58ème journée de l'hôpital Claude-Bernard

Suivi Thérapeutique Pharmacologique (STP) des Antifongiques : utiles ?

Christophe PADOIN
Hôpital Avicenne, APHP, Bobigny

STP des antifongiques : utiles ?

Clinical Pharmacokinetics in the 21st Century

Does the Evidence Support Definitive Outcomes?

(i) Is there a good relationship between drug concentration and pharmacological response?
(ii) Does wide interpatient variation exist in drug absorption, distribution, metabolism or excretion?
(iii) Does the drug have a narrow therapeutic range?
(iv) Is the drug's pharmacological response not readily assessable?

Clinicians need to remember that the therapeutic range is no more than a confidence interval.

Regardless of whether we take the target concentration or the therapeutic range approach, we need to 'treat the patient and not the level'. This

Ensom, Clin Pharmacokinet, 1998

Antifongiques : caractéristiques PK/PD

	Activité *Aspergillus*	Activité *Candida*	Effet post-antifongique	Index PK/PD	Cible[a]
Azolés	Fongicide	Fongistatique	Long	AUC/CMI	25
Polyène (AmB)	Fongicide	Fongicide	Long	Cmax/CMI	4 (10)
Flucytosine	-	Fongistatique	Court	%T>CMI	25%
Echinocandines	Fongistatique	Fongicide	Long	Cmax/CMI AUC/CMI	3 (10) 25

a 50% de l'effet max dans des modèles animaux

Andes, Curr Opin Infect Dis, 2004
Andes, AAC, 2008
Sinnollareddy, UAA, 2012

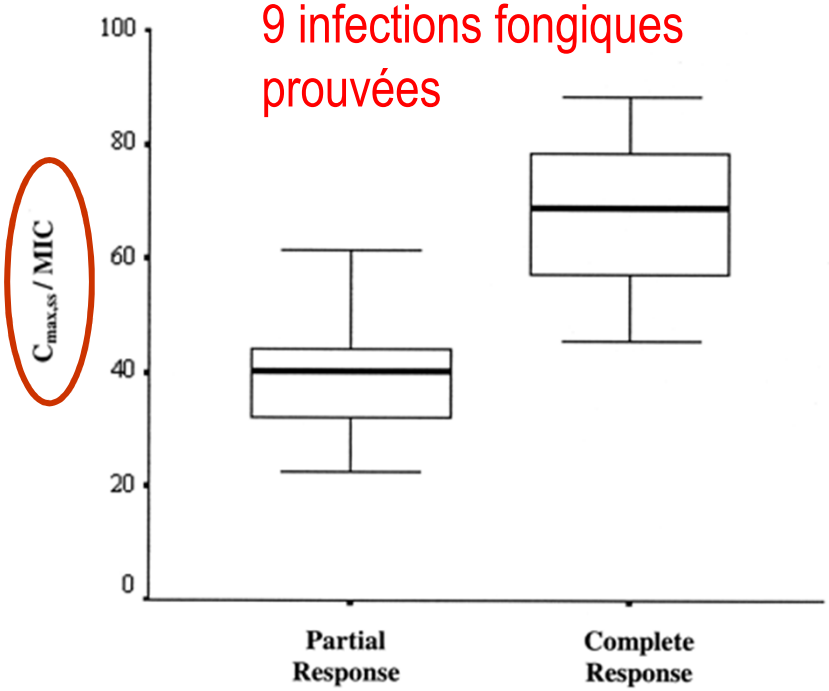
Relation PK/PD chez l'homme

Ambisome en pédiatrie 0,2 à 17 ans (n=39) - 0,8 à 5,9 mg/kg/j

TABLE 5. Microbiological, pharmacokinetic, and pharmacodynamic information for patients with proven fungal infection

ID[a]	Dose (mg/kg/day)	Pathogen (n = 11 cases)		$C_{max,ss}$/MIC	Efficacy[c]
		Fungi	MIC[b]		
3	5.4	*C. albicans*	0.50	88.4	C
		A. fumigatus	1.00	44.2	P
		A. niger	1.00	44.2	P
8	2.9	*A. fumigatus*	1.00	22.5	P
10b	3.1	*A. fumigatus*	1.00	36.5	P
20b	3.5	*C. krusei*	1.00	32.1	P
22	3.0	*Rhodotorula rubra*	0.25	68.8	C
32	4.8	*Scedosporium prolificans*	4.00	4.3	F
36a	4.9	*C. albicans*	0.25	45.6	C
38	5.3	*C. albicans*	0.50	61.6	P
40	4.1	*C. albicans*	0.25	68.8	C

9 infections fongiques prouvées

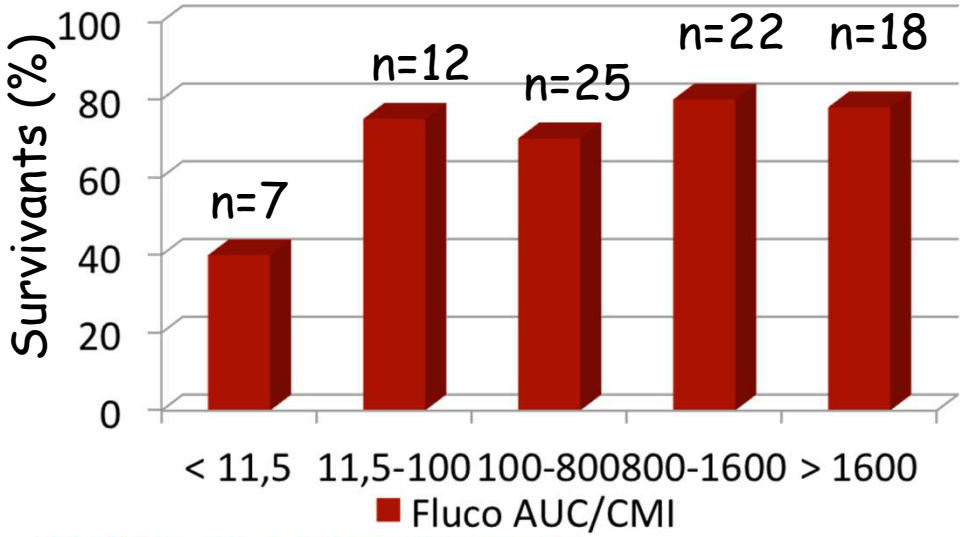


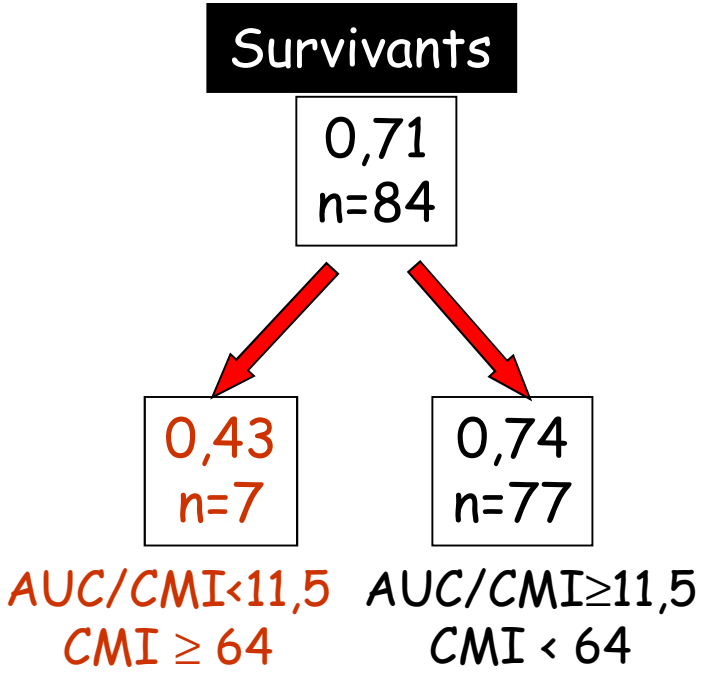
Hong, AAC, 2006

Relation PK/PD chez l'homme : Fluconazole

Etude prospective - Candidémies (n=96)
C. albicans (44%), *C. glabrata* (20%), *C. parapsilosis* (20%)

10% de souches Fluco-R (CMI ≥ 64 mg/L)
84 isolats dont 7 fluco-R, 24 décès

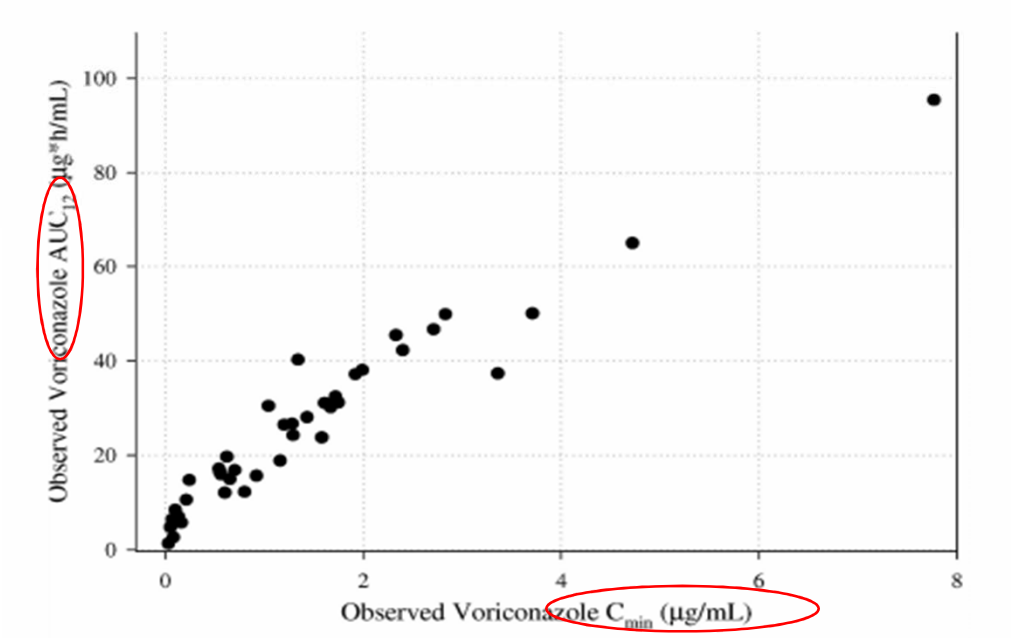




Baddley, AAC, 2008

« Subrogate »

Comparison of Pharmacokinetics and Safety of Voriconazole Intravenous-to-Oral Switch in Immunocompromised Adolescents and Healthy Adults▽



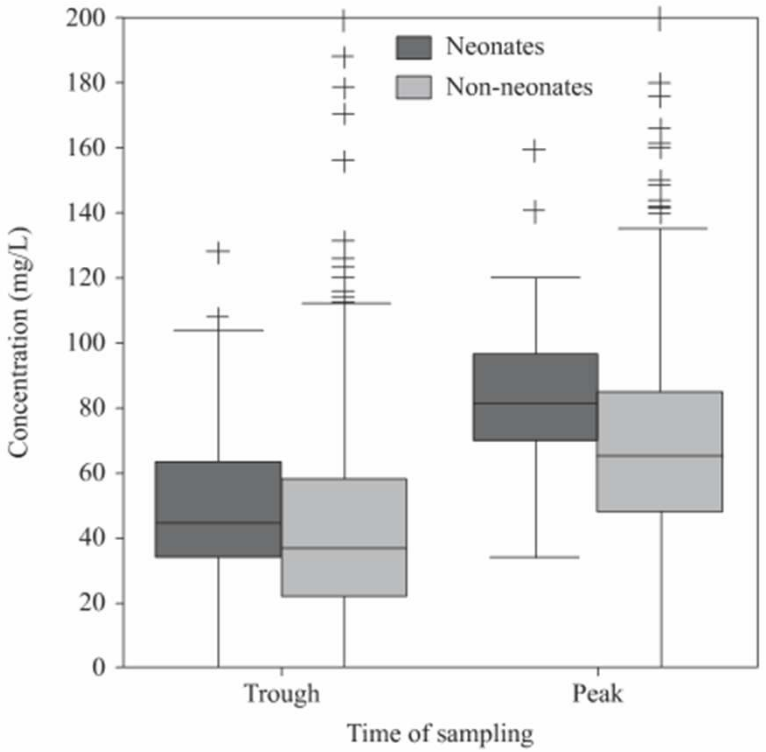
Driscoll, AAC, 2011

Les antifongiques

- Flucytosine
- Amphotéricine B : LAmB
- Echinocandines
- Azolés

Flucytosine

Flucytosine therapeutic monitoring: 15 years experience from the UK



- Pic > 100 mg/L : Toxique

(Vermes, Chemotherapy, 2000)

Conc cible (mg/L)	Résiduelle	Pic
Adultes	30-40	40-80
Néonat.	20-40	50-80

233 patients, 1071 prélèvements

Les concentrations sont :

- Faibles : 40%
- Élevées : 40%

Pasqualotto, JAC, 2007

Amphotéricine B : LAmB

- Index PK/PD : C_{max}/CMI
- Forme liposomale : organes cibles (foie, rate, poumon)

TABLE 1. Subject demographic characteristics by treatment group

Characteristic	Value for group	
	Liposomal amphotericin B	Amphotericin B deoxycholate
Dose (mg/kg)	2.0	0.6
Male/female	4/1	4/1
Mean age ± SD (yr)	49 ± 16	30 ± 5
Mean height ± SD (cm)	171 ± 10	175 ± 6
Mean weight ± SD (kg)	77 ± 9	79 ± 11

TABLE 2. Clinical pharmacokinetic parameters of amphotericin B after a 2-h infusion of liposomal amphotericin B (2 mg/kg) or amphotericin B deoxycholate (0.6 mg/kg)

Parameter (unit)[b]	Result for[a]:		P^c
	Liposomal amphotericin B (2 mg/kg)	Amphotericin B deoxycholate (0.6 mg/kg)	
C_{max} (μg/ml)	22.9 ± 10	1.43 ± 0.2	<0.01
C_{24h} (μg/ml)	1.9 ± 1.8	0.25 ± 0.03	NS
AUC_{0-24} (μg · h ml^{-1})	171 ± 126	13.9 ± 2.0	NS
$AUC_{0-\infty}$ (μg · h ml^{-1})	288 ± 209	46.6 ± 7.2	NS
$t_{1/2\alpha}$ (h)	0.56 ± 0.48	0.17 ± 0.14	NS
$t_{1/2\beta}$ (h)	6.0 ± 2.1	6.8 ± 1.6	NS
$t_{1/2\gamma}$ (h)	152 ± 116	127 ± 30	NS
V_1 (ml/kg)	50.1 ± 19	136 ± 60	<0.05
V (ml/kg)	1,628 ± 876	2,340 ± 202	NS
V_{ss} (ml/kg)	774 ± 550	1,807 ± 239	<0.01
CL (ml h^{-1} kg^{-1})	9.7 ± 5.4	13.1 ± 2.0	NS
CL_R (ml h^{-1} kg^{-1})	0.495 ± 0.25	4.1 ± 0.68	<0.01
CL_F (ml h^{-1} kg^{-1})	0.488 ± 0.46	5.4 ± 0.91[d]	<0.01
F_{urine}	0.053 ± 0.006	0.32 ± 0.06	<0.01
F_{feces}	0.047 ± 0.04	0.43 ± 0.11[d]	<0.01

Bekersky, AAC, 2002

Echinocandines : propriétés pharmacocinétiques

Table 1. Pharmacokinetic Properties of the Echinocandins[37-40]

Property	Caspofungin	Micafungin	Anidulafungin
Half-life (h)	β-phase of 9–11 h, followed by γ-phase of 40–50 h	13.4 ± 2.0 h[a]	40–50 h
Volume of distribution	not determined	0.39 L/kg	30–50 L
Protein binding (%)	97	>99	>99
Metabolism	hydrolysis *N*-acetylation spontaneous degradation	arylsulfatase COMT hydroxylation	spontaneous degradation
Excretion (%)	feces: 35 urine: 41 urine (unchanged): 1.4	feces: 71	feces: 30 feces (unchanged): <10 urine: <1

COMT = catechol-*O*-methyltransferase.
[a]Mean ± SD in otherwise healthy patients with *Candida* infections.

Sucher, Annals Pharmacother, 2011

Echinocandines

Phase II Dose Escalation Study of Caspofungin for Invasive Aspergillosis

Patients immunodéprimés, Aspergilloses Invasives prouvées/problables

TABLE 3. Estimated steady-state pharmacokinetic plasma pharmacokinetics

No. of patients in group	Dose (mg QD)	Geometric mean (geometric coefficient of variation)[a]			Favorable (CR/PR)	
		AUC (mg/liter/h)	C_{MAX} (mg/liter)	C_{MIN} (mg/liter)		
44	70	175 (32%)	14.2 (28%)	4.1 (58%)	25 (1/24)	56%
9	100	250 (32%)	20.3 (28%)	5.9 (58%)	4 (0/4)	44%
8	150	375 (32%)	30.4 (28%)	8.9 (58%)	3 (0/3)	33%
7	200	500 (32%)	40.6 (28%)	11.8 (58%)	6 (1/5)	80%
20					12 (0/12)	60%

Cornely, AAC, 2011

Echinocandines

Using pharmacokinetics and pharmacodynamics to optimise dosing of antifungal agents in critically ill patients: a systematic review

Table 2 Comparison of exposures achieved in this study with other studies (mean (%CV))

Parameter	Anidulafungin			Caspofungin			Fluconazole		
	This study (ICU patients)	Liu et al. [25] (ICU patients)	Liu et al. [25] (healthy volunteers)	This study (ICU patients)	Wurthwein et al. [26] (general patients)	Stone et al. [27][a] (healthy volunteers)	This study[b] (ICU patients)	Buijk et al. [23][a] (surgical patients)	Sobue et al. [24][b] (Healthy volunteers, 800 mg)
AUC_{0-24}	55 (28)	93.0 (41)	105.0 (22)	52.0 (53)	170.0 (34)	97.0 (87–109)	359 (259)	409 (336–482)	608 (118)
C_{max}	3.9 (29)	7.7 (56)	7.0 (22)	3.9 (55)	13.8 (31)	12.1 (11–13)	20 (14)	25 (22–28)	34 (6)
C_{min}	1.8 (30)	3.0 (44)	3.1 (25)	1.5 (57)	4.2 (2.56)	1.4 (1.1–1.8)	14 (11)	15 (10–20)	20 (NR)

Sinnollareddy, Int J Antimicrob Agents , 2012

Echinocandines

Pharmacokinetics of caspofungin in ICU patients

Clinical characteristics	
Post-abdominal surgery, *n* (%)	8 (38.1)
Kidney function/renal replacement therapy, *n* (%)	
MDRD >50 mL/min/1.73 m^2	7 (33.3)
MDRD 31–50 mL/min/1.73 m^2	5 (23.8)
MDRD 10–30 mL/min/1.73 m^2	4 (19.0)
CVVH	4 (19.0)
intermittent haemodialysis	1 (4.8)
Hepatic dysfunction, Child–Pugh B, *n* (%)	21 (100)
SOFA score, mean (95% CI)	8.7 (6.5–10.9
APACHE II score	
≤20, *n* (%)	7 (33.3)
>20, *n* (%)	14 (66.7)
median (range)	25 (13–47)
Neutropenia, *n* (%)	0 (0)
Hypoalbuminaemia, *n* (%)	
25–34 g/L	4 (19.0)
15–24 g/L	14 (66.7)
<15 g/L	3 (14.3)

	PK curve day 3 ($n=21$)	PK curve day 7 ($n=13$)
AUC_{0-24} (mg·h/L)	88.7 (72.24–97.54)	107.2 (90.39–125.28)
CL (L/h)	0.57 (0.54–0.77)	0.54 (0.44–0.60)
V (L)	7.72 (6.12–9.01)	7.03 (5.51–7.73)
C_{min} (mg/L)	2.15 (1.40–2.48)	2.55 (1.82–3.08)
C_{max} (mg/L)	7.51 (6.05–8.17)	8.65 (7.16–9.34)
$t_{1/2}$ (h)	15.67 (14.44–18.94)	18.49 (12.27–22.05)

Muilwijk, JAC, 2014

Echinocandines

Low but Sufficient Anidulafungin Exposure in Critically Ill Patients

200mg DC puis 100 mg/j

AUC = 69,8 ± 24,1 mg.h/L

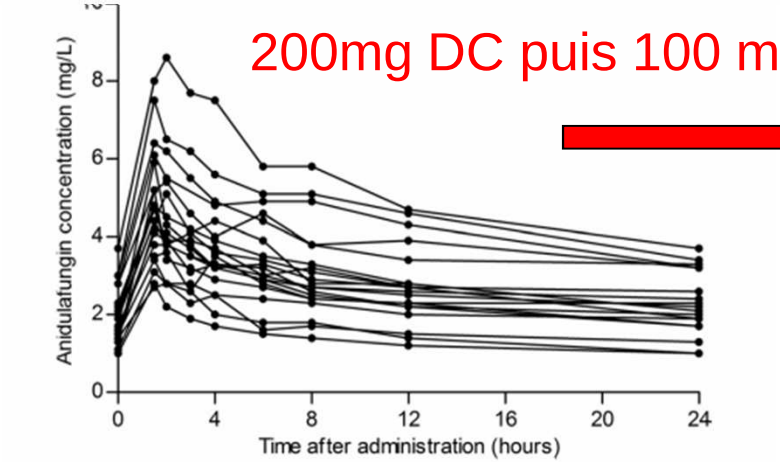


FIG 1 Concentration-time curves of the 20 critically ill patients receiving 100 mg anidulafungin once daily.

Pharmacokinetic parameter[a]	Arithmetic mean (%CV)[b] for: ICU patients (n = 20)	General patient population (n = 262)[c]	Healthy subjects (n = 35)[d]
AUC_{0-24} (mg · h/liter)	92.7 (41)	110.3 (32.5)	105.9 (21.6)

Lui, AAC, 2013

TABLE 3 Multiple linear regression analysis for anidulafungin exposure

Variable	β (95% CI)[a]	*P* value
Total body water	−2.566 (−4,192 to −0.941)	0.004
Total bilirubin	0.232 (0.036 to 0.428)	0.023

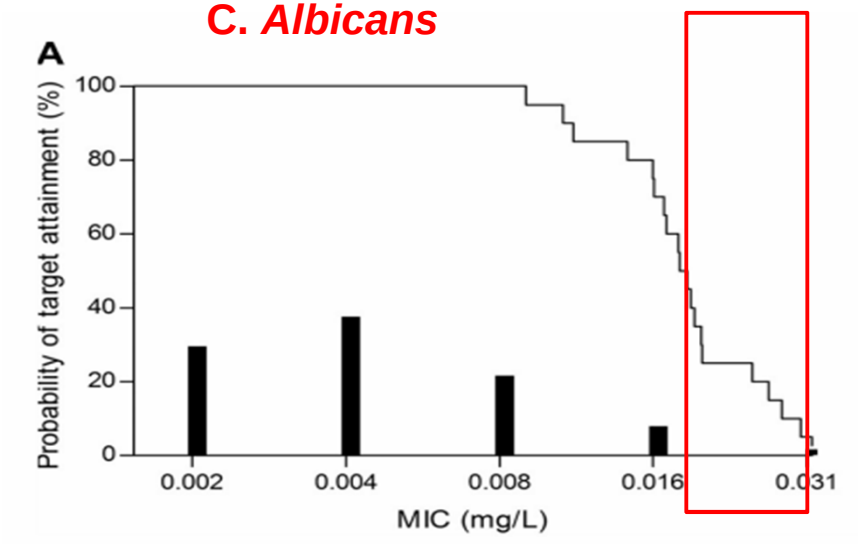
van Wanrooy, AAC, 2014

Echinocandines

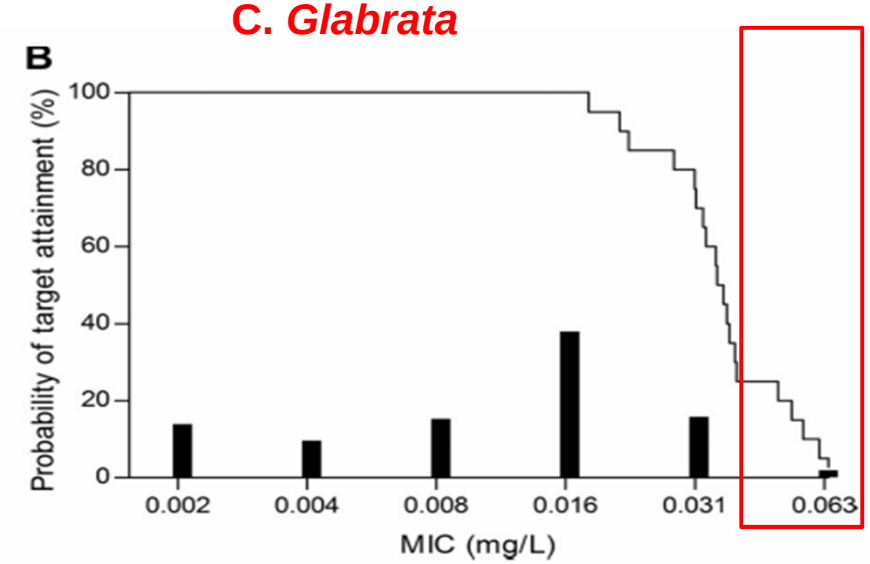
Limited-Sampling Strategies for Anidulafungin in Critically Ill Patients

AUC/CMI cible 110

C. *Albicans*



C. *Glabrata*



van Wanrooy, AAC, 2014-2015

Azolés : propriétés pharmacocinétiques

	Fluconazole	Itraconazole	Voriconazole	Isavuconazole	Posaconazole
Métabolisme	10 à 25 %	**95 %** (P450; OH-itraco)	**95 %** (P450)	**95%** (P450)	14 % (UGT)
Fixation Prot	10%	99%	60%	98%	99%
% élimination rénale	**70 à 90**	< 5	< 5	**< 1**	**biliaire**
$t_{1/2}$ (h)	30 - 35	34 - 72	6	56-130	25 - 30
Vd (L/Kg)	0,7	10	4,6	6	6,5
Diffusion SNC	> 60%	< 10%	> 50%	Faible LCR, forte cerveau	Faible
Délai équilibration (j)	6 - 10	14 - 15	1 - 6	> 10	5
Dose de charge	Oui	Oui	Oui	Oui	Non/Oui
Formes dispo	Orales / IV	Orales	Orales /IV	Orale /IV	Orales/IV

Azolés : relation concentration/efficacité

Itraconazole : prophylaxie chez le patient neutropénique

Table 3. Comparison of cofactors for invasive fungal infections, itraconazole trough concentrations and the percentage of days during antifungal prophylaxis with trough concentrations above cut-off values

Etude prospéctive 1994 – 1998

	Patients with invasive fungal infections ($n=20$)	Courses without invasive fungal infections ($n=287$)[a]	P
Cofactors for occurrence of invasive fungal infections (n)			
Relapsed or refractory disease (n)	11 (55%)	70 (24.5%)	0.006
Chemotherapy with high-dose cytarabine (n)	11 (55%)	119 (41.5%)	0.251
Itraconazole concentrations (median, interquartile range)			
End of week 1 (ng ml^{-1})	490 (350–1030)	640 (340–1100)	0.281
End of week 2 (ng ml^{-1})	660 (460–1100)	870 (500–1370)	0.109
End of week 3 (ng ml^{-1})	650 (440–1800)	1000 (570–1510)	0.405
Efficacy of antifungal prophylaxis (percentage of days above cut-off value)			
% of days with $\geq$ 250 ng ml^{-1} itraconazole	78% (33–100%)	100% (58–100%)	0.161
% of days with $\geq$ 500 ng ml^{-1} itraconazole	48% (0–100%)	100% (35–100%)	0.039

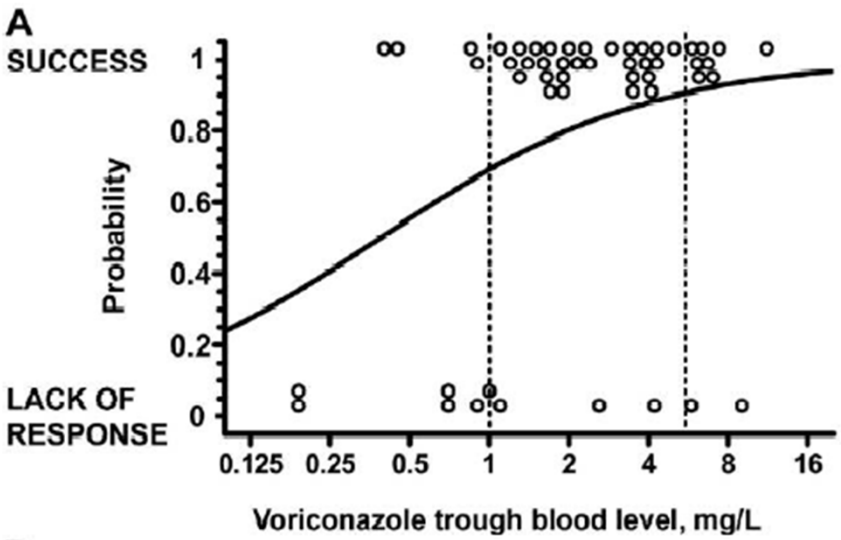
[a]287 courses of antifungal prophylaxis with itraconazole in 150 neutropenic patients with haematological malignancies.

Glasmacher, Mycoses, 1999

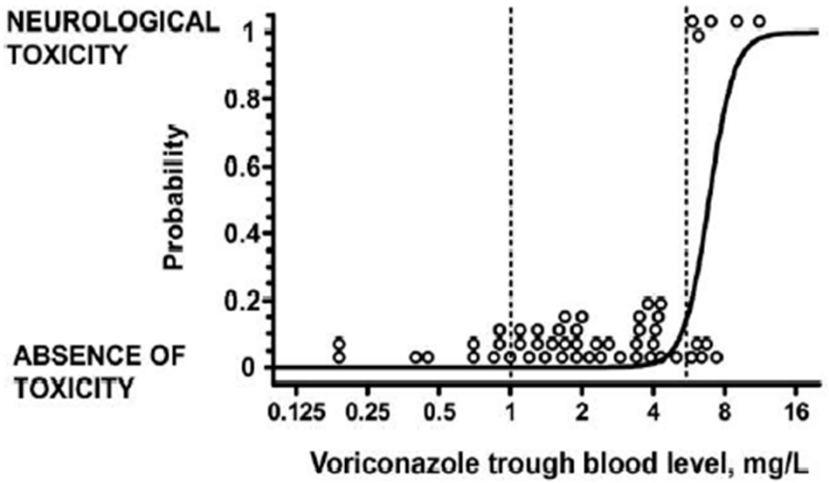
Azolés : relation concentration/efficacité

Suivi thérapeutique du voriconazole

Relation conc/efficacité



Relation conc/toxicité

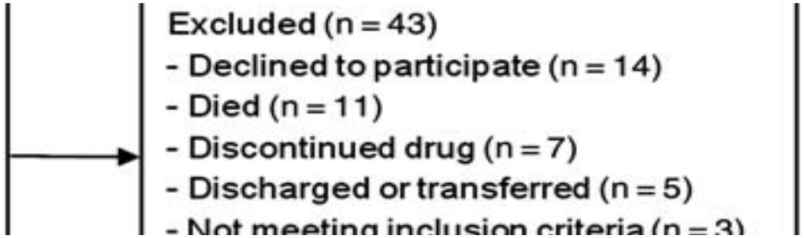


Zone thérapeutique : C_{min} = 1 - 5,5 mg/L

Pascual, CID, 2008

Azolés : relation concentration/efficacité

Voriconazole : Etude prospective, randomisée (n=110)

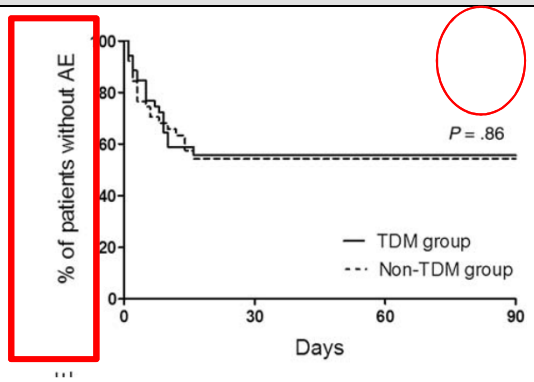


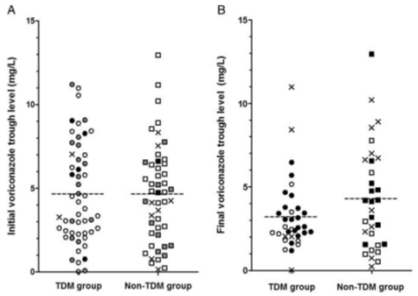
	TDM (n = 55)	Non-TDM (n = 53)	Total (N = 108)
Underlying condition			
Hematologic disease	44 (80)	39 (74)	83 (77)
Steroid use	4 (7)	6 (11)	10 (9)
Others[a]	7 (13)	8 (15)	15 (14)
Invasive fungal infection			
Proven	9 (16)	10 (19)	19 (18)
Probable	29 (53)	33 (62)	62 (57)
Possible	9 (16)	4 (8)	13 (12)
Empirical use	8 (15)	6 (11)	14 (13)
Fungal organisms[e]			
Aspergillus	37 (97)	39 (91)	76 (94)
Candida	1 (3)	3 (7)	4 (5)
Phialophora	…	1 (1)	1 (1)
CYP 2C19 genotype[b]			
Homozygous extensive metabolizer	23 (44)	21 (42)	44 (43)
Heterozygous extensive metabolizer	20 (39)	24 (48)	44 (43)
Poor metabolizer	9 (17)	5 (10)	14 (14)
Heterozygous ultra-rapid metabolizer	0	0	0
Initial voriconazole trough level, mg/L	4.7 ± 3.0	4.7 ± 3.0	4.7 ± 3.0
>5.5 mg/L	21 (40)	18 (37)	39 (38)
<1.0 mg/L	5 (9)	6 (12)	11 (11)
Duration of voriconazole use, days	41 ± 31	37 ± 30	39 ± 30

Park, CID, 2012

Azolés : relation concentration/efficacité

	TDM (n = 37)	Non-TDM (n = 34)	*P* Value
Treatment success	30 (81)	20 (59)	.04
Complete response	21 (57)	13 (38)	.12
Partial response	9 (24)	7 (21)	.71
Stable response	1 (3)	2 (6)	.60
Treatment failure	6 (16)	12 (35)	.07





Park, CID, 2012

Azolés : relation concentration/efficacité

Posaconazole : Aspergilloses invasives réfractaires ou patients intolérants

Posologie : 800 mg/j, 200mg x 4/j hopsi Puis 400mg x 2/j

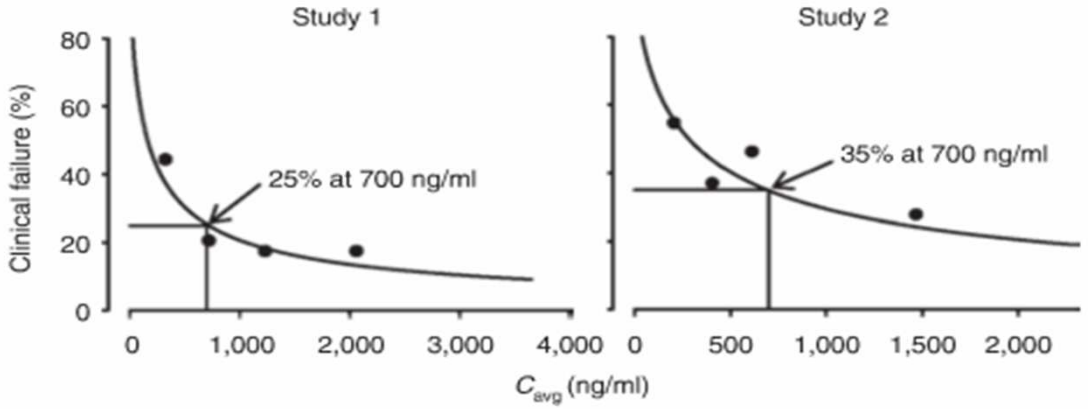
		Plasma C_{max}		Plasma C_{avg}		
Quartile	No. of subjects[a]	Mean ng/mL	CV, %	Mean ng/mL	CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

Walsh, CID, 2007

Azolés : relation concentration/efficacité

Posaconazole : Prophylaxie

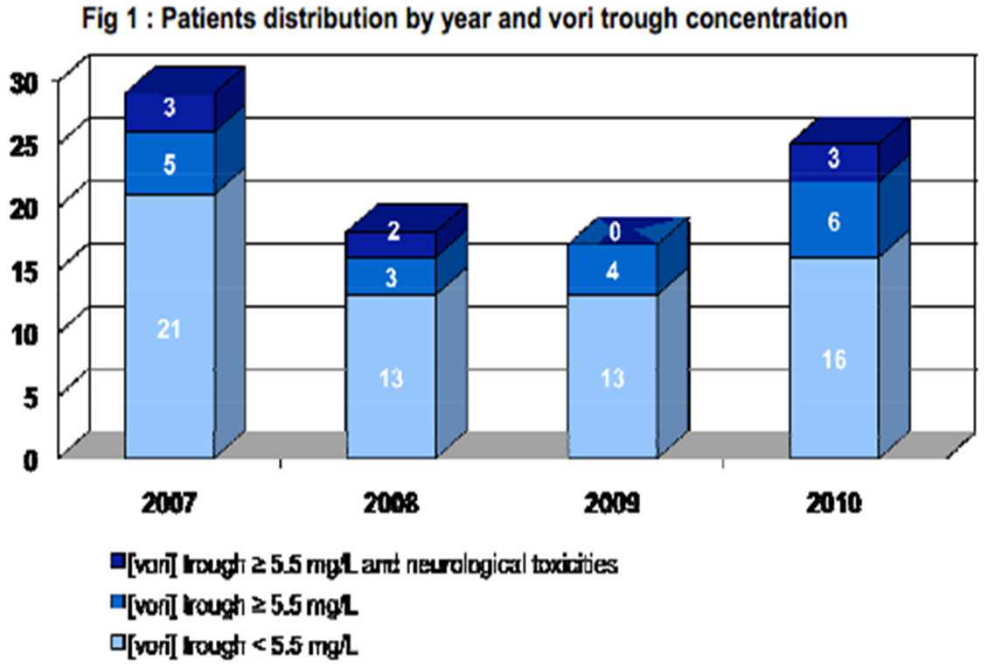
	Study 1 ($N = 252$)[a]		Study 2 ($N = 215$)[a]	
Quartile	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate
1st Q	21.5–557 (289)	44% (28/63[c])	89.65–322 (206)	55% (29/53)
2nd Q	557–915 (736)	21% (13/63)	322–490 (406)	37% (20/54)
3rd Q	915–1,563 (1,239)	18% (11/63)	490–733.5 (612)	46% (25/54)
4th Q	1,563–3,650 (2,607)	18% (11/63)	733.5–2,200 (1,467)	28% (15/54)



Jang, CPT, 2010

Azolés : relation concentration/toxicité

Toxicité neurologique du voriconazole



- 8/ 25 developed neurotoxic symptoms (32%)
- Means ± SD and range vori trough concentrations are :

2.4 ± 2.1 mg/L [0.2 - 12.6 mg/L]
80 patients

7.9 ± 2.2 mg/L [5.5 - 12.6 mg/L]
when occurs neurotoxicity

- In 2010, no patient with trough concentration < to 5.5 mg/L (n=16) developed neurotoxicity

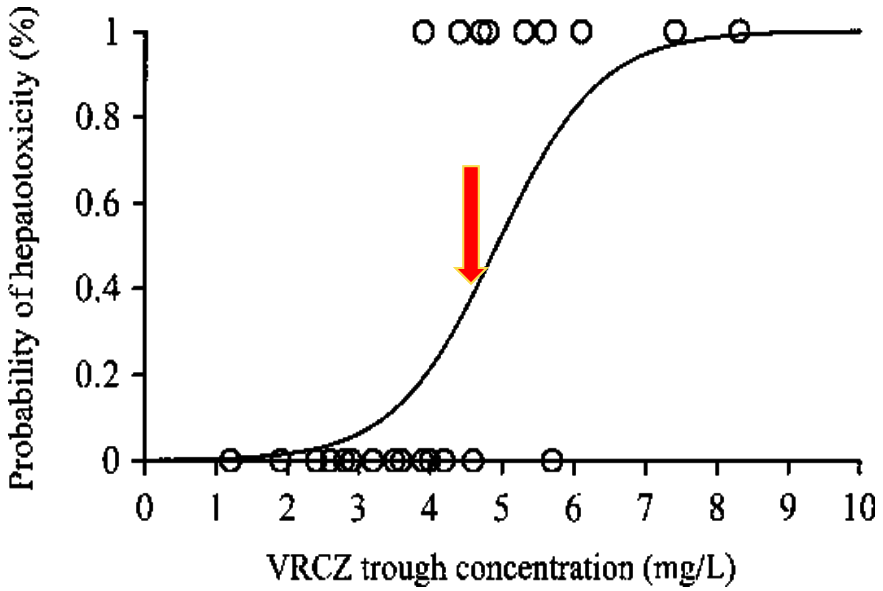
1.8 ± 1.4mg/L [0.2 – 4.5 mg/L]
without neurotoxicity

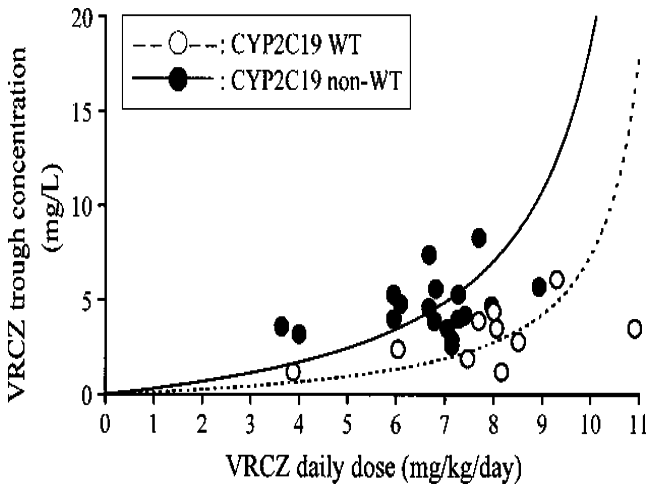
Padoin, ICAAC, 2011

Azolés : relation concentration/toxicité

Toxicité hépatique du voriconazole

n=29 patients japonais
CYP2C19 : 10 wild-type ; 19 non wild-type





Matsumoto, Int J Antimicrob Agents, 2009

Azolés : variabilité interindividuelle

Voriconazole chez des patients allogreffés de moelle

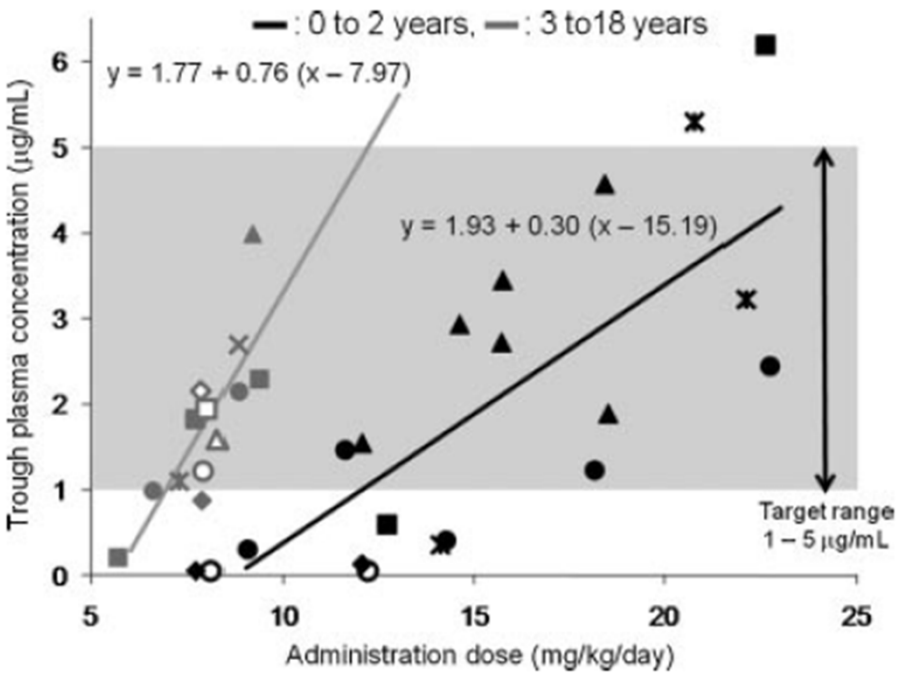
	All	Initial	200 mg BID	300 mg BID
N	41	25	34	7
Range	0,2 - 6,8	0,2 - 6,8	0,2 - 6,8	0,6 - 6,6
Median	1,6	1,2	1,1	2,1
Mean	2,1	1,9	2,0	2,5
SD	1,8	1,6	1,8	1,9
< 1 mg/L	15 (37%)	10 (40%)	**14 (41%)**	**1 (14%)**

Dose : ↗ si conc < 0,5 mg/L ; ↘ si conc > 7 mg/L

Trifilio, Bone Marrow Transplant, 2005

Azolés : variabilité interindividuelle

Voriconazole : prophylaxie primaire en pédiatrie



n=16 (6 < à 3 ans), 7 LAL, 3 LAM
33 prélèvements

<u>Posologie recommandée</u> :

- 5 mL x 2/j soit 200 mg x 2/j

(Karlsson, AAC, 2009)

- 7 mg/kg x 2/j en IV

Modifications RCP :
Enfants 2 -12 ans
DC : 9 mg/kg x 2
DE : 8 mg/kg x 2

Shima, Pediatr Blood Cancer, 2010

Azolés : Facteurs limitant la biodisponibilité

Posaconazole suspension : PK chez patient de réanimation

Table 1: Information on study drug administration and plasma concentration.

	Regimen	
	400mg twice daily	200mg four times daily
C_{max}	113 ng/ml (74-126)	69 ng/ml (39-105)
T_{max} (first dose)	9 h	5 h
Steady state concentration (C_{min}) Day 4 Day 7	187 ng/ml (86-390) 167 ng/ml (104-340)	115 ng/ml (84-157)
First dose s (AUC_{0-t})		
Steady stat		
Died bef		
Drug sto / patient		
Poor abs		
>250ng/ml 7)		

Table 2: Summary of patient characteristics.

Regimen	400mg twice daily	200mg four times daily
Total patients	13	14
Male	8	11
Age	56.8 +/- 17.3 (17-89)	44.8 +/- 22.7 (31-83)
APACHE III	74.62 +/- 38.69 (22-161)	72.62 +/- 35.32 (19-129)
Indication: prophylaxis	11	11
Indication: treatment	2	3
Use of PPI	All	All
Use of phenytoin	2	5
Median pH of gastric aspirates	7	7

Ray, ICAAC, 20

Azolés : Facteurs limitant la biodisponibilité

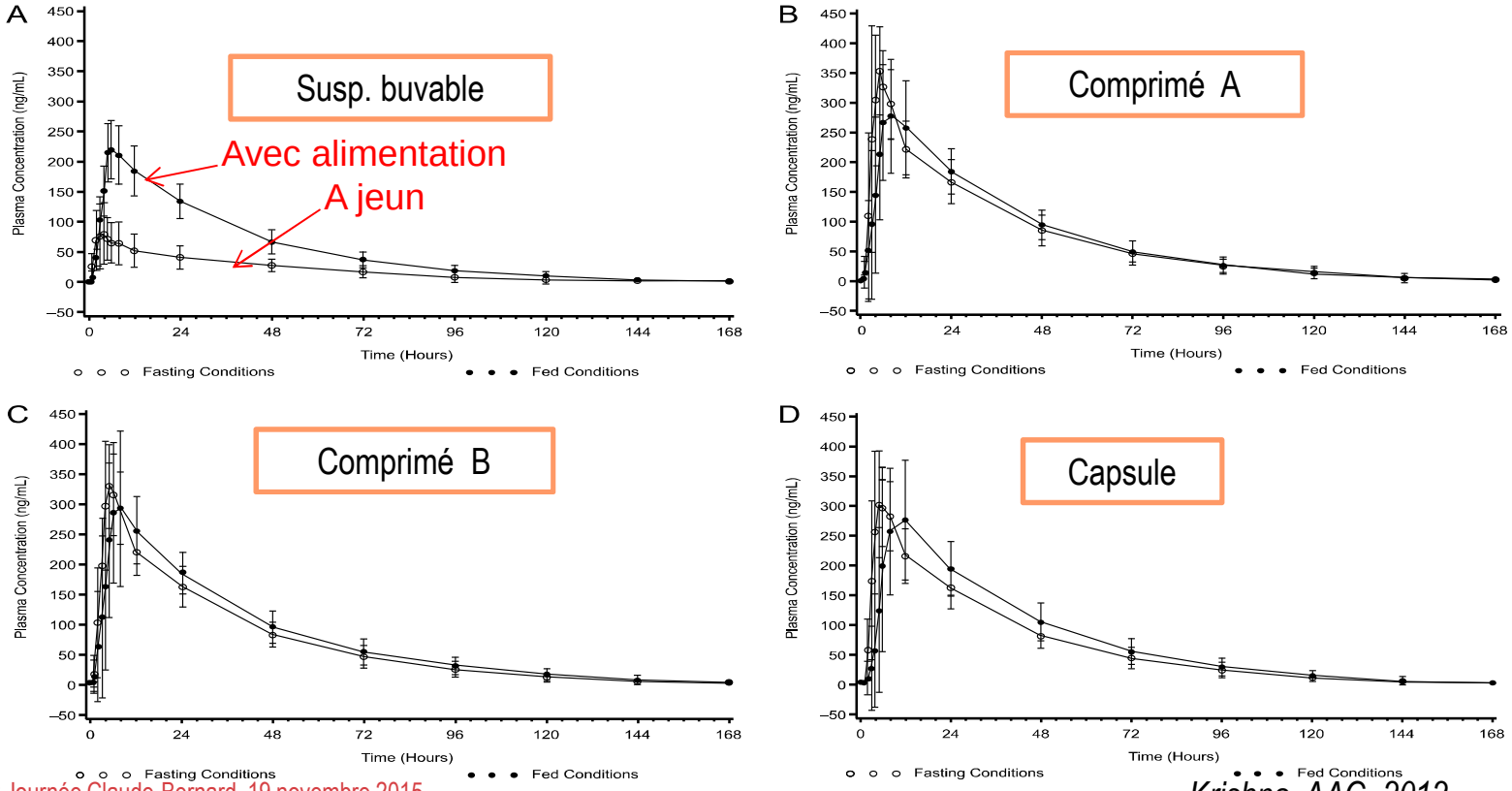
Posaconazole comprimé : Impact des modificateurs du pH et de la mobilité gastrique

Treatment	Arithmetic mean (%CV)				
	C_{max}, ng/ml	$AUC_{0\text{-}inf}$, h·ng/ml	$AUC_{0\text{-}last}$, h·ng/ml	T_{max},[a] h	$t_{½}$, h
POS alone	1,090 (43)	42,406 (49)	40,967 (47)	4 (2–8)	27.3 (37)
POS + antacid	1,112 (36)	42,468 (39)	41,247 (39)	4.8 (3–12)	27.7 (29)
POS + ranitidine	1,094 (37)	39,287 (37)	38,046 (35)	4 (3–5)	26.9 (35)
POS + esomeprazole	1,104 (35)	41,574 (43)	40,083 (40)	4.5 (3–24)	28.0 (30)
POS + metoclopramide	935 (44)	38,513 (43)	36,975 (40)	4 (2–6)	29.0 (38)

Kraft, AAC, 2014

Azolés : Facteurs limitant la biodisponibilité

Posaconazole comprimé : Impact de l'alimentation



Krishna, AAC, 2012

Azolés : Facteurs limitant la biodisponibilité

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

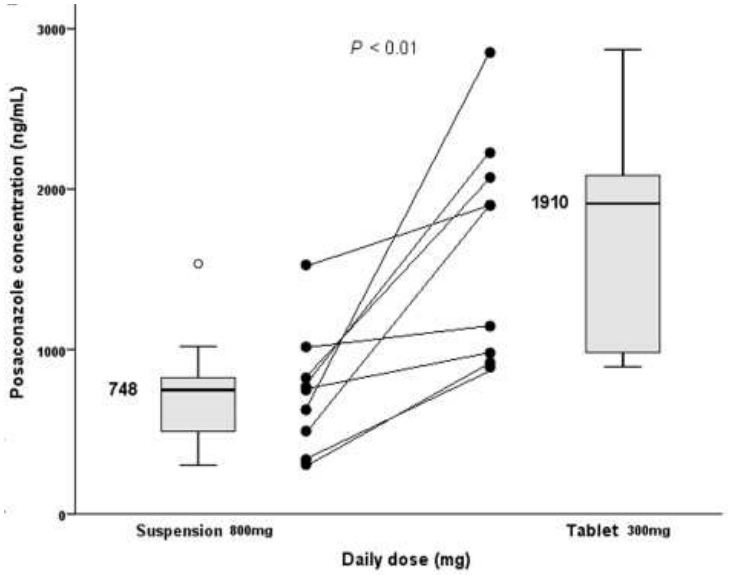
DONG-A UNIVERSITY HOSPITAL

Switching from Posaconazole Suspension to Tablets Increased Serum Levels in Leukemia Patients without Clinically Relevant Hepatotoxicity

Dong Sik Jung, MD[1,3], Frank P. Tverdek, PharmD[2], and Dimitrios P. Kontoyiannis, MD, ScD[1]
Department of [1]Infectious Diseases, Infection Control, and Employee Health and [2]Pharmacy Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Dong-A University Hospital, Busan, Korea

Table 1. Baseline Demographic and Clinical Characteristics of the 12 leukemia Patients Switched from Posaconazole Suspension to Delayed-Release Tablets.

Variable	N (%)
Median age, years (range)	58 (25-73)
Male sex	8 (67)
Body weight, Kg	
Mean (SD)	74.2 (21.7)
Median (range)	72.4 (51-128)
Height, cm	
Median (range)	174.5 (159-193)
Underlying hematologic malignancy	
Acute myeloid leukemia	8 (67)
Acute lymphoblastic leukemia	2 (17)
Chronic myeloid leukemia	1 (8)
Chronic lymphocytic leukemia	1 (8)
HSCT	5 (42)
Underlying condition at the time of sampling [a]	
ANC < 500/μL	6 (50)
Graft versus Host Disease	3 (25)
[illegible] [b]	1 (8)
[illegible] [b]	4 (33)
Concomitant PPI or H2 antagonist	6 (50)
Concomitant tacrolimus	5 (42)
GFR < 50 mL/min/1.73m^2	3 (25)
Indication for posaconazole	
Prophylaxis	3 (25)
Presumed or documented fungal infection (species identified)[c]	9 (75)

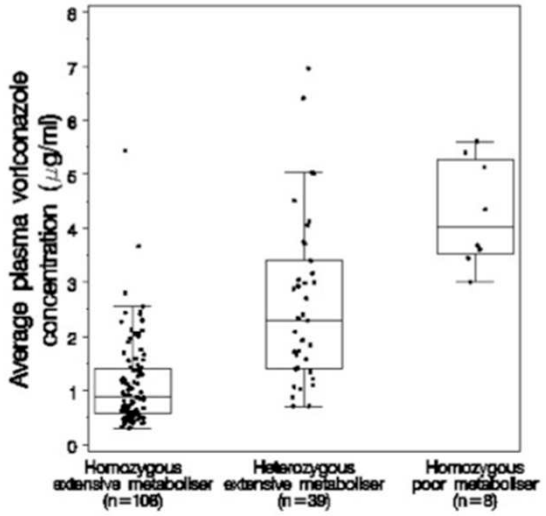


Jung, AAC, 2014

Azolés : Facteurs modifiant le métabolisme

Voriconazole : Polymorphisme génétique CYP2C19

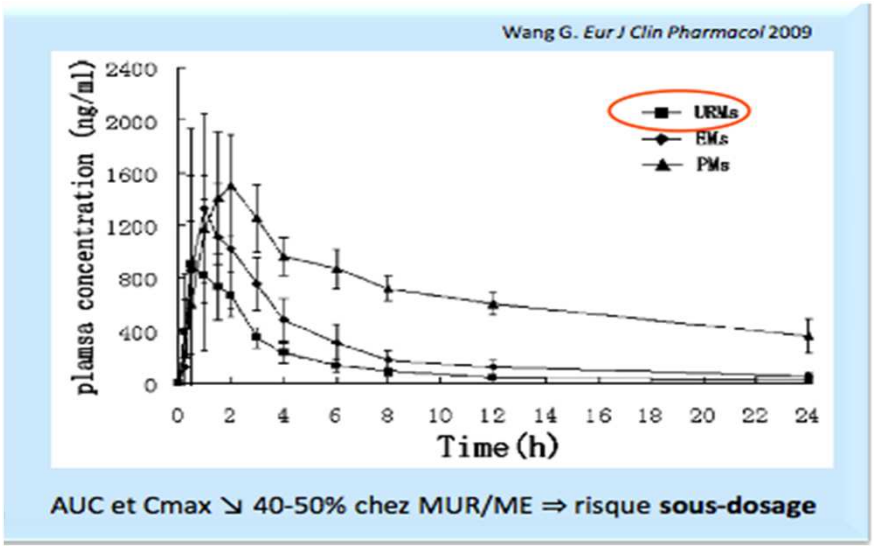
FDA Advisor Committee 2001



CYP2C19*2
CYP2C19*3

Métab. limités
- 20% asiatiques
- 3 à 5 % caucasiens

Wang, Eur J Clin Pharmacol, 2009



CYP2C19*17

Métab.ultra-rapides
- 20% caucasiens
- 1 à 4 % asiatiques

STP des antifongiques : utiles ?

- **Flucytosine : OUI**
- **Amphotéricine B (LAmB) : NON**
- **Echinocandines : NON mais**
- **Azolés : OUI**

→ **Rendu résultat + proposition posologique à 48h**

STP des antifongiques : utiles

- **Flucytosine**
  - **Pic < 100 mg/L (Toxicité)**
  - **Zone thérapeutique : C_{res} 20 à 50 mg/L**
- **Fluconazole**
  - **Neurotoxicité : OUI (C_{res} > 80 mg/L)**
- **Voriconazole**
  - **Zone thérapeutique : C_{res} 1 à 5,5 mg/L (cible 2 mg/L)**
    - **Neurotoxicité : OUI (C_{res} > 5,5 mg/L)**
    - **Toxicité cutanée : NON**
    - **Hépatotoxicité : NON**
- **Itraconazole**
  - **Curatif : C_{res} > 1 mg/L**
  - **Prophylaxie : Cres > 0,5 mg/L**
- **Posaconazole**
  - **Curatif : C_{res} > 1 mg/L**
  - **Prophylaxie : C_{res} > 0,7 mg/L (suspension vs comprimé)**

STP des antifongiques : ECIL-6

Triazole Antifungal Therapeutic Drug Monitoring

Russell Lewis (Chair, Italy)
Roger Brüggemann (Netherlands)
Christophe Padoin (France)
Johan Maertens (Belgium)
Oscar Marchetti (Switzerland)
Andreas Groll (Germany)
Elizabeth Johnson (UK)
Maiken Arendrup (Denmark)

Merci