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Therapeutic Drug Monitoring in Antifungal Therapy

Why, When and How

Roger Brüggemann

Radboud University Nijmegen Medical Centre and

Nijmegen Institute for Infection, Inflammation and Immunology (N4i)

Trends in Medical Mycology, Athens, October 18-21, 2009

TIMM

Trends in Medical Mycology

Question 1

Who believes Therapeutic Drug Monitoring is beneficial for patient outcome whether this is toxicity or efficacy?

Question 2

Who performs Therapeutic Drug Monitoring on a regular basis for routine patient management?

Since there is no prospective randomized trial to support the use of TDM, we follow a decision making algorithm to determine if TDM of a certain drug is useful……

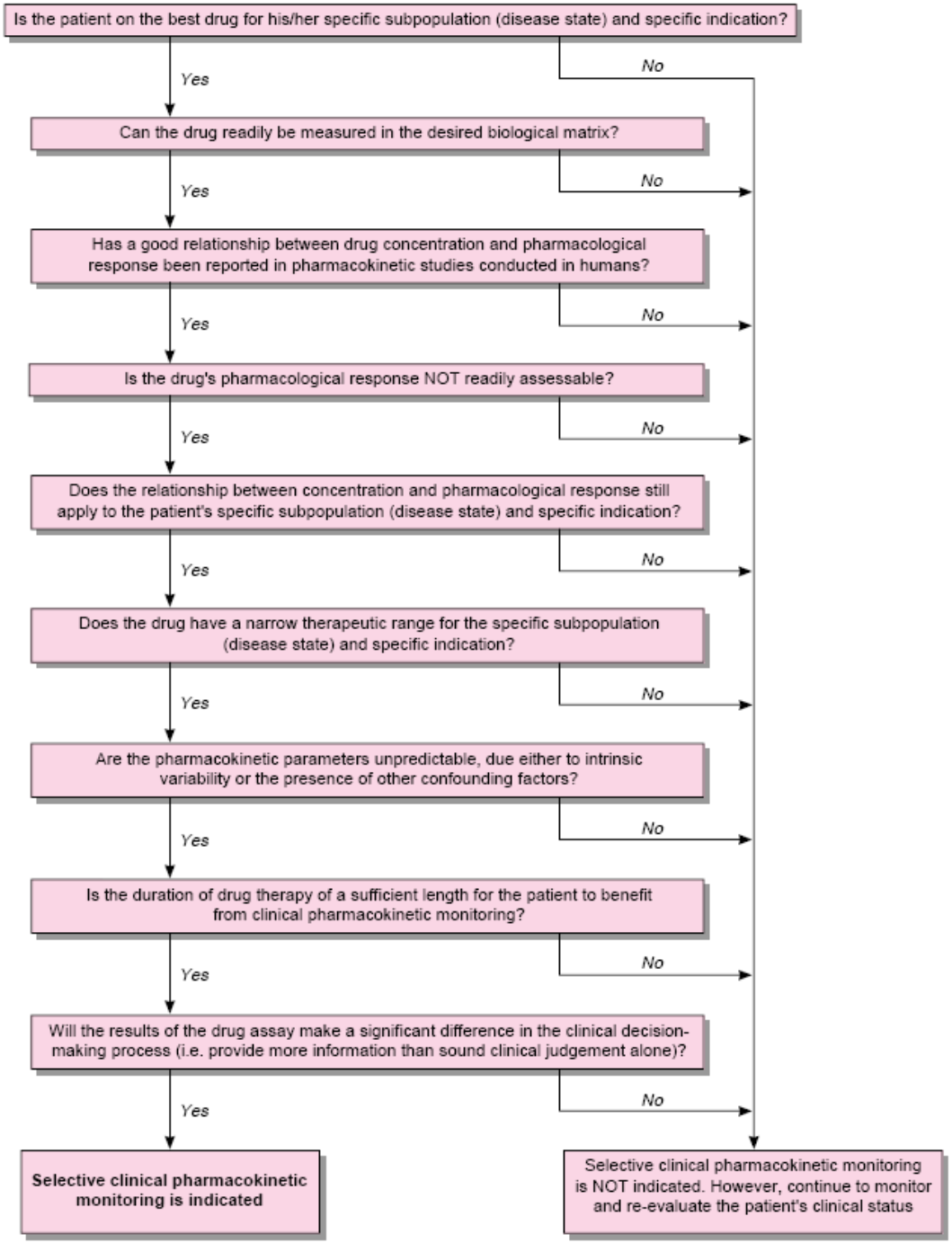


Fig. 1. Decision-making algorithm for clinical pharmacokinetic monitoring in the 21st century.

CURRENT OPINION

Clin Pharmacokinet 1998 Apr; 34 (4): 265-279
0312-5963/98/0004-0265/$07.50/0

Clinical Pharmacokinetics in the 21st Century

Does the Evidence Support Definitive Outcomes?

Mary H. H. Ensom,[1,2] *George A. Davis,*[1] *Cheryl D. Cropp*[1] and *Robin J. Ensom*[2,3]

Sites of Action of Systemic Antifungal Agents

Cell membrane

Polyenes:

Amphotericin B

Lipid formulations of amphotericin B

Nystatin

Cell wall

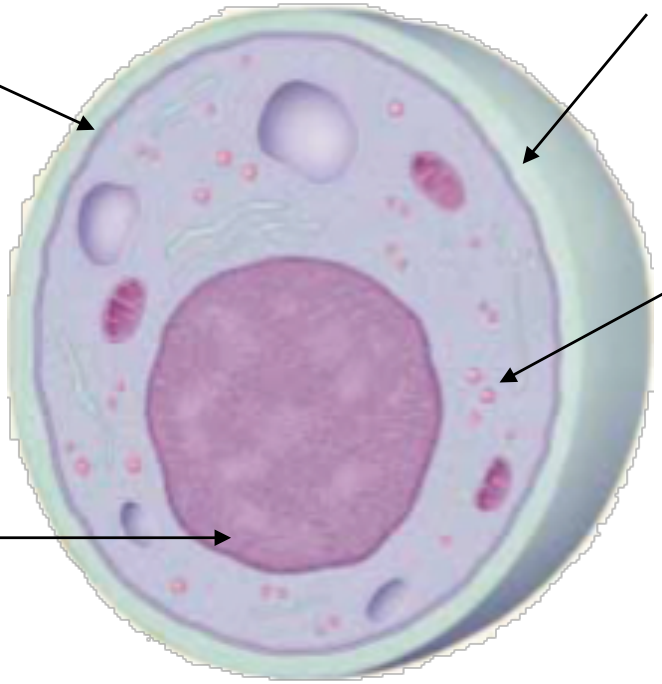
Echinocandins:

Caspofungin

Micafungin

Anidulafungin

?



Cytoplasm

Azoles:

Ketoconazole

Fluconazole

Itraconazole

Voriconazole

Posaconazole

Isavuconazole

DNA

Antimetabolites:

5-fluorocytosine

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Therapeutic drug monitoring for triazoles

William W. Hope[a], Eliane M. Billaud[b], Jodie Lestner[a] and David W. Denning[a]

Current Opinion in Infectious Diseases 2008, 21:580–586

(1) clinically relevant exposure–response relationships,
(2) clinically relevant exposure–toxicity relationships,
(3) compounds with a narrow therapeutic window,
(4) variable pharmacokinetics,
(5) physiological instability,
(6) drug–drug interactions,
(7) infections at sanctuary sites,
(8) children and neonates,
(9) degree of compliance,
(10) change of dosage,
(11) patient failing therapy and
(12) serious/poor prognostic disease.

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PK/PD of voriconazole in Aspergillosis

Efficacy and Safety of Voriconazole in the Treatment of Acute Invasive Aspergillosis

David W. Denning,[1] Patricia Ribaud,[2] Noel Milpied,[3] Denis Caillot,[4] Raoul Herbrecht,[5] Eckhard Thiel,[7] Andrea Haas,[6] Markus Ruhnke,[8] and Hartmut Lode[9]

- 5 patients average conc < 0,25 mg/L, of which 4 failures
- 6 patients average conc between 0,25 mg/L - 0,50 mg/L, of which 1 failure

- 22 patients average conc > 6 mg/L, of which 6 liver toxicity
- 7 patients average conc > 10 mg/L, of which 6 ceased VRC due to AEs

Denning DW, et al. Clin Infect Dis 2002 March 1;34(5):563-71

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1570–1572 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1570–1572.2006

Voriconazole Therapeutic Drug Monitoring

J. Smith,[1] N. Safdar,[1] V. Knasinski,[1] W. Simmons,[2] S. M. Bhavnani,[3] P. G. Ambrose,[3] and D. Andes[1,4]*

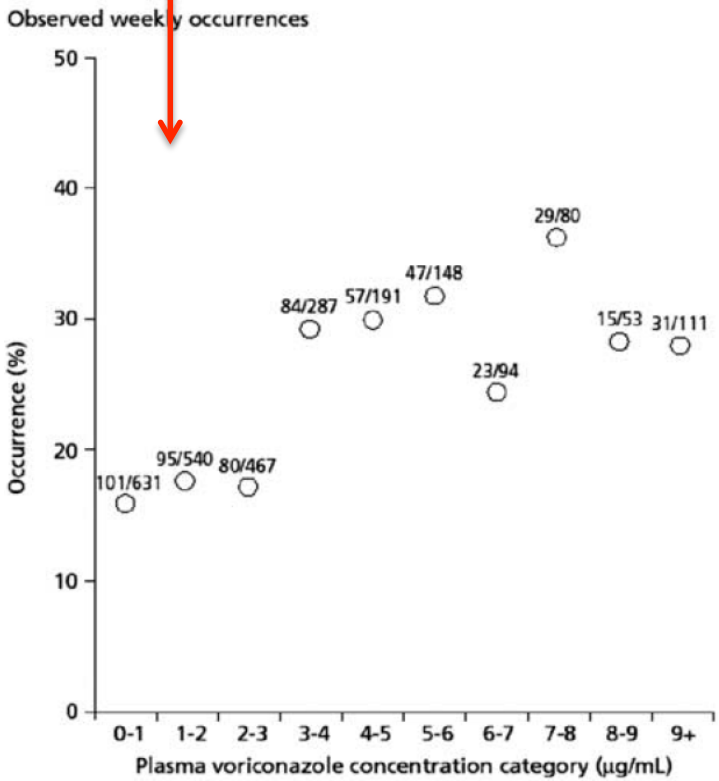
University of Wisconsin, Department of Medicine, Section of Infectious Diseases, Madison, Wisconsin[1]; University of Wisconsin, Department of Pharmacy, Madison, Wisconsin[2]; Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York[3]; and University of Wisconsin, Department of Medical Microbiology and Immunology, Madison, Wisconsin[4]

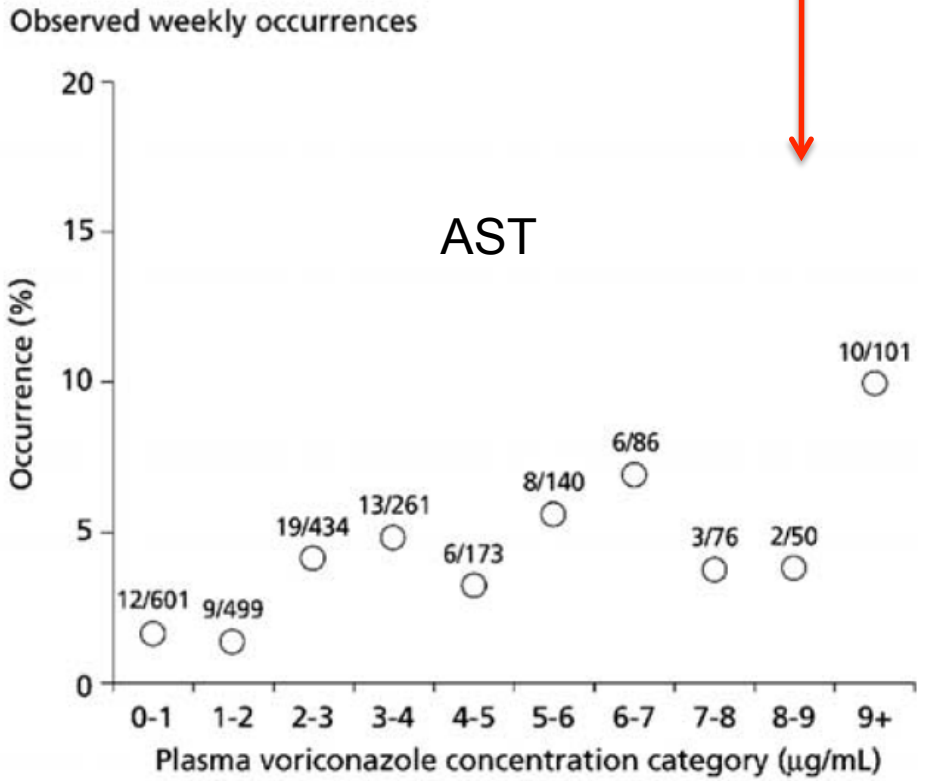
- Retrospective analysis of 28 patients
- 17 because of disease progression; 11 because of toxicity
- PK/PD analysis: 10/10 patients with conc >2 mg/L had positive response vs. 10/18 with concentrations < 2 mg/L

Both the prior breakthrough infection reports and the current data suggest that clinicians should escalate doses for serum concentrations of below 2 μg/liter in patients failing therapy.

Investigation of the Potential Relationships Between Plasma Voriconazole Concentrations and Visual Adverse Events or Liver Function Test Abnormalities

Keith Tan, PhD, Nigel Brayshaw, MSc, Konrad Tomaszewski, PhD, Peter Troke, PhD, and Nolan Wood, PhD





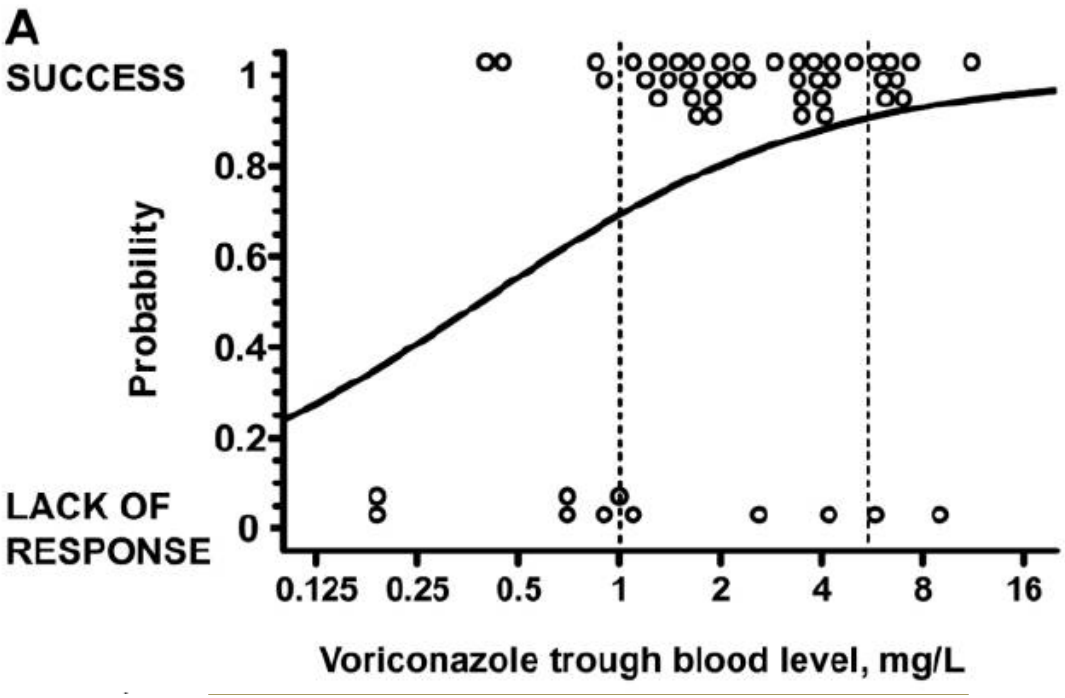
Tan K, et al. J Clin Pharmacol 2006 February;46(2):235-43.

Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

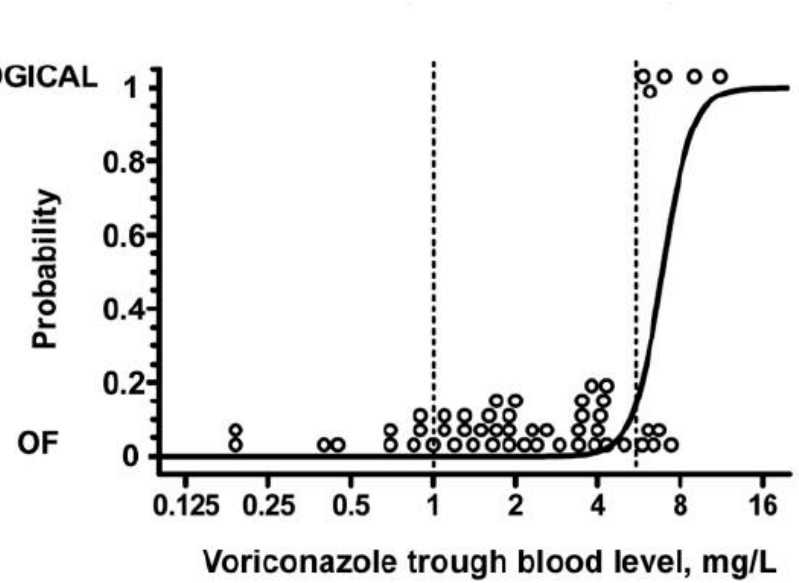
Andres Pascual,[1] Thierry Calandra,[1] Saskia Bolay,[1] Thierry Buclin,[2] Jacques Bille,[3] and Oscar Marchetti[1]

[1]Infectious Diseases Service, [2]Division of Clinical Pharmacology, and [3]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Efficacy



Neurological toxicitity

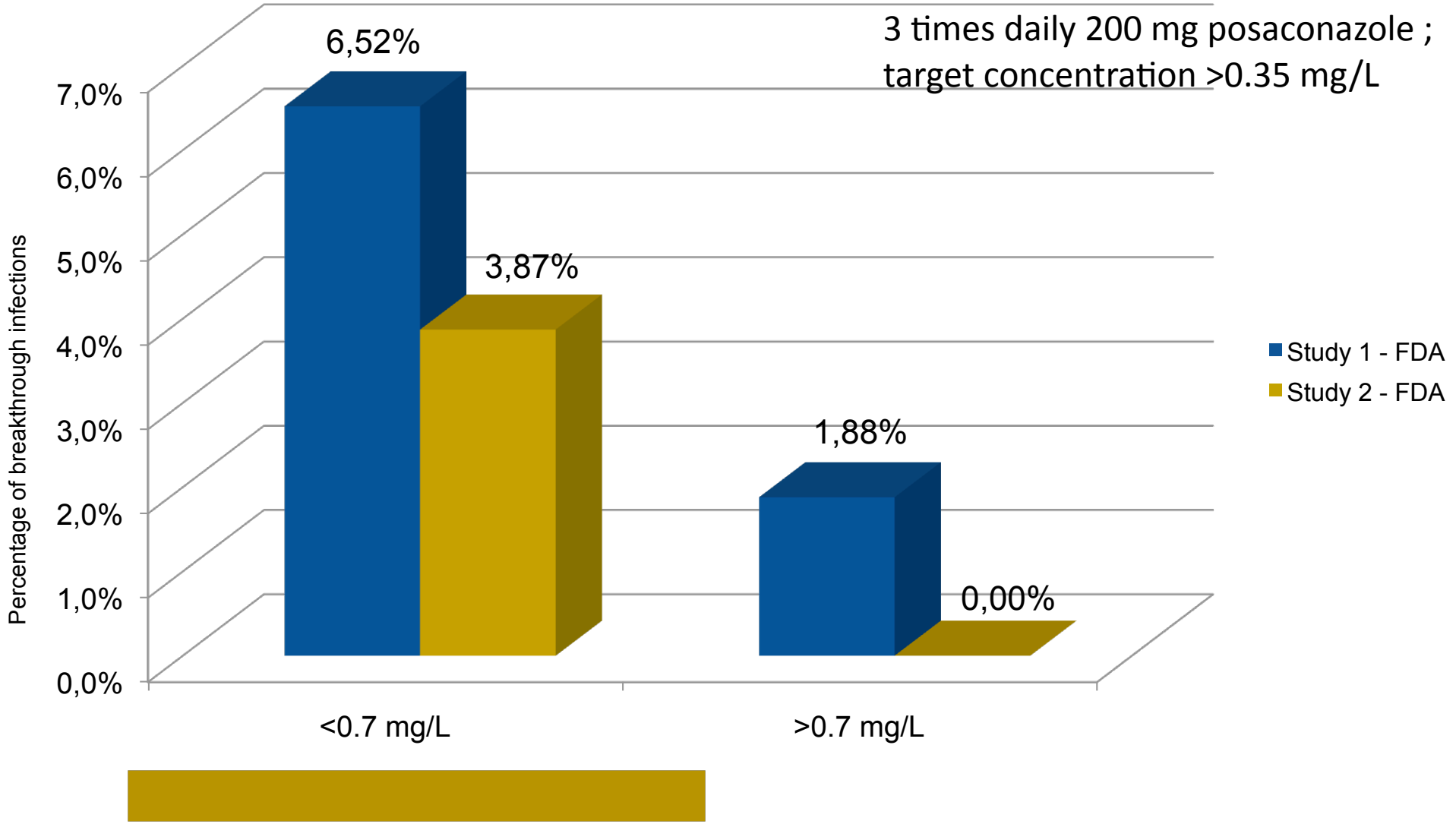


Journal of Antimicrobial Chemotherapy (2008) **61**, 17–25
doi:10.1093/jac/dkm389
Advance Access publication 12 November 2007

JAC

Antifungal serum concentration monitoring: an update

Megan L. Goodwin[1]* and Richard H. Drew[2,3]



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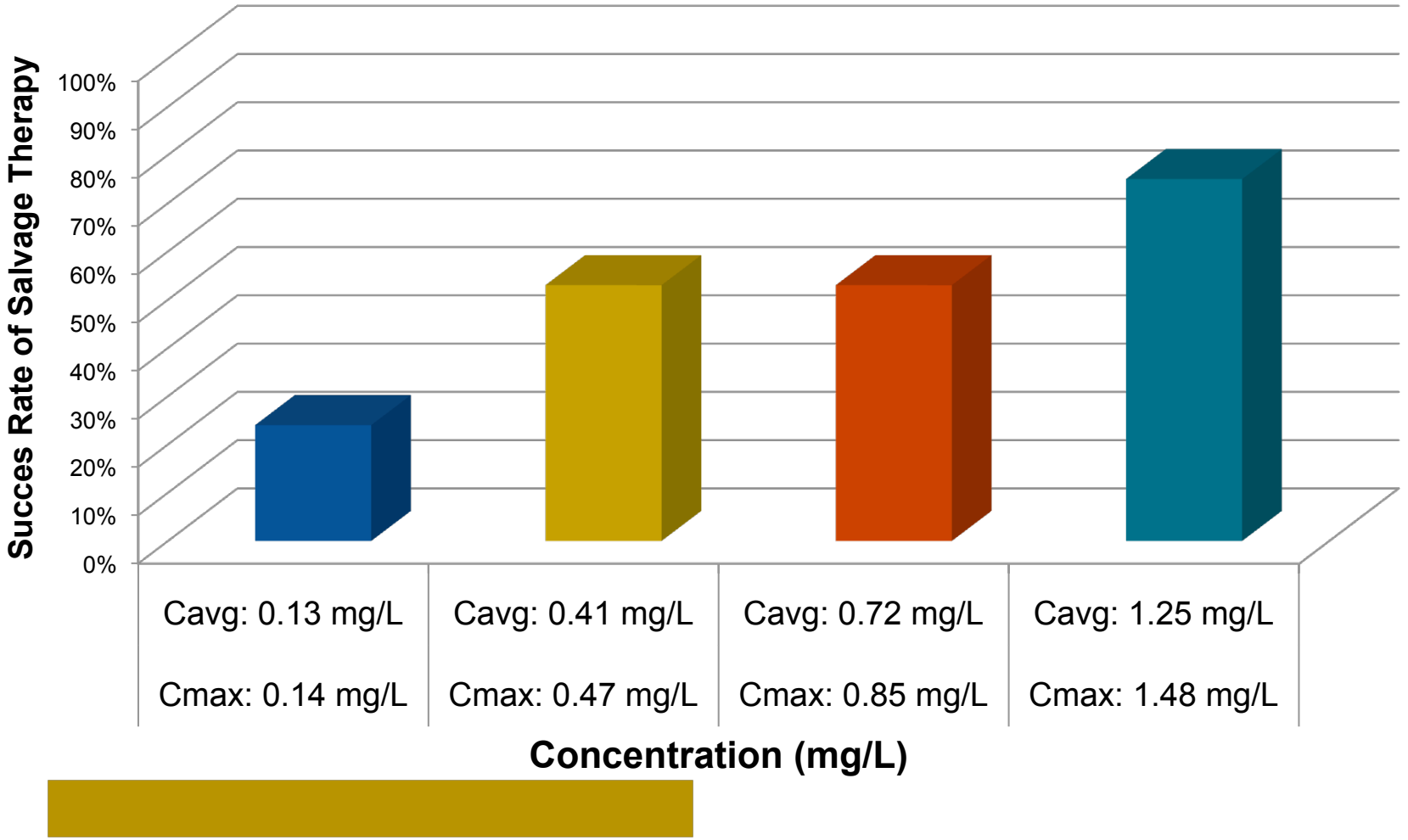
Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

Thomas J. Walsh,[1] Issam Raad,[3] Thomas F. Patterson,[4] Pranatharthi Chandrasekar,[5] Gerald R. Donowitz,[6] Richard Graybill,[4] Reginald E. Greene,[7] Ray Hachem,[3] Susan Hadley,[8] Raoul Herbrecht,[16] Amelia Langston,[9] Arnold Louie,[10a] Patricia Ribaud,[17,a] Brahm H. Segal,[11] David A. Stevens,[12] Jo-Anne H. van Burik,[13] Charles S. White,[2] Gavin Corcoran,[14,a] Jagadish Gogate,[14,a] Gopal Krishna,[14] Lisa Pedicone,[14] Catherine Hardalo,[14] and John R. Perfect[15]



D Lebeaux, F Lanternier, C Elie, et al.
Therapeutic drug monitoring of posaconazole:
a monocentric study in 54 adults;
Antimicrob. Agents Chemother
Published online ahead of print on 14 September 2009

54 Adult patients on posaconazole: TDM

- 36 Prophylaxis (200 mg TID)
  - 16/36 had concentrations below provisional cut-off point of 0.5 mg/L.
  - 2 patients had a breakthrough infection, both with conc < 0.5 mg/L
- 18 patients in curative setting (400 mg BID)
  - Wide variety of infections
  - Response: 8 complete, 4 partial, 2 stable, 2 failure, 2 died of other cause
  - Low pos conc: 2 complete response (1 was optimized after this finding), 1 died (other cause), and 2 stable disease
  - Failures (*A. fumigatus and T. rubrum)* or stable disease had conc ranging from 0.29 – 1.33 mg/L

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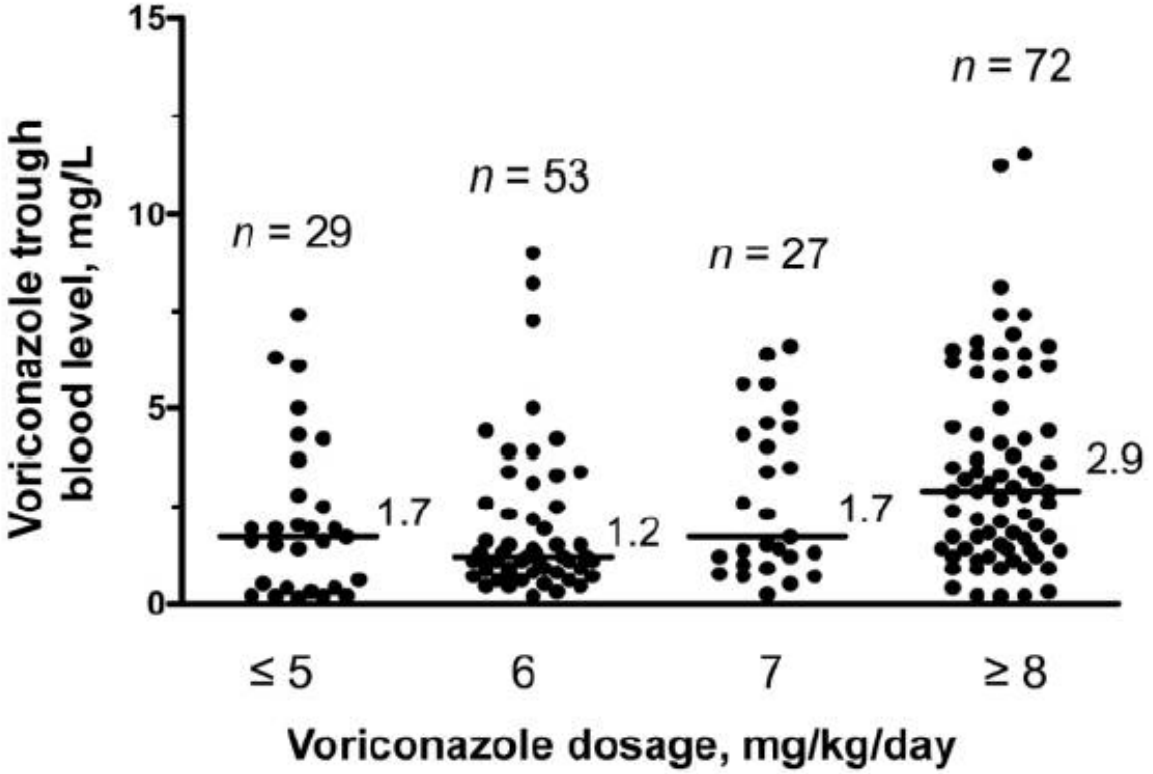
Therapeutic Drug Monitoring in Antifungal Therapy

Pharmacokinetic variability

No strong correlation between dose administered and plasma concentration



Pascual et al, CID 2008

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2009, p. 2223–2224 Vol. 53, No. 5
0066-4804/09/$08.00+0 doi:10.1128/AAC.00240-09

George R. Thompson III
Division of Infectious Diseases
Department of Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas 78229

Posaconazole Therapeutic Drug Monitoring: a Reference Laboratory Experience[▽]

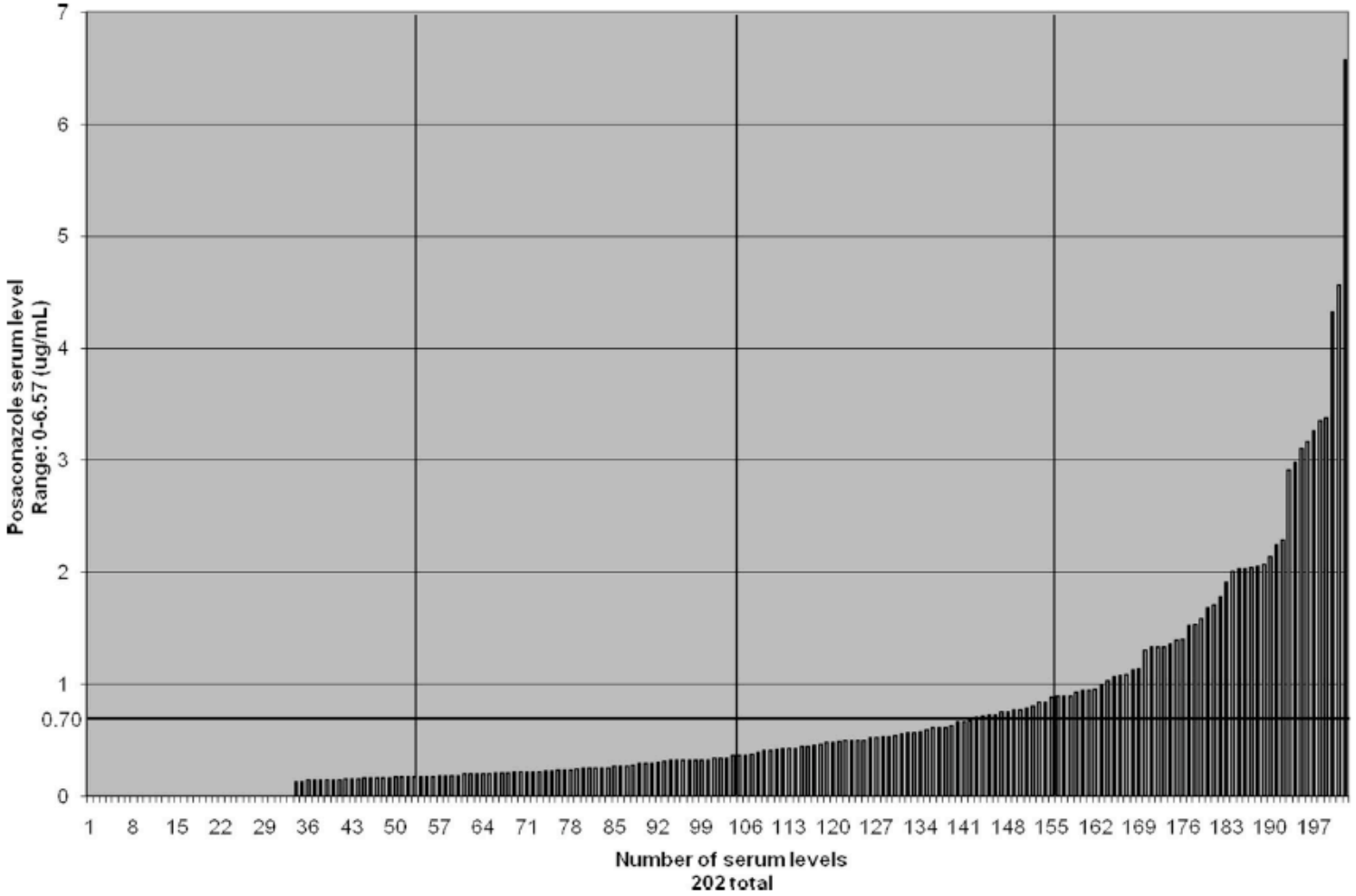
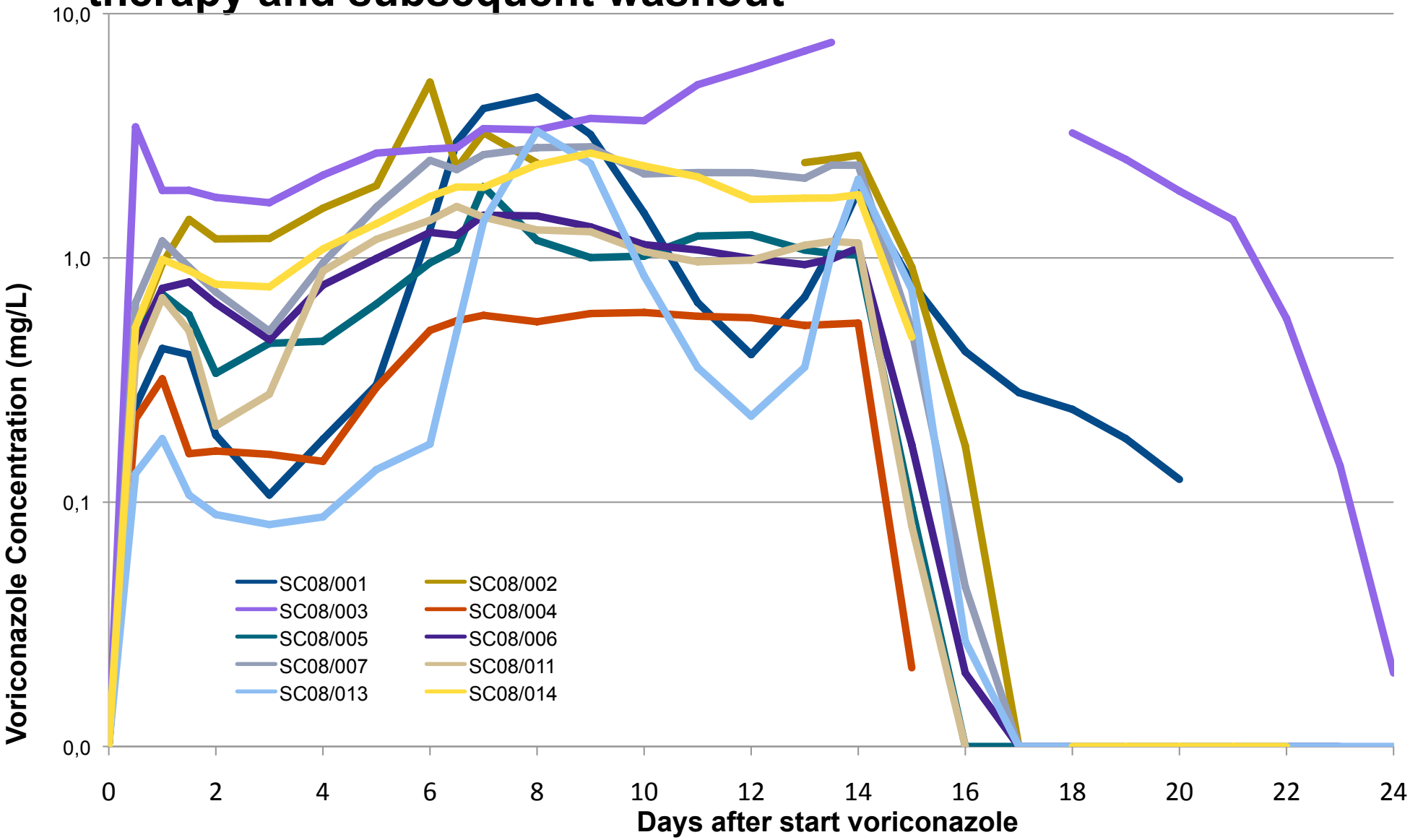


FIG. 1. Distribution of serum posaconazole levels obtained by the Fungus Testing Laboratory, San Antonio, TX, from 26 December 2007 through 30 December 2008.

When to perform TDM – variable pharmacokinetics

- When there is substantial inter- and intrapatient variation

Plasma concentrations of VRZ during 14 days of intravenous therapy and subsequent washout



Brüggemann et al, JAC, accepted for publication

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Therapeutic Drug Monitoring in Antifungal Therapy

Pharmacogenetics and Drug Metabolism

Inter-individual variability - pharmacogenetics

- Genetic polymorphism of CYP2C19 is important for VRC

15–20% of Asian populations expected to be poor metabolisers, whereas the prevalence is 3–5% amongst Caucasians and Blacks.[23,24] Clinical studies have shown that poor metabolisers achieve 4-fold higher voriconazole concentrations (AUC_τ) than extensive metabolisers.[8] However, currently, no dosage adjustments are recommended with regard to this observation.

FDA. Background Document for the Antiviral Drug Products Advisory Committee Meeting. 4-10-2001. Accessed: 2-5-2007

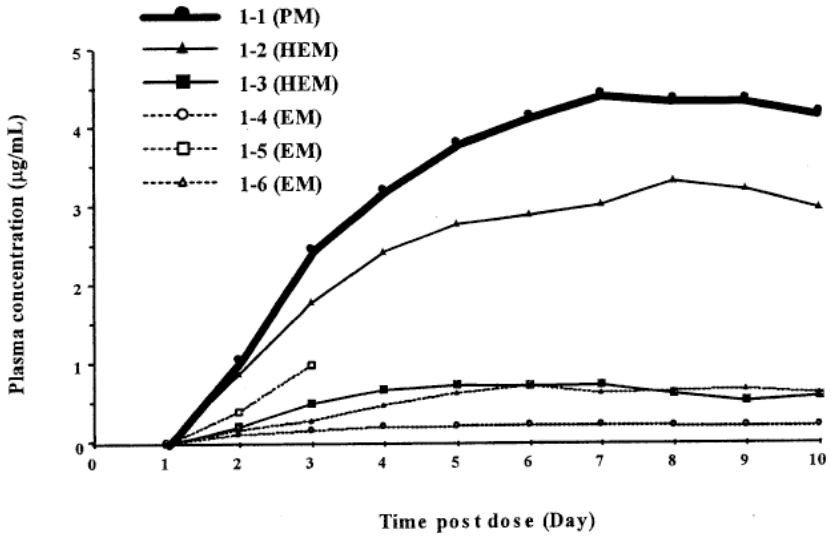
- Absence of SNPs (wildtype) means extensive metabolizers (EM)

- Genetic polymorphism of CYP2C9 has no significant influence on pharmacokinetics of voriconazole

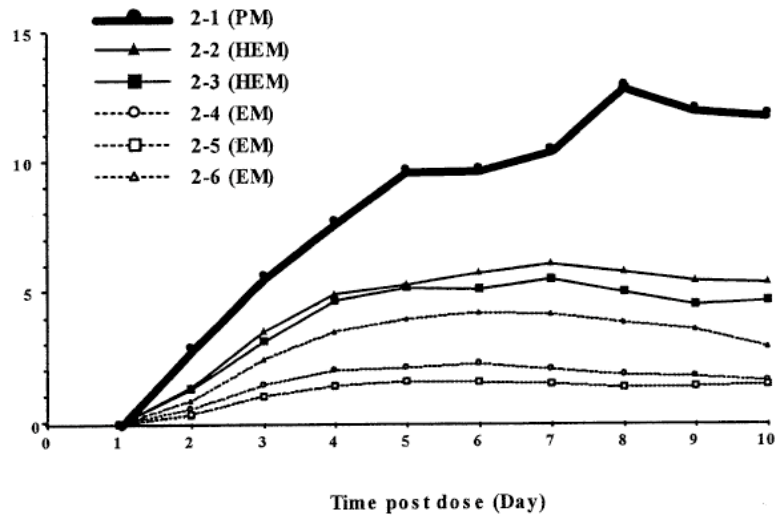
Geist MJ, et al. Antimicrob Agents Chemother 2006 September;50(9): 3227-8

Pharmacogenetics II – voriconazole metabolism

400 mg/day



600 mg/day



The values for area under the plasma concentration–time curve on day 10 in the 200- and 300-mg administration groups were approximately 5.8 and 3.8 times higher, respectively, among the 2 PMs than the EMs. Trough concentrations

Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004 June;75(6):587-8.

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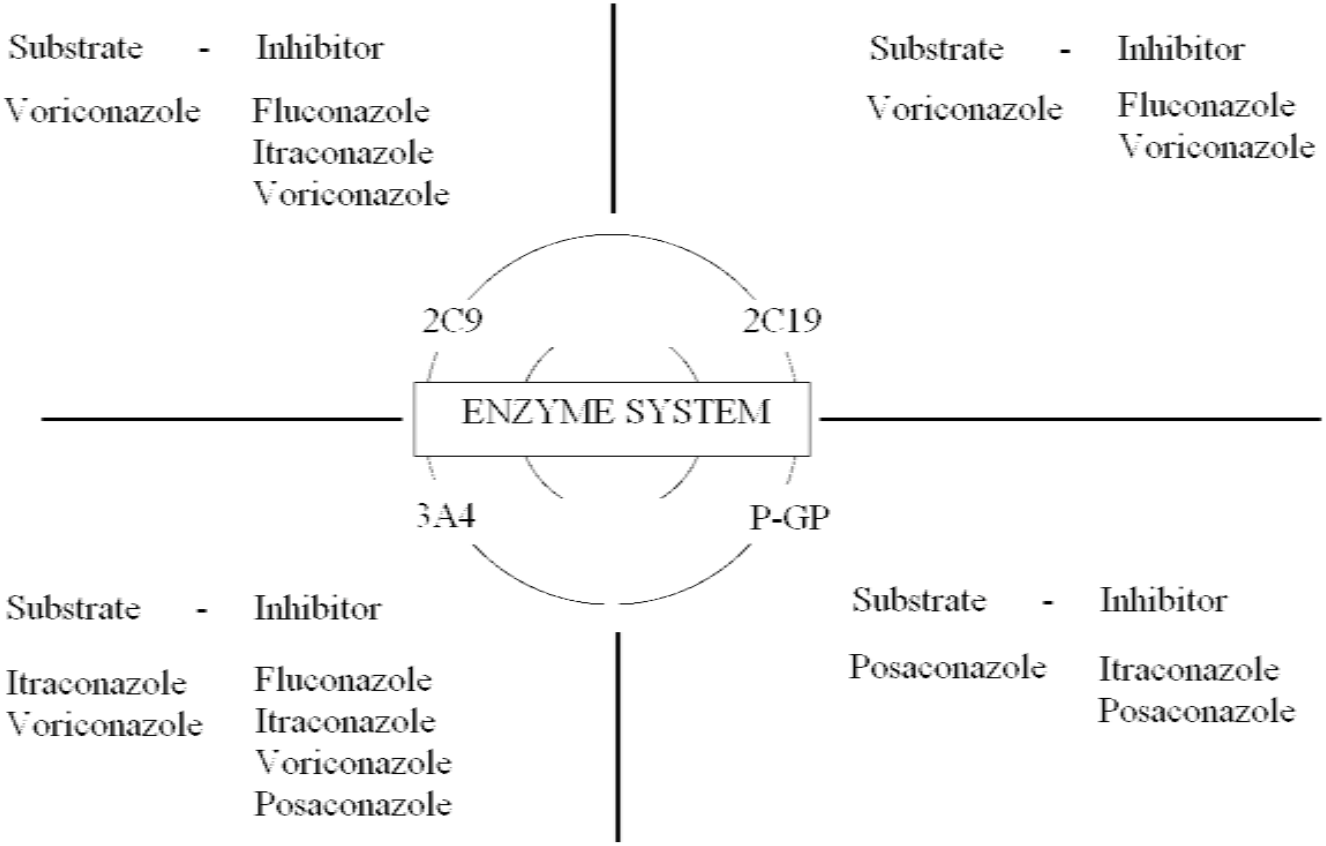
Drug – drug and drug – food interactions

Especially the class of azole cause significant interactions



R.J.M. Brüggemann, J.W. Alffenaar, N.M.A Blijlevens, E.M. Billaud, J.G. Kosterink, P.E Verweij; D.M. Burger.
Clinical relevance of pharmacokinetic drug interactions with antifungal azole drugs
Clin Infect Dis. 2009 May 15;48(10):1441-58

Interaction between voriconazole and ritonavir

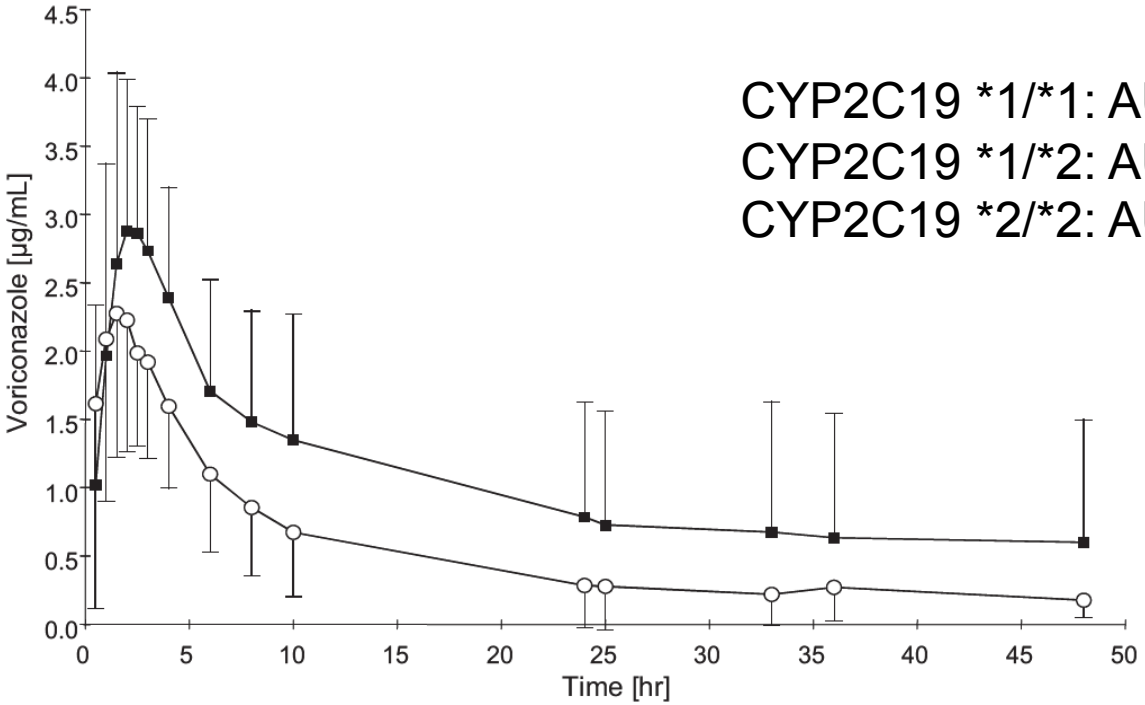


Fig 1. Mean (±SD) voriconazole plasma concentration–time profile after single oral administration of 400 mg voriconazole in combination with placebo (*circles*) or 300 mg ritonavir twice daily (*squares*) to 20 healthy subjects.

CYP2C19 *1/*1: AUC 16.5 vs 25.5 (+55%)
CYP2C19 *1/*2: AUC 22.7 vs. 44.1 (+94%)
CYP2C19 *2/*2: AUC 48.0 vs. 435 (+806%)

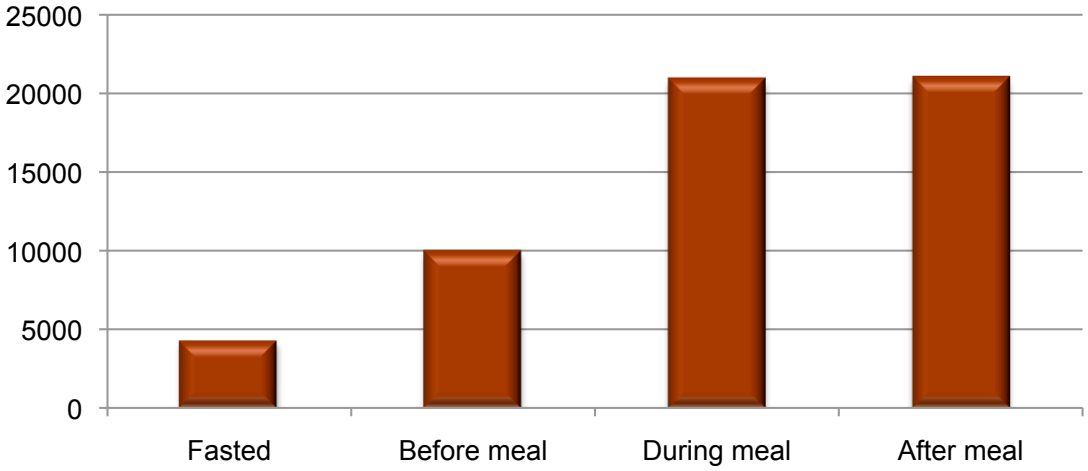
Mechanism: inhibition of CYP3A4 by ritonavir in CYP2C19 poor metabolizers

Mikus G, Schowel V, Drzewinska M, Rengelshausen J, Ding R, Riedel KD et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006 August;80(2):126-35

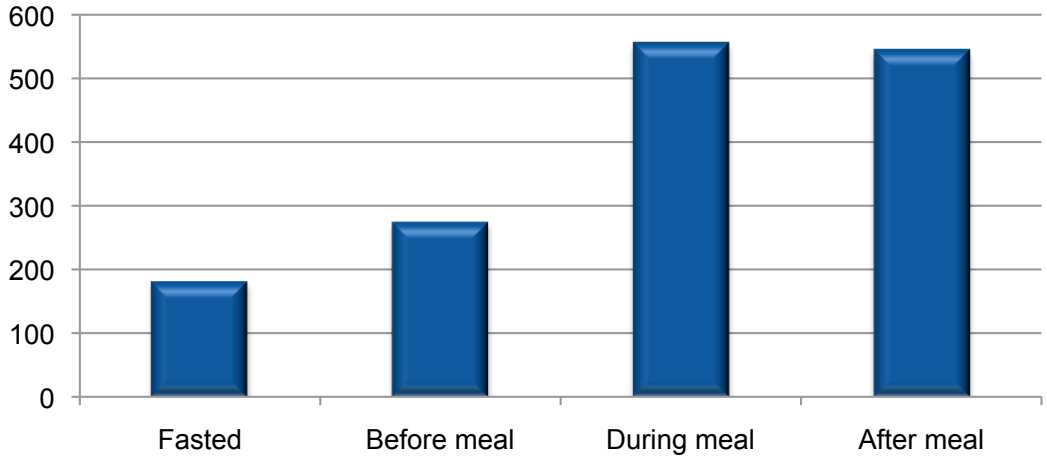
Drug- food interaction

Krishna G, Moton A, Ma L, Medlock MM, McLeod J; Pharmacokinetics and Absorption of Posaconazole Oral Suspension under Various Gastric Conditions in Healthy Volunteers. Antimicrobial Agents and Chemotherapy, 2009 Mar; 53 (3):958-966

AUC (ng*h/mL) after POS 400 mg SD



Cmax (ng/ml) after POS 400 mg SD



Absorption of posaconazole 400 mg single dose relative to meal timing

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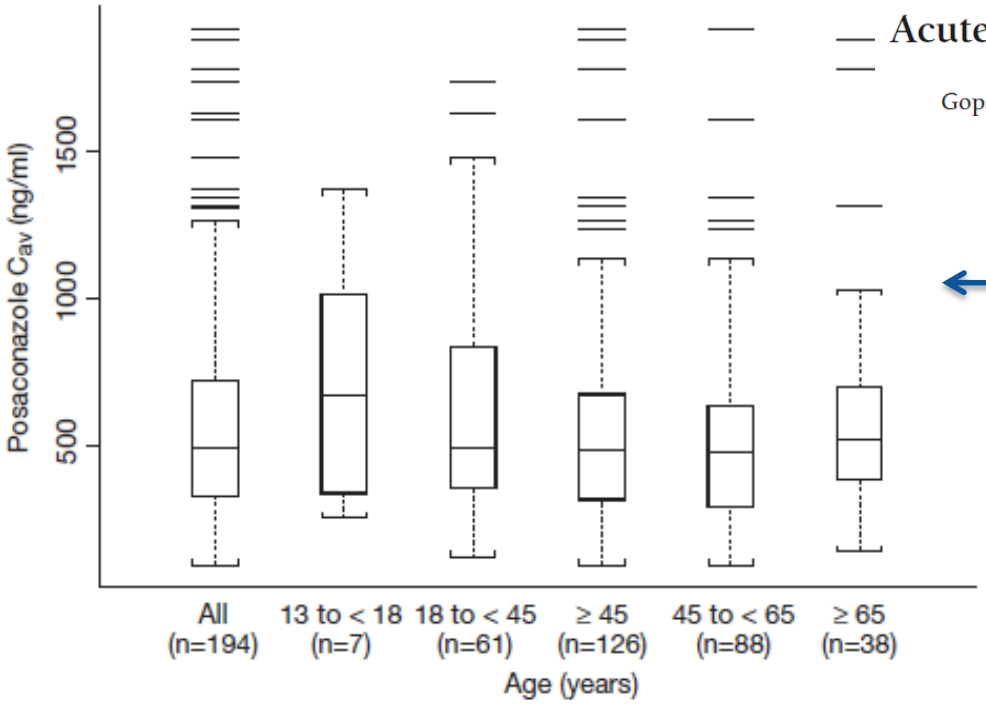
Therapeutic Drug Monitoring in Antifungal Therapy

Special patient populations

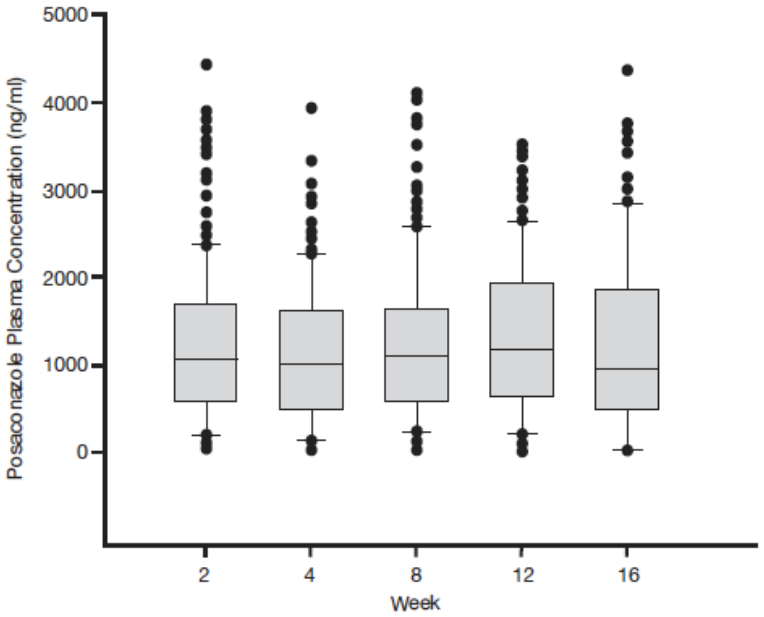
Does the relationship between concentration and pharmacological response still apply to the patient's specific subpopulation (disease state) and specific indication?

Pharmacokinetics of Oral Posaconazole in Neutropenic Patients Receiving Chemotherapy for Acute Myelogenous Leukemia or Myelodysplastic Syndrome

Gopal Krishna, Ph.D., Malaz AbuTarif, Ph.D., Fengjuan Xuan, Ph.D., Monika Martinho, M.S., David Angulo, M.D., and Oliver A. Cornely, M.D.



In both studies posaconazole was given as prophylaxis at 200 mg TID
Sampling: at steady state



Pharmacokinetics of Oral Posaconazole in Allogeneic Hematopoietic Stem Cell Transplant Recipients with Graft-versus-Host Disease

Gopal Krishna, Ph.D., Monika Martinho, M.S., Pranatharthi Chandrasekar, M.D., Andrew J. Ullmann, M.D., and Hernando Patino, M.D.

Pediatric Patients

Free communications 2 - *Santorini 4-6*

Monday 17.30 - O2.6
Therapeutic drug monitoring of voriconazole in pediatric patients

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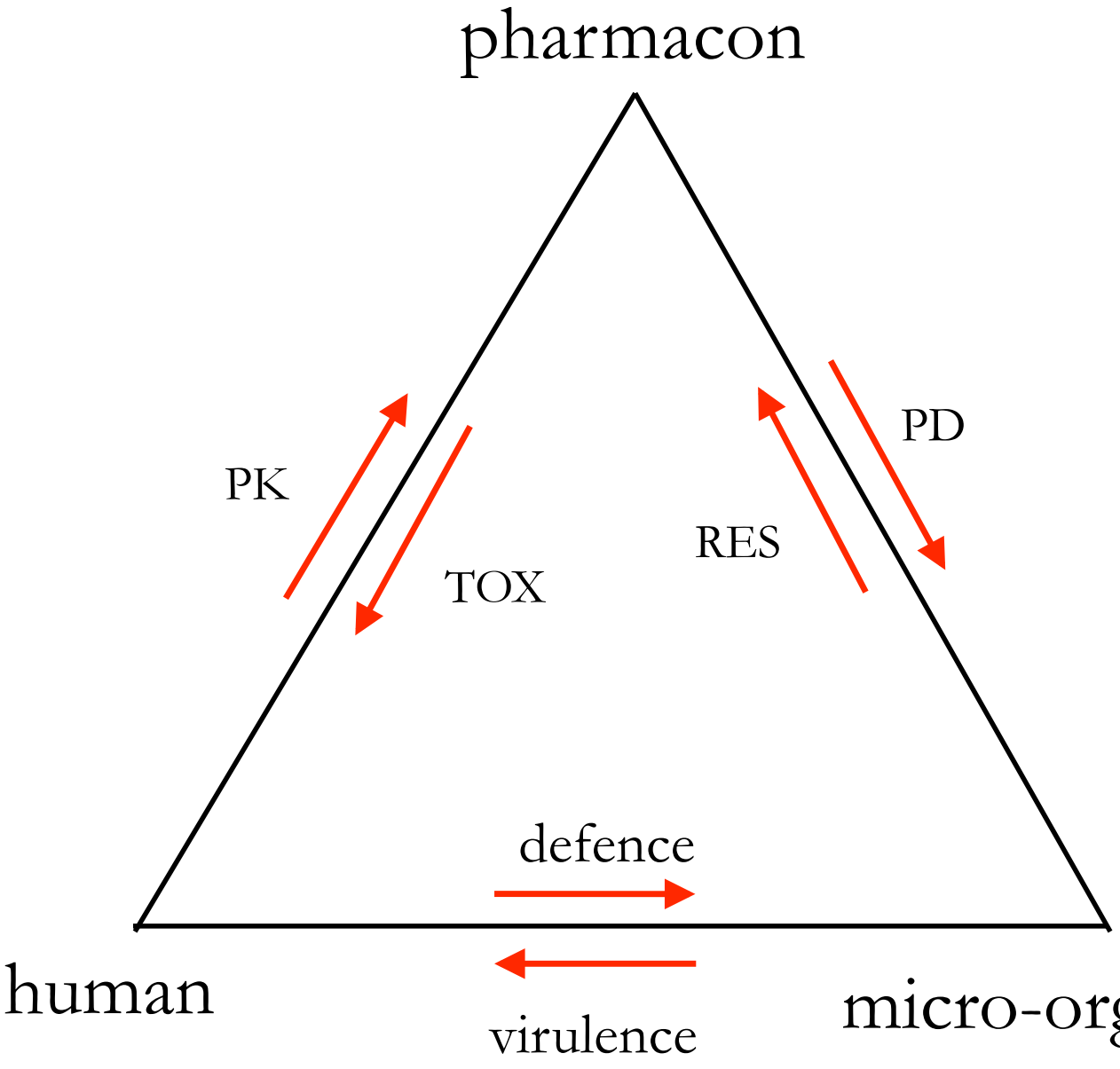
Therapeutic Drug Monitoring in Antifungal Therapy

Non-aspergillus and resistance



Other than Aspergillus species?

Resistant fungi / increased in vitro MIC?

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Therapeutic Drug Monitoring in Antifungal Therapy

Analytical procedures

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2009, p. 303–305 Vol. 53, No. 1
0066-4804/09/$08.00+0 doi:10.1128/AAC.00901-08

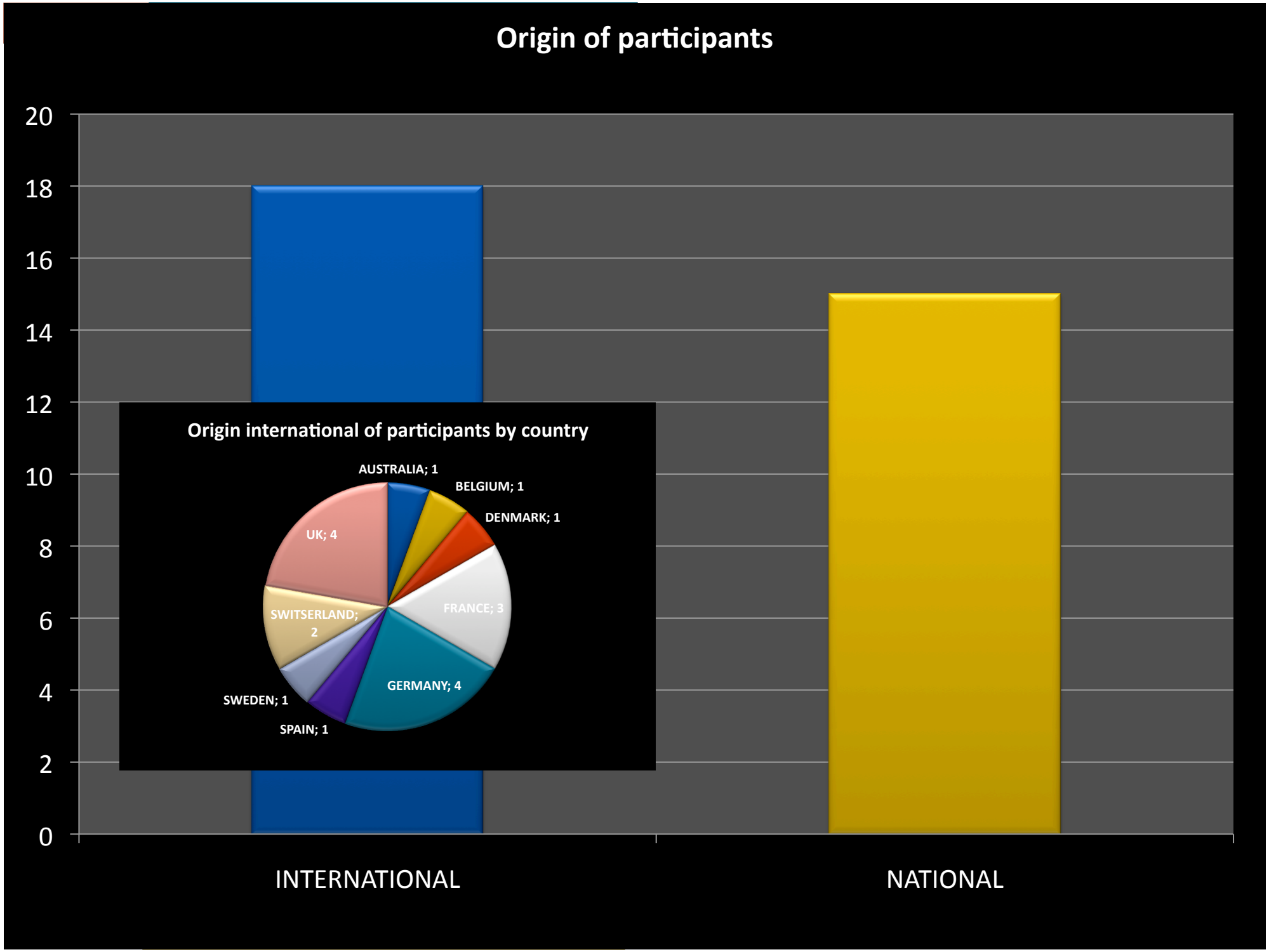
International Interlaboratory Proficiency Testing Program for Measurement of Azole Antifungal Plasma Concentrations▽

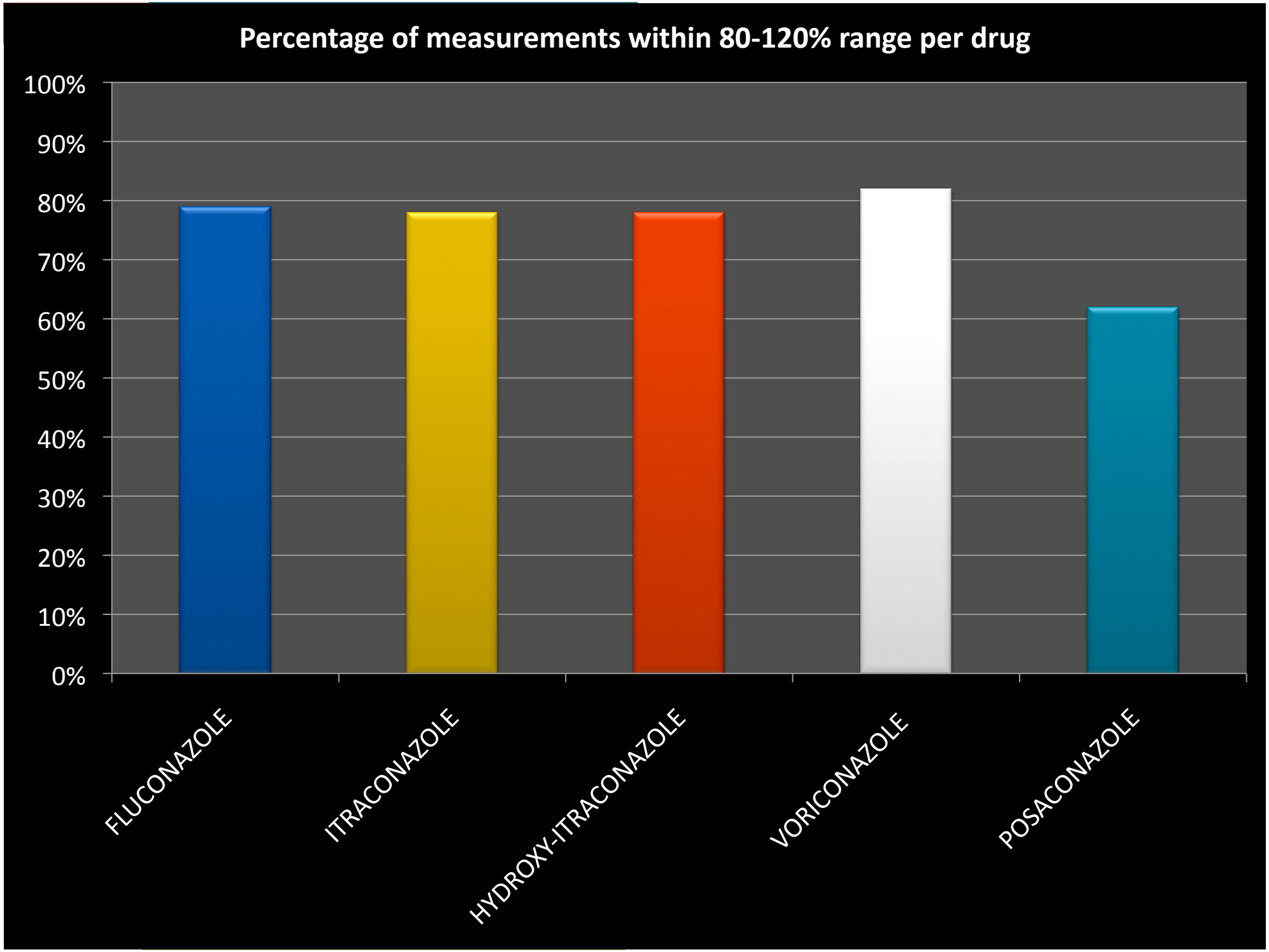
Roger J. M. Brüggemann,[1,2]* Daan J. Touw,[3,4] Rob E. Aarnoutse,[1,2] Paul E. Verweij,[2,5] and David M. Burger[1,2]

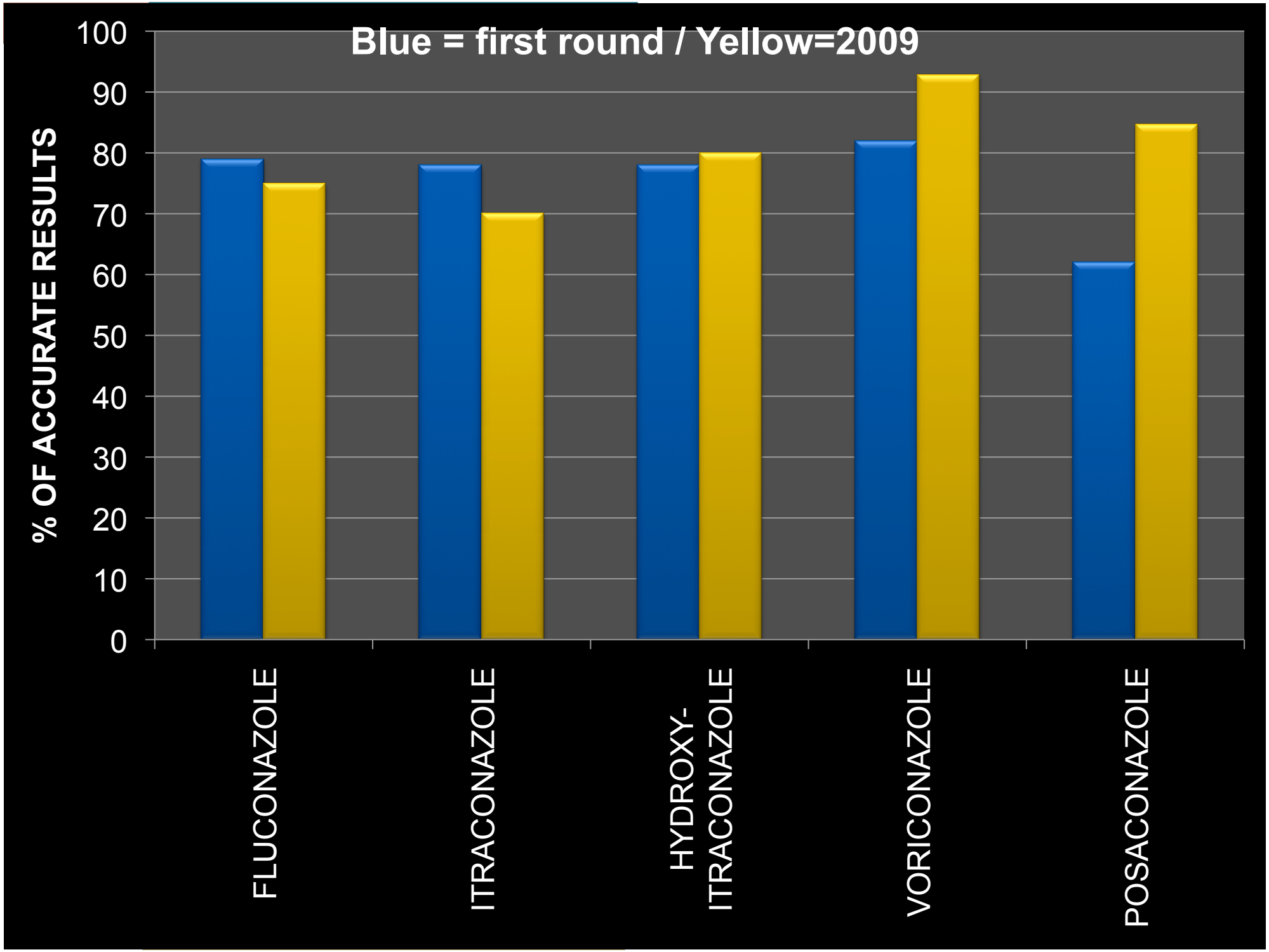
Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands[1]; Nijmegen University Centre for Infectious Diseases, Nijmegen, The Netherlands[2]; Department of Hospital Pharmacy, The Hague Central Hospital Pharmacy, The Hague, The Netherlands[3]; Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology (KKGT), The Hague, The Netherlands[4]; and Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands[5]

Received 8 July 2008/Returned for modification 14 August 2008/Accepted 4 November 2008

An international interlaboratory proficiency testing program for the measurement of antifungal drugs was initiated in 2007. This first round was limited to azole antifungals: fluconazole, itraconazole and hydroxyitraconazole, voriconazole, and posaconazole. The results demonstrate the need for and utility of an ongoing proficiency testing program to further improve the analytical methods for routine patient management and clinical research.


Origin of participants
20
18
16
14
12
10
8
6
4
2
0
INTERNATIONAL
NATIONAL
Origin international of participants by country
AUSTRALIA; 1
BELGIUM; 1
DENMARK; 1
FRANCE; 3
GERMANY; 4
SPAIN; 1
SWEDEN; 1
SWITSERLAND; 2
UK; 4


Percentage of measurements within 80-120% range per drug
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
FLUCONAZOLE
ITRACONAZOLE
HYDROXY-ITRACONAZOLE
VORICONAZOLE
POSACONAZOLE


Blue = first round / Yellow=2009
% OF ACCURATE RESULTS
100
90
80
70
60
50
40
30
20
10
0
FLUCONAZOLE
ITRACONAZOLE
HYDROXY-ITRACONAZOLE
VORICONAZOLE
POSACONAZOLE

Discussion

- No evidence for TDM for current antifungal drugs (randomized CT)
- Indications where TDM can be useful
  - Timing of sampling is pivotal in defining cut-off points for efficacy and toxicity
- Good analytical method
- Other issues
  - Timing of sampling (trough / peak / AUC)
  - At what time assess first samples
  - Repetitive sampling
  - Do cutt-off points still apply when using combination therapy
  - When to judge outcome with regards to plasma concentrations
- When to perform TDM
  - Special patient populations (children, disease, genotype)
  - Drug-drug or drug–food interactions
  - Others ……

Will the results of the drug assay make a significant difference in the clinical decision-making process and provide more information than sound clinical judgement alone?

Don’t treat the number, treat the patient