiotics

Current approved indications

- The Netherlands:
  - Treatment of cystitis
  - Short term prophylaxis (up to 3 days)
  - *Long term prophylaxis not mentioned in paragraph indications, but only in the paragraph on dosing*
- United Kingdom
  - For the **treatment** of and **prophylaxis** against **acute or recurrent**, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Dosing

- The Netherlands:
  - Therapy: 4 times daily 50mg
  - Short term Prophylaxis: 4 times daily 50mg
  - Long term prophylaxis: 50-100mg once daily[warning]
- United Kingdom
  - Therapy (acute UTI): 4 times daily 50mg
  - Therapy severe recurrent UTI: 4 times daily 100mg
  - Short term Prophylaxis: 4 times daily 50mg
  - Long term prophylaxis: 50-100mg once daily

Current medical knowledge

- Pharmacokinetics
- Pharmacodynamics
- Clinical studies

MCH
Medisch Centrum Haaglanden

Pharmacokinetics

4. Pharmacokinetics				
Dosage (mg)	**100 mg**			
Cmax (mg/L)	<2 after 1-4 h			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	0.5-1			
AUC24h (mg.h/L)				
Fraction unbound (%)	25-50			
Volume of distribution (L/kG)	0.6			
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption >95 % • Concentration in urine >100 mg/L			
References	• Mazzei et al Int J Ant Agents 2006; 28 suppl 1: 35-46. • Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 396-8.			

- Oral administration

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Pharmacokin

But…. Wasn't there someting about macro or microcrystals???

4. Pharmacokinetics				
Dosage (mg)	**100 mg**			
Cmax (mg/L)	<2 after 1-4 h			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	0.5-1			
AUC24h (mg.h/L)				
Fraction unbound (%)	25-50			
Volume of distribution (L/kG)	0.6			
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption >95 % • Concentration in urine >100 mg/L			
References	• Mazzei et al Int J Ant Agents 2006; 28 suppl 1: 35-46. • Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 396-8.			

- Oral administration

Does the size of the crystals matter?

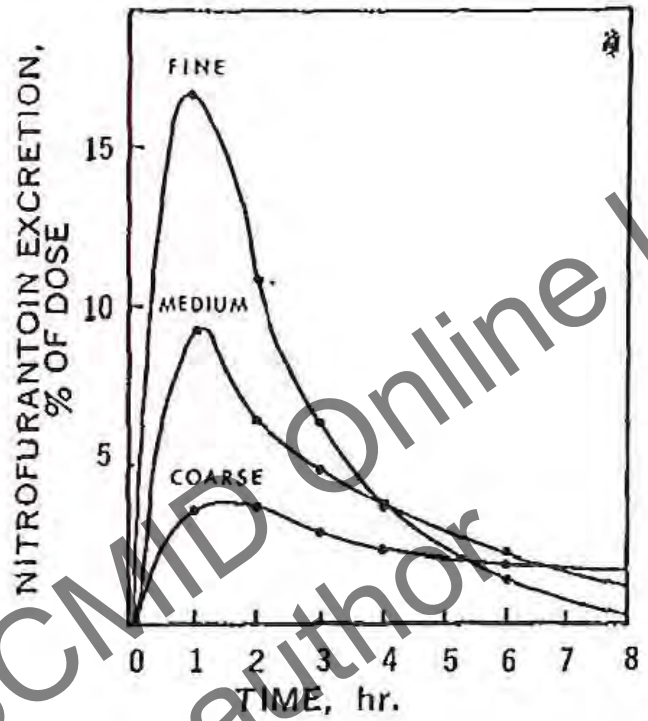


Fig. 1—Effect of crystal size of orally administered nitrofurantoin on urinary recovery rate in the rat. Key: coarse, 50–80 mesh (300–180 μ); medium, 80–200 mesh (180–75 μ); fine, 200 mesh to micronized (75–10 μ or less).

- Study in rats
- The smaller the size of the crystals, more nitrofurantoine is excreted in the urine.

Paul 1967 J Pharm Sc 56(7); p882-5

humans

TABLE II—SUMMARY OF CRITERIA MEASURED IN HUMAN VOLUNTEERS RECEIVING VARIOUS SIZES OF NITROFURANTOIN CRYSTALS[a]

Crystal Size[b] of Nitrofurantoin	(1) Max. % Excreted in Any 2-hr. Period	(2) Av. Time of Max. % Excretion, hr.	(3) Max. Urinary Concn. Attained, mg./L.	(4) Av. Time Max. Urinary Concn. Attained, hr.	(5) Total % of Initial Dose Excreted
50–60 mesh	8.3	4.9	83	5.5	19.6
80–120 mesh	12.9	4.6	124	5.0	29.8
140–200 mesh	16.6	3.8	159	4.1	32.3
200–400 mesh small	17.8	3.6	156	3.4	35.4
Marketed nitrofurantoin tablets (Provide fine crystals in the 10 μ range)	20.0	3.6	151	3.0	36.1

[a] Each value based on 15 complete individual studies—no pooling of samples. Exceptions: 10 individuals only were available from same population for 200–400 mesh and 14 for tablets. [b] Size checked by microscopic measurement.

Paul 1967 J Pharm Sc 56(7); p882-5

Mean cumulative excretion

Fasting vs nonfasting

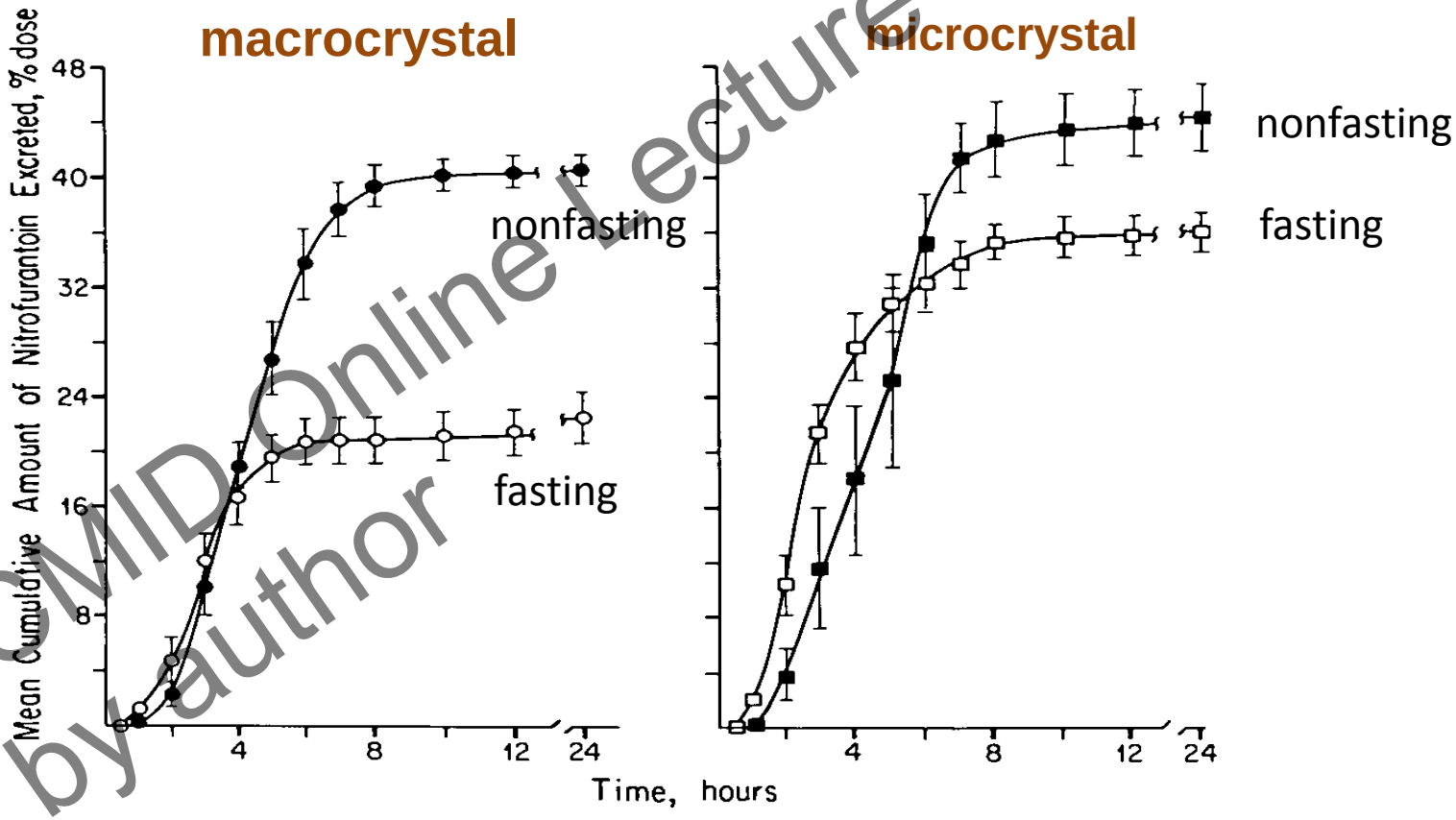


Fig. 1. Mean cumulative urinary excretion of nitrofurantoin after oral administration of a 100 mg macrocrystalline capsule to fasting (○) and nonfasting (●) subjects, and a 100 mg microcrystalline tablet to fasting (□) and nonfasting (■) subjects. N = 4; Vertical bars represent standard errors of the mean.

Bates 1974, Clin Pharm Ther 16(1); p63-8

Summary of pharmacokinetics

- Well absorbed (primarily small intestine)
- Absorption enhanced by food
- Macrocrystalline dissolves more slowly ("slow release")
- Drug accumulates in urine
- Low serum concentrations
- Excretion by kidney and inactivated in body
- Differences between the formulations

Next step

- To discuss the results of the pharmacokinetics we need some pharmacodynamics

Figure obtained from: http://ydyc.org/media/funny-pictures/conversation-between-friends/

Pharmacodynamics

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

5. Pharmacodynamics				
*f*AUC/MIC for bacteriostasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Pharmacodynamic parameters for nitrofurantoin have not been determined. • Cells are left empty when data are not readily available.			
References				

Clinical studies

- Nitrofurantoin compared to:
  - Cotrimoxazole
  - Ciprofloxacin
  - Fosfomycin
  - amoxicillin
  - Placebo
- Clinical cure rates comparable to the other drugs: between 50-100%
- Same for micobiological effect: 40-90%
- Placebo: ~40% cure both clinical and microbiological

toxicity

- Short term use:
  - nausea, abdominal discomfort and headaches
  - 5-16% of patients (one study 49%)

- Long term use:
  - Taking nitrofurantoin for months or years
  - pulmonary fibrosis and hepatotoxicity
  - Fatalities have been described
  - Calculated frequencies
    - Pulmonary effects: 0.001%
    - Hepatic toxicity: 0.0003%

Recent warning in the French guidelines

- Warning on toxicity for prophylaxis

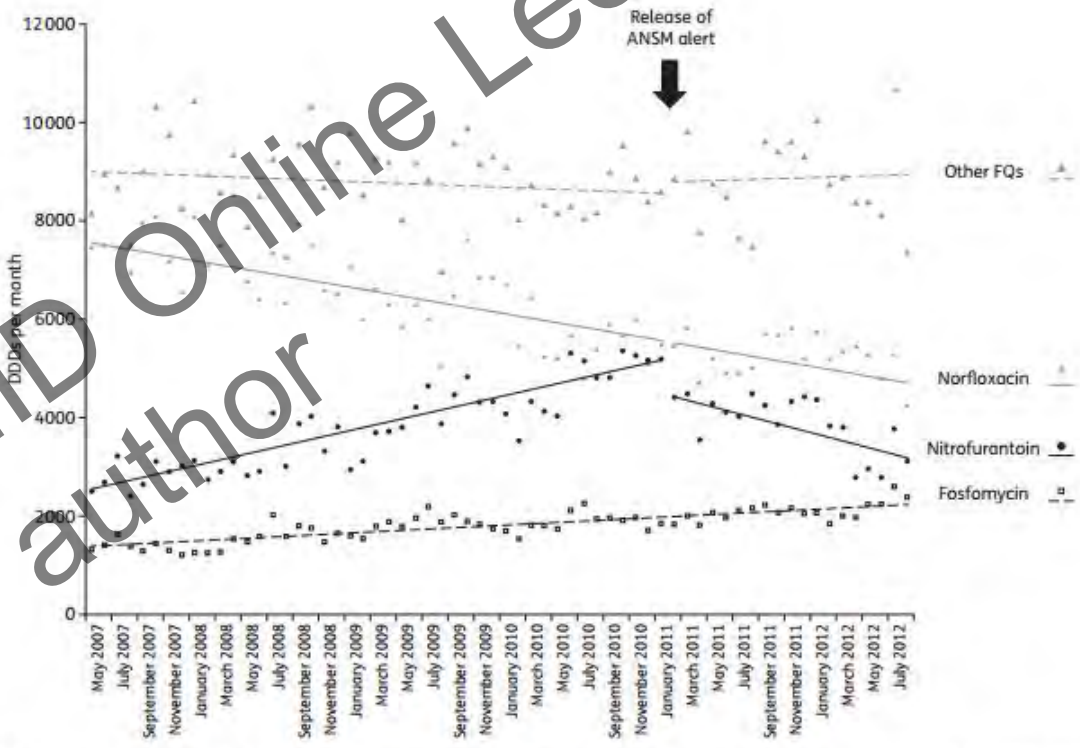


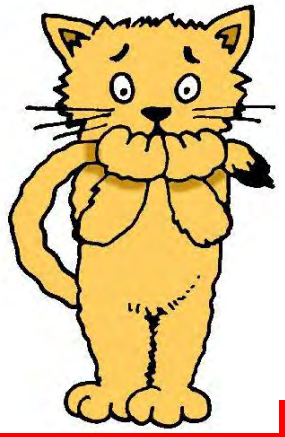
Figure 1. Graphical representation of the segmented regression modification of antibiotic use before and after the release of the ANSM alert. FQs, fluoroquinolones.

C. Slekovec, J. Leroy, A. Huttner et al. JAC, p282,2014

Gaps

- Detailed PK information on different formulations
- Pharmacokinetics of nitrofurantoin in the elderly
- The PK/PD-target

- So actually, we need the correct dose



Actions on the Gaps

- Detailed PK information on different formulations
  - Within the AIDA FP7 project PK-studies is being performed in Geneva and Tilburg.
- The PK/PD-target
  - Within the AIDA FP7 project a study on the target is being performed in Nijmegen and in Copenhagen
- So actually, we need the correct dose
  - Hopefully, we will get the correct dose for one of the formulations

We're balancing in the gap and do what we think is good

Figure obtained from http://nistmep.blogs.govdelivery.com/

acknowledgment

- FP7 project AIDA

- Angela Huttner
- Els Verhaegh