



Pharmakokinetik von Antimykotika in spezifischen Kompartimenten

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PK von Antimykotika in spezifischen Kompartimenten

- Gelangen die Antimykotika in das Kompartiment der Pilzinfektion?
- Erreichen sie in den Zielkompartimenten wirksame Konzentrationen?
- Welche Konsequenzen ergeben sich für die Therapie verschiedener Mykosen?
- Wirken die Antimykotika am Ort einer Pilzinfektion?
- Beeinflusst das Kompartiment die Pharmakodynamik der Antimykotika?



Relevante Kompartimente

Gewebe

- Gehirn
- Auge
- Lunge
- Leber, GI-Trakt, Pankreas
- Milz
- Myokard
- Skelettmuskel, Haut
- Knochen

Körperflüssigkeiten

- Blut/Plasma/Serum
- Liquor cerebrospinalis
- Alveoläre „Epithelial Lining Fluid ELF“
- Pleuraerguss
- Perikarderguss
- Aszites
- Galle
- Harn
- Diverse Sekrete

Antimykotika am Markt

Amphotericin B AMB	AMB Deoxychololat liposomales AMB kolloidales AMB AMB Lipidkomplex
„Antimetabolite“	5-Flucytosin
Triazole	Fluconazol Itraconazol Voriconazol Posaconazol Isavuconazol
Echinocandine	Caspofungin Anidulafungin Micafungin

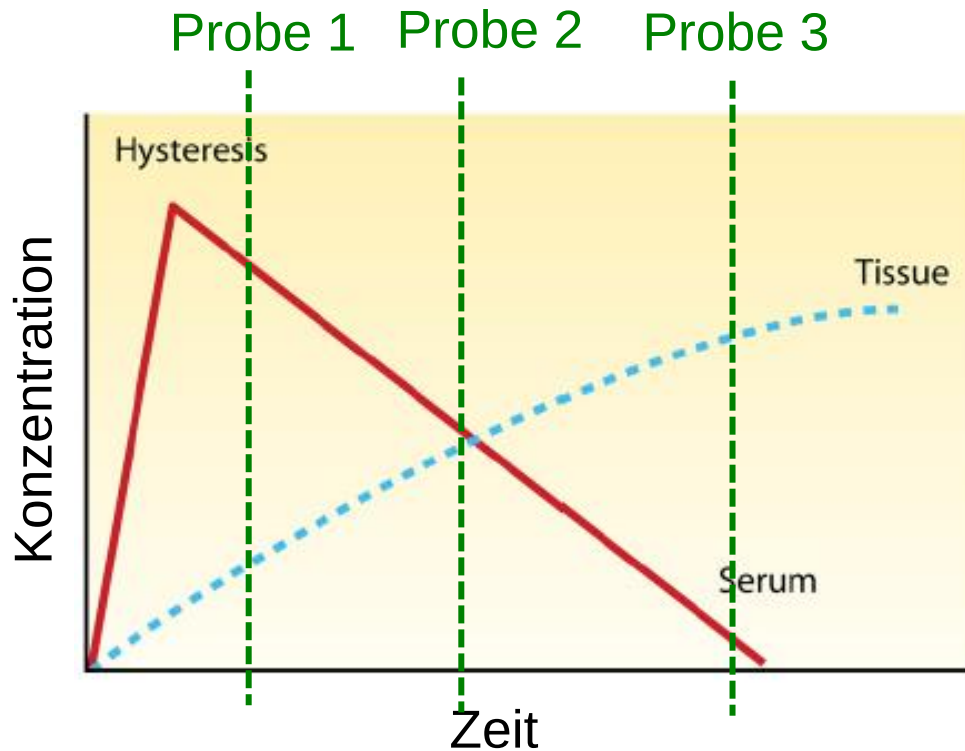
Chemie und Pharmakokinetik

Compound	Mol wt ^a (particle size [μm])	Log D at pH 7.4	% Plasma protein binding	<i>t</i> _{1/2} (h)	AUC _{0–24} (mg · h/liter)	<i>V</i> _{ss} ^b (liters/kg)
Triazoles						
Fluconazole ^{c,d}	305	0.5	12	24–30	38	0.7
Itraconazole ^{e,f}	706	>5	99.8	34	8.7–25	11
Posaconazole ^c	700	2.15	>98	20–31	33–39	7–25
Voriconazole ^e	349	1.8	58	6	13	4.6
Polyenes						
AmBd (conventional amphotericin B) ^e	924 (<0.04)	–2.8	95–99	10–24	1–30	0.5–5
ABLC (Abelcet) ^e	924 (1.6–11)	–2.8	95–99	24	9.5–14 ± 7	1.12–8.8
L-AMB (Ambisome) ^e	924 (0.08)	–2.8	95–99	6–23	131 ± 126	0.11–0.7
Nucleoside						
5-Fluorocytosine ^{c,d}	120	–2.34	5	3–5	576, 1289 ^g	0.6–2.23
Echinocandins						
Anidulafungin ^c	1,140	–3.32	84–99	26	110.3	0.8
Caspofungin ^e	1,093	–3.88	97	9–11	57–96	0.15
Micafungin ^c	1,291	–1.62	>99	15–17	29.6 ± 4.6	0.24–0.39

log D *n*-Octanol-Wasser-Verteilungskoeffizient = log (C_{oct}/C_w) = log C_{oct} – log C_w
 log D > lipophil, log D < 1 hydrophil

Felton et al. 2014 Clin Microbiol Rev 27:68–88

Penetrationsratio



Probe	Penetrationsratio $PR = C_{tiss}/C_{pl}$
1	$\ll 1$
2	1
3	$\gg 1$

$$\text{Aussagekräftiger PR} = AUC_{\tau \text{ tiss}} / AUC_{\tau \text{ pl}}$$

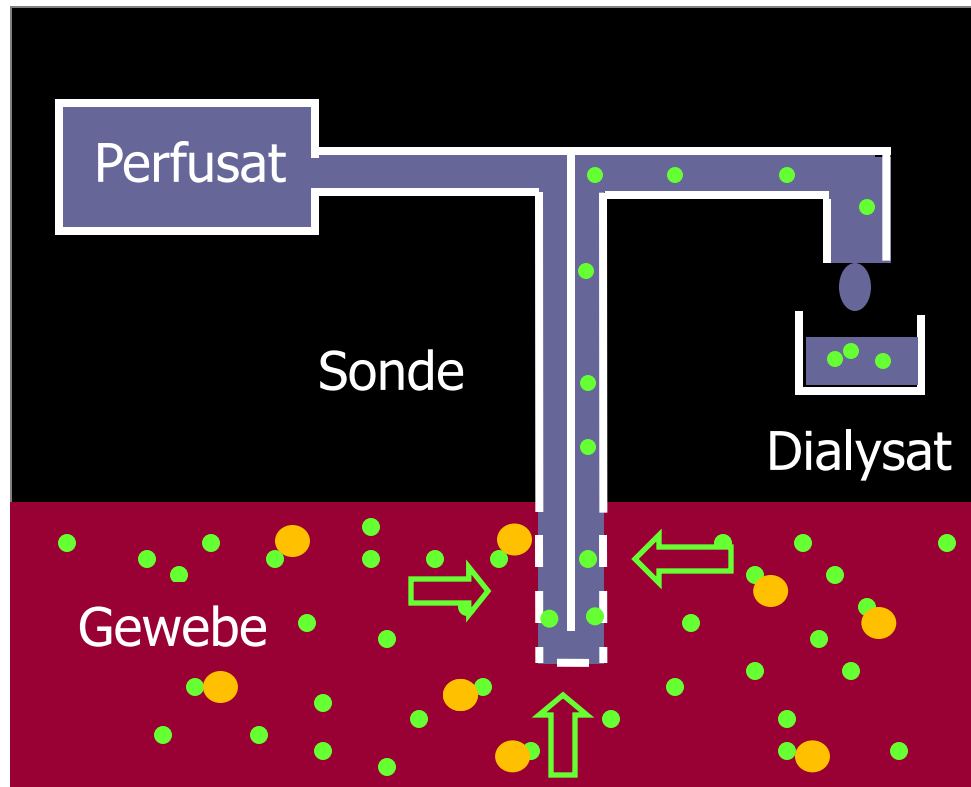
Felton et al. 2014 Clin Microbiol Rev 27:68–88

R. Bellmann, Innsbruck, 2018

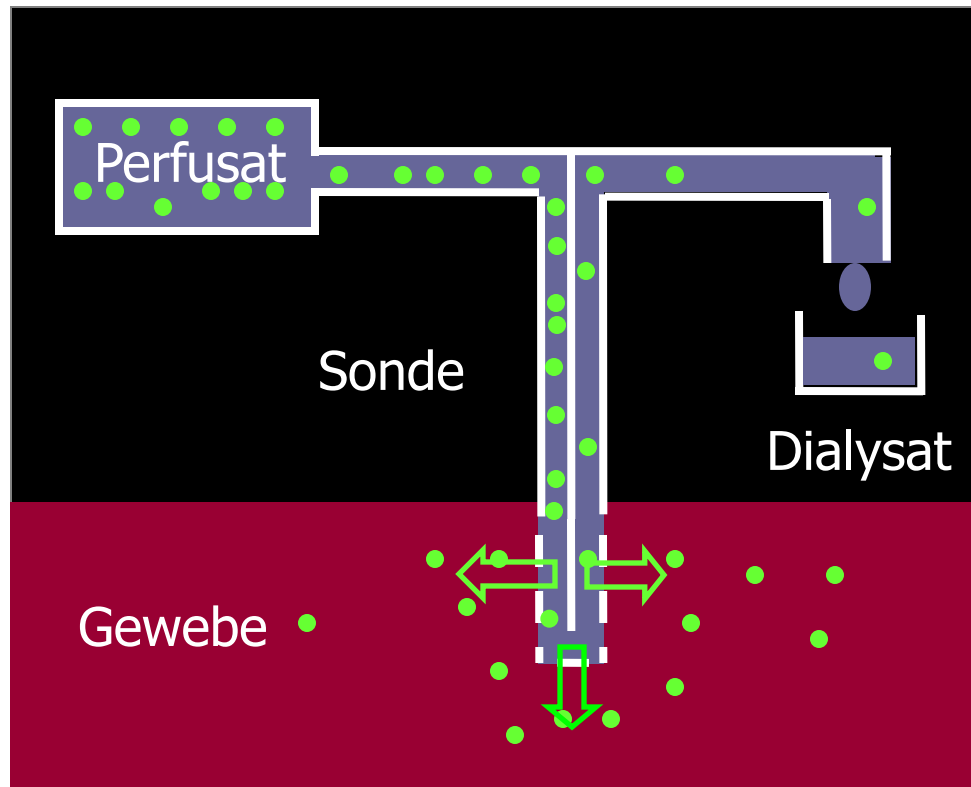
Probenmaterial, Methodik

Homogenisierte Gewebe-Blöcke	Biopsie-, OP-, Autopsiematerial
Spiegel in Flüssigkeiten	Punktion
PK in Flüssigkeiten	Drainage
Penetration in die Lungenalveolen	Epithelial Lining Fluid ELF
Target-site PK in Geweben	<i>In-vivo</i> -Mikrodialyse
Lokalisation auf zellulärem Niveau	
Interzellularraum	<i>In-vivo</i> -Mikrodialyse
Zelluläre Aufnahme, - Lokalisation	Zellkultur, Immunhistochemie Tiermod.

In-vivo-Mikrodialyse: Gewebe- penetration und -Pharmakokinetik



Mikrodialysetechnik - Retrodialyse

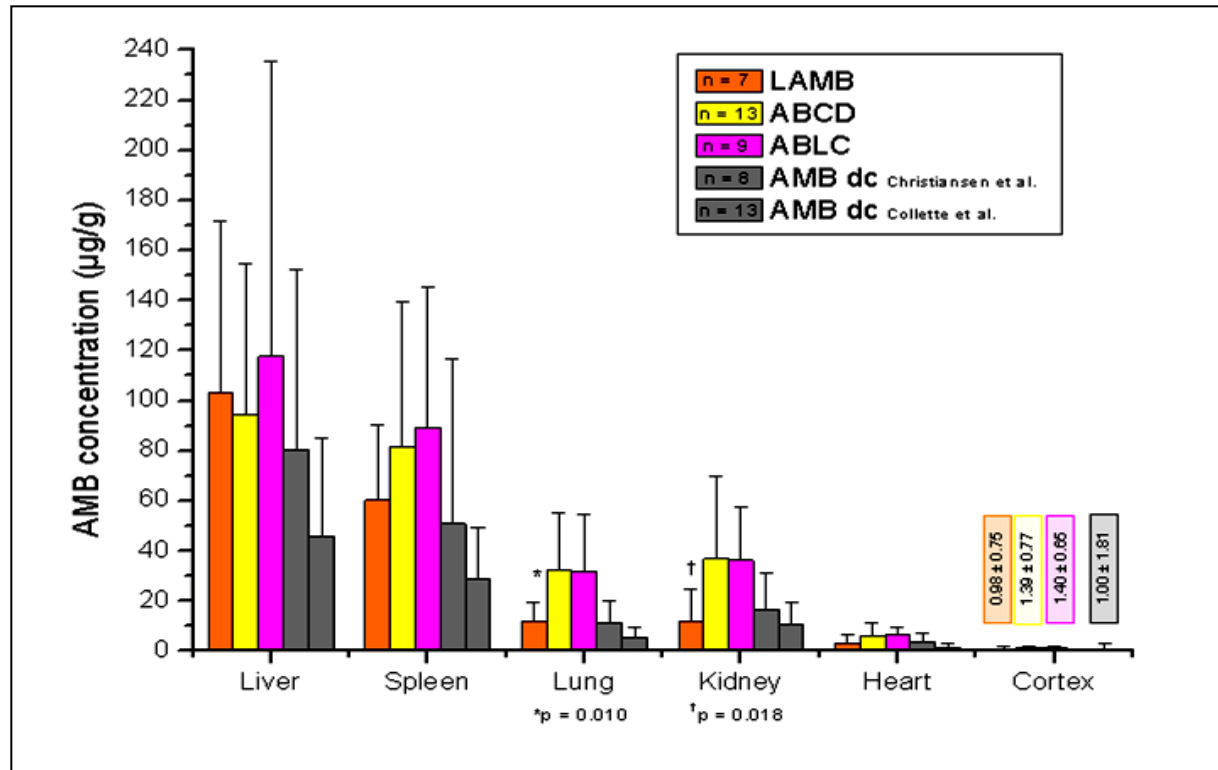


$$R [\%] = 100 - (100 \cdot C_{\text{dialysate}} / C_{\text{perfusate}})$$

$$C_{\text{ec}} = 100 \cdot (C_{\text{sample}} / R)$$

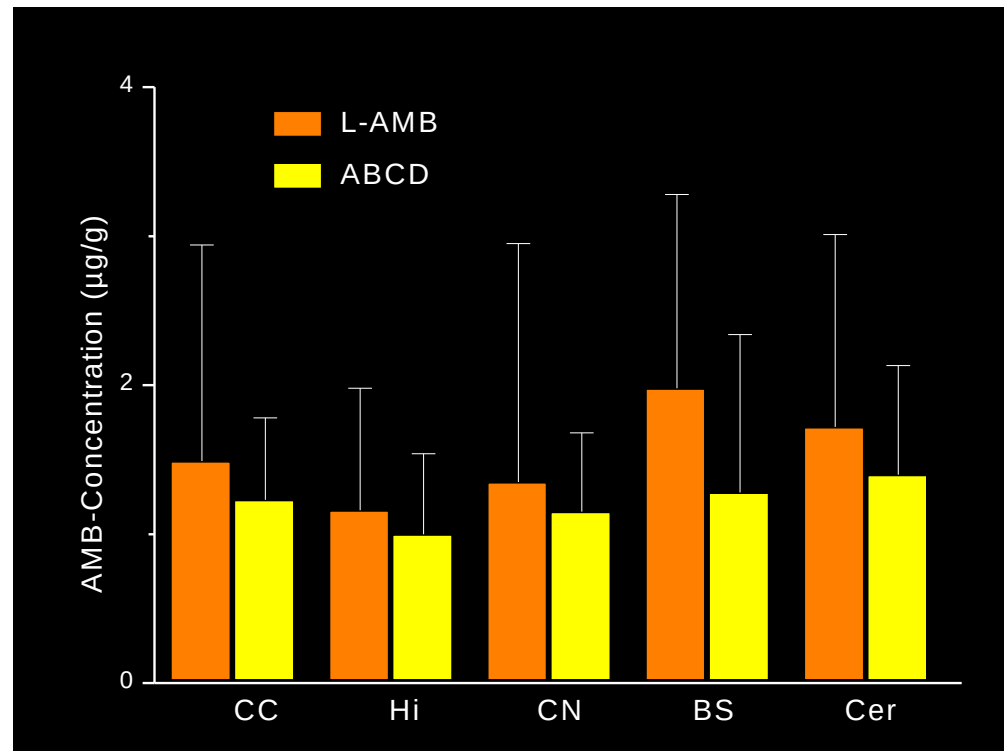
R [%]	<i>in-vivo</i> -Recovery
$C_{\text{dialysate}}$	Konzentration im Dialysat
$C_{\text{perfusate}}$	Konzentration im Perfusat
C_{ec}	Gewebe-Konzentration im Extrazellarraum

Amphotericin B in Autopsie-Proben



Vogelsinger et al. 2006 JAC 57:1153; Vogelsinger et al. 2006 Mycoses; 49: 377;
Christiansen et al. 1985 JID 152:1037; Collette et al. 1989 AAC 33:362

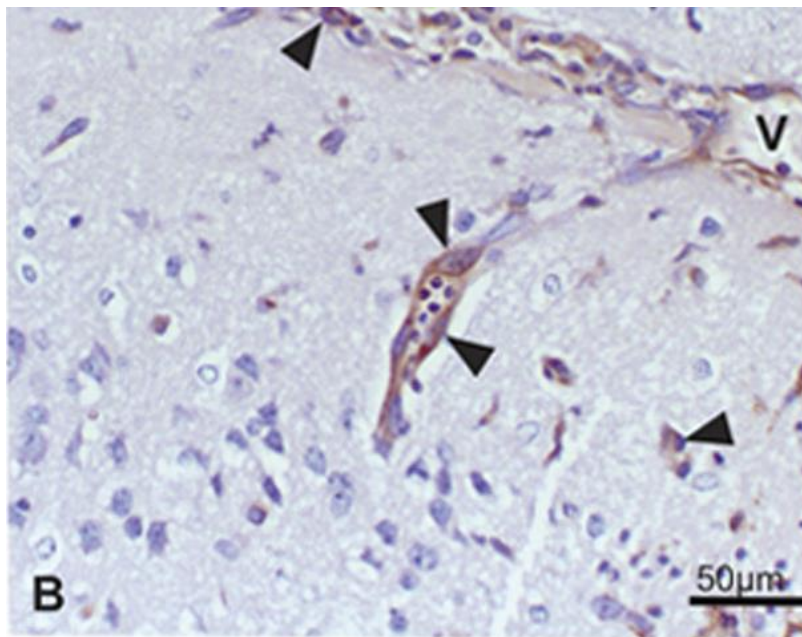
AMB Konzentrationen in verschiedenen Hirnregionen nach Behandlung mit LAMB oder ABCD



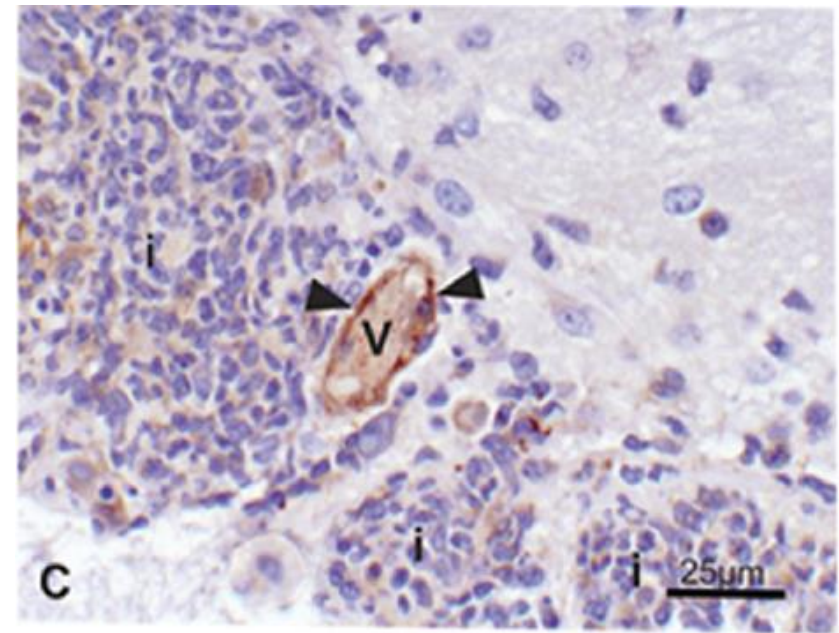
Vogelsinger et al.2006 JAC 57:1153

AMB in *A. fumigatus*-Encephalitis-Maus-Modell

Amphotericin B-positive Kapillar-Endothelien



AMBd 1 mg/kg



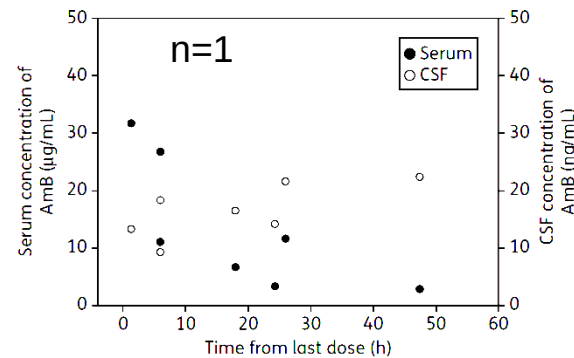
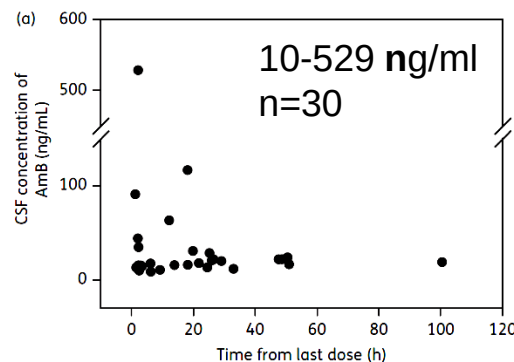
LAMB 3 mg/kg

Clemons et al 2012 AAC 56:4439–4449

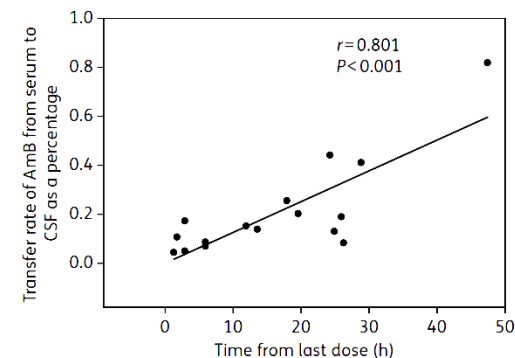
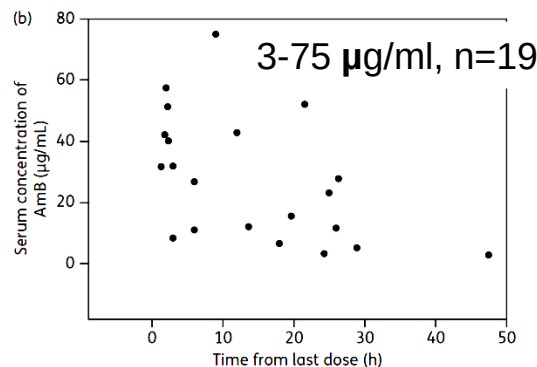
AMB im Liquor unter LAMB-Therapie

- 14 Kinder mit Malignomen, Indikation zur Liquor-Punktion,
- 30 Liquor-Proben, LAMB-Dosen: 2-28 (Median 3)

Liquor



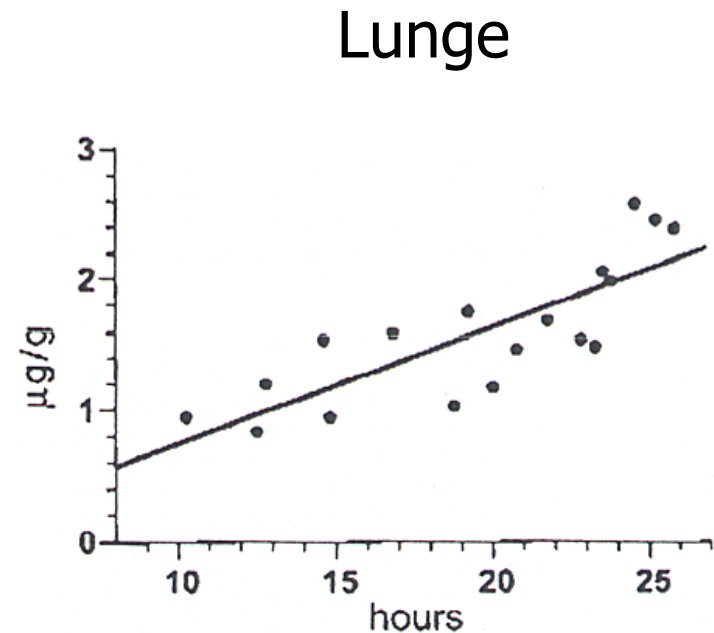
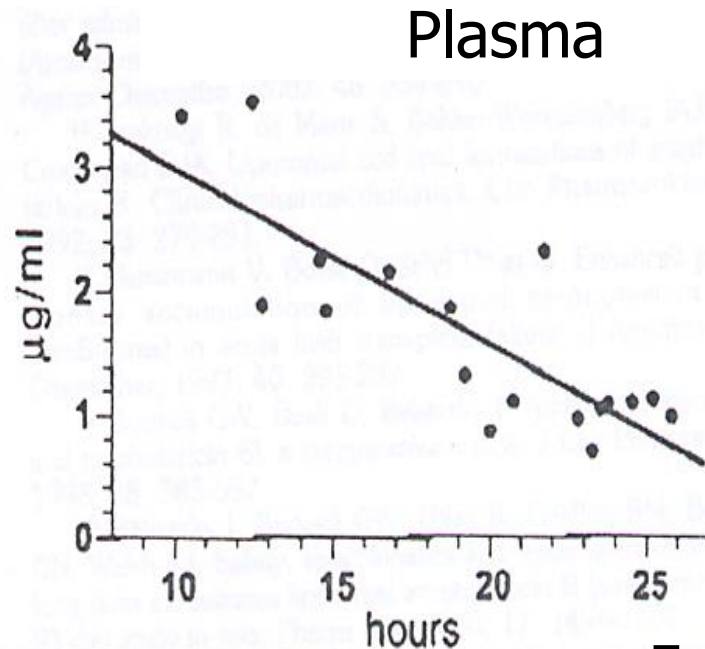
Serum



AMB Liquor-Konzentrationen << AMB Serum-Konzentrationen

LAMB in Operations-Präparaten aus der Lunge

LAMB 1.5 mg/kg single dose, T_{inf} 1h, 10-25 h vor TU-Resektion, n=18



Zeit Infusion-OP

AMB im alveolären Flüssigkeitsfilm “Epithelial Lining Fluid” ELF

Parameter	Value for treatment group ^b		
	LAMB n=11	ABCD n=28	ABLC n=5
Mean concn in ELF $\pm$ SEM ($\mu\text{g/ml}$)	1.60 $\pm$ 0.58**	0.38 $\pm$ 0.07*	1.29 $\pm$ 0.71
Mean concn in plasma $\pm$ SEM ($\mu\text{g/ml}$)			
Liberated	1.08 $\pm$ 0.31	0.57 $\pm$ 0.09	NA
Lipid associated	4.11 $\pm$ 1.61‡	0.54 $\pm$ 0.15‡	NA
Total	5.17 $\pm$ 1.89**	1.12 $\pm$ 0.21*	0.48 $\pm$ 0.18
Mean penetration ratio $\pm$ SEM (%)			
ELF/total plasma	61 $\pm$ 25†	125 $\pm$ 52†	447 $\pm$ 224†
ELF/liberated plasma	154 $\pm$ 44	153 $\pm$ 53	NA
Cumulative dose (mg)	1,688 $\pm$ 285	2,176 $\pm$ 340	2,061 $\pm$ 1,259
Time from start of last infusion	22.0 $\pm$ 12.7	12.6 $\pm$ 2.5	7.3 $\pm$ 3.1

Weiler et al. 2009 AAC 53 4934-7

Lipid-formuliertes Amphotericin B in Pleuraerguss

Pleuraerguss

Plasma

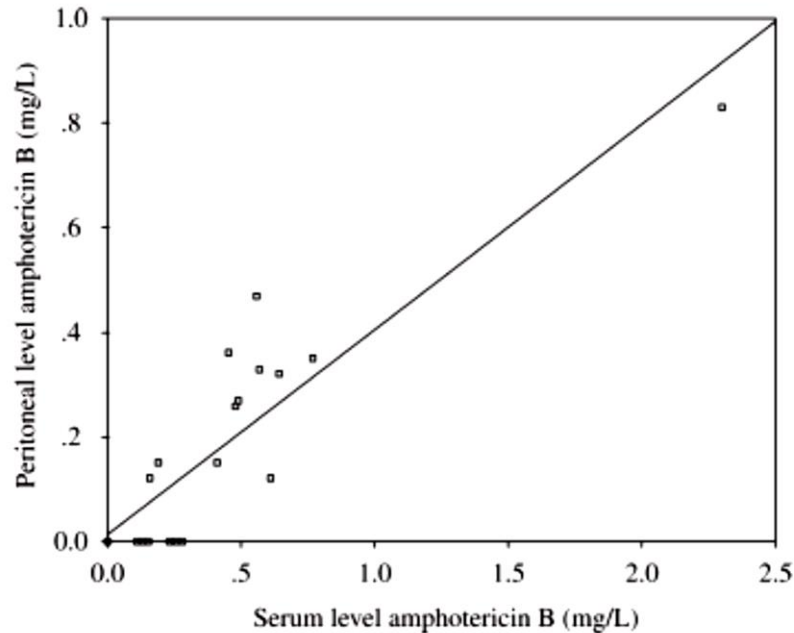
Patient	Sample set	Pleuraerguss			Plasma			Total penetration ratio (%)
		Concn of liberated AMB (µg/ml)	Concn of lipid-associated AMB (µg/ml)	Total concn of AMB (µg/ml)	Concn of liberated AMB (µg/ml)	Concn of lipid-associated AMB (µg/ml)	Total concn of AMB (µg/ml)	
1	A	0.40	0.03	0.43	3.10	3.81	6.91	6
	B	0.13	0.02	0.15	3.38	2.51	5.89	3
2		0.02	0.00	0.02	NA	NA	NA	NA
3		0.05	0.00	0.05	0.52	0.09	0.61	8
4		0.04	0.02	0.06	0.49	0.00	0.49	11
5		0.12	0.00	0.12	0.41	0.00	0.41	29
6		0.25	0.00	0.25	1.02	0.49	1.51	16
7		NA	NA	0.18	NA	NA	0.40	44

^a Two sets of samples were obtained from patient 1; one sample set was obtained from each of the other patients. NA, not available. For ABLC, the chromatographic separation of lipid-associated and liberated AMB fractions was not feasible. Total concentrations of AMB in plasma and pleural effusion samples are shown in boldface.

Weiler et al. 2007 AAC 51:4211-3

AMB in Aszites

AMB-Deoxycholat



Pat. mit post-OP Peritonitis, n=19

van der Voort et al. 2007 JAC 59, 952–956

Lipidformuliertes AMB

Pat. No.	AMB LF	Cum. Dose mg	Time from AMB h	AMB in ascites mg/l		
				LIB	LF	TOT
1	ABCD	3125	1	0.335	0.000	0.335
2 A	ABCD	1050	27	0.154	0.067	0.221
2 B	ABCD	3450	4	0.307	0.000	0.307
3 A	LAMB	2550	3.5	0.151	0.107	0.258
3 B	ABLC	4867	3	0.153	0.064	0.217
MEAN		008	7.7	0.22	0.05	0.27
SD		1388	10.9	0.09	0.05	0.05

Weiler et al. 2008 JAC 62:1163-4

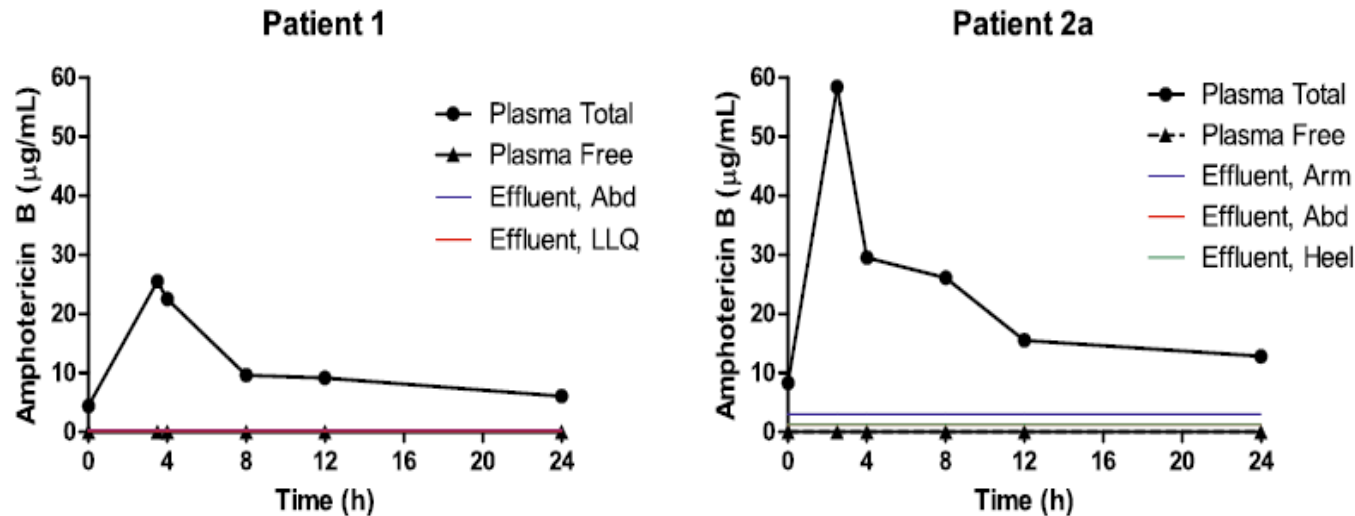
Aszites-Konzentrationen meist < 0.5 µg/ml unter AMBdc und LF-AMB

Amphotericin B in Wundsekret

Polytrauma-Patienten n. Kriegsverletzungen: Pat. 1: *A. flavus*, *A. terreus*, *Fusarium* sp., nicht-identifizierte *Mucorales*, *Saksenea erythrospora*;

Therapie: LMAB 5 mg/kg

Pat. 2: *A. flavus* Therapie: LMAB 5 mg/kg, VRC 2x4mg/kg



Amphotericin B concentrations in plasma and wound effluent in two patients with 5 wounds. Abd, abdomen; LLQ, left lower quadrant.

Subtherapeutische AMB-Konzentrationen im Wundsekret

Akers et al. 2015 BMC Infectious Diseases 15:184

R. Bellmann, Innsbruck, 2018

AMB im Muskel unter LAMB

3 Verbrennungspatienten mit *Mucor circinelloides*-Infektion Material
von Debridement nicht-nekrotischer Muskel-Areale
LAMB 10 mg/kg d 12-15, Tal-Spiegel in Muskel und Plasma

Plasma concentrations (µg/ml)		Muscle µg/g		Tissue/plasma ratio
Patient 1	2.17	Sample 1	41.8	19
		Sample 2	17.8	8
Patient 2	2.58	Sample 1	50.2	19
		Sample 2	30.7	12
Patient 3	4.76	Sample 1	81.3	17

Hohe Konzentrationen im Muskel, relativ niedrige Plamaspiegel

Ressaire et al. 2015 ICM;41:948-9

Amphotericin B: Galle- u. Plasmaspiegel

AMB deoxycholate for *Candida* cholecystitis

=> **biliary AMB $\sim 5 \mu\text{g/ml}$** $\sim 5 \times C_{\text{AMB plasma}}$

Adamson et al. 1989 *Pediatr Infect Dis J*;8:408-11

Biliary drainage after cancer surgery

AmB deoxycholate D= 35 mg x 10d

=> **$C_{\text{max Bile}}$ 41 $\mu\text{g/ml}$** ; $C_{\text{max PL}}$ 1.64 $\mu\text{g/mL}$

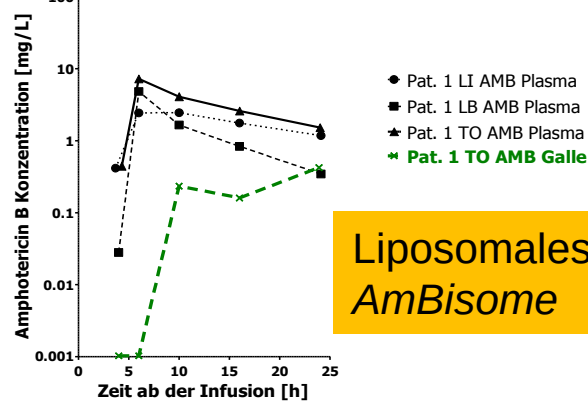
ABLC D= 350 mg x 15d

=> **$C_{\text{max Bile}}$ 60 $\mu\text{g/ml}$** ; $C_{\text{max PL}}$ 3 $\mu\text{g/mL}$

Duflo et al. 2000 *Scan J Inf Dis* 32:581

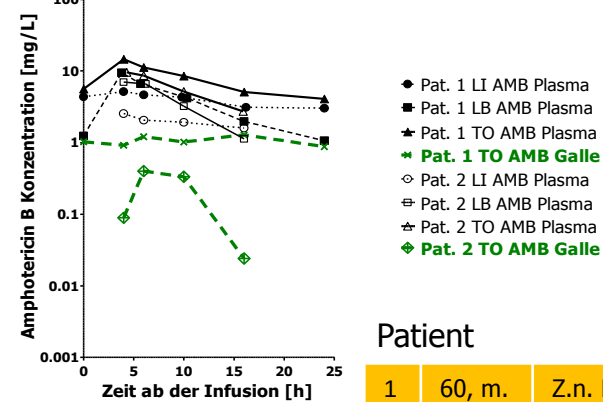
Amphotericin B: Galle- u. Plasmaspiegel

Liposomales Amphotericin B (LAMB) 1. Dosis



Liposomales AMB
AmBisome

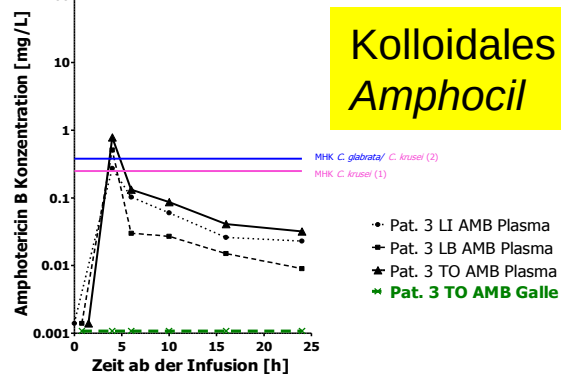
LAMB Steady State



Patient

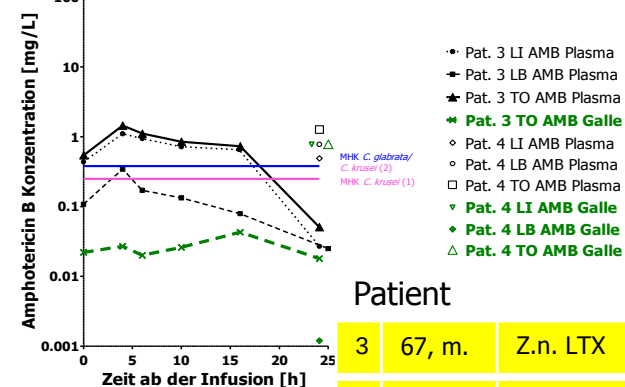
1	60, m.	Z.n. LTX
2	57, w.	Z.n. LTX

Kolloidales Amphotericin B (ABCD) 1. Dosis



Kolloidales AMB
Amphocil

ABCD Steady State



Patient

3	67, m.	Z.n. LTX
4	58, w.	Chol-angitis

AMB: *in-vitro*- und *ex-vivo*-Simulation

Candida in Schweinegalle

AMB mg/L	0	0.025	0.05	0.5	1.0	5.0
<u><i>C. albicans</i></u>						
Schweinegalle	++	++	++	++	++	+/-
RPMI pH 7.2	++	++	++	+	+/-	--
RPMI pH 7.8	++	++	++	+	+	--
<u><i>C. tropicalis</i></u>						
Schweinegalle	++	+	+	+	++	+/-
RPMI pH 7.2	++	+	++	+	-	--
RPMI pH 7.8	++	++	++	+	+/-	--
<u><i>C. glabrata</i></u>						
Schweinegalle	+	+	+	+	+/-	+/-
RPMI pH 7.2	++	++	++	++	+/-	--
RPMI pH 7.8	++	++	++	++	--	--
<u><i>C. krusei</i></u>						
Schweinegalle	+/-	+/-	+/-	+/-	+/-	+/-
RPMI pH 7.2	++	++	++	++	++	--
RPMI pH 7.8	++	++	++	++	+/-	--

Candida in Patientengalle

Zeit n.AMB	vor	4 h	6 h	10 h	16 h	24 h
Patient 1						
<i>LAMB</i> Tag 1						
<i>C. tropicalis</i>	+/-	n. u.	n. u.	+/-	+/-	+/-
AMB mg/L	<0.025	-	-	0.23	0.16	0.42
<i>LAMB</i> Tag 7						
<i>C. albicans</i>	n. u.	+/-	+/-	+/-	+/-	+/-
AMB mg/L	-	0.92	1.21	1.02	1.28	0.88
Patient 2						
<i>LAMB</i> Tag 5						
<i>C. albicans</i>	n. u.	+	+	+	+/-	n. u.
AMB mg/L	-	0.09	0.40	0.33	0.02	-
Patient 3						
<i>ABCD</i> Tag 1						
<i>C. krusei</i>	n. u.	+	+/-	+/-	+/-	+/-
<i>C. glabrata</i>	n. u.	++	+/-	+/-	+/-	+/-
AMB mg/L	-	<0.025	<0.025	<0.025	<0.025	<0.025
<i>ABCD</i> Tag 4						
<i>C. krusei</i>	+	+	+	+	++	+/-
<i>C. glabrata</i>	+/-	+/-	+/-	+/-	+	+/-
AMB mg/L	0.02	0.03	0.02	0.03	0.04	0.02

Flucytosine 5FC *Ancotil*®

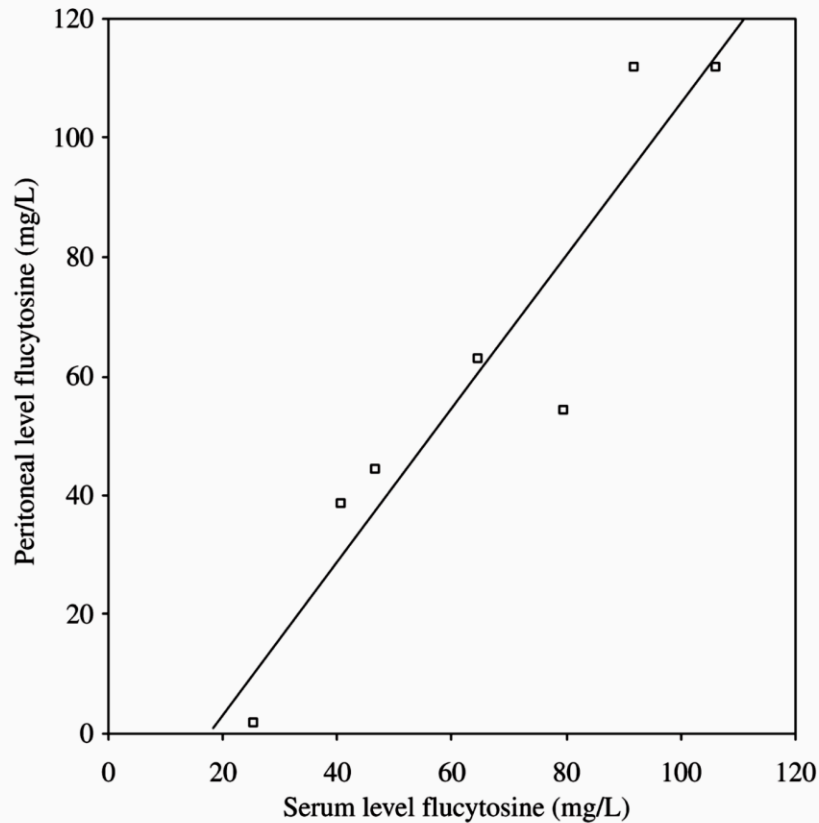
	Concentr. µg/mL	Serum level µg/mL	%
CSF	38 + 19	53 + 17	71 + 85
Bronchial secretion	34	45	76
Saliva	8 – 24	14 – 47	ca. 50
Bone	3	10	30
Synovia	26	64	41
Aqueous humour	10	50	20
Aszites	2 – 8	8 – 20	25 – 40
Urine	2350 200	20 20	> 1000 1000

Polak Ancotil Flucytosin Status Quo & Perspektiven Utz Verl. München 1999

Flucytosin

Flucytosin in Peritonealflüssigkeit
bei post-OP Peritonitis nach
Darmperforation, n=7

Flucytosin-Konzentration in
Peritonealflüssigkeit ~Plasmaspiegel



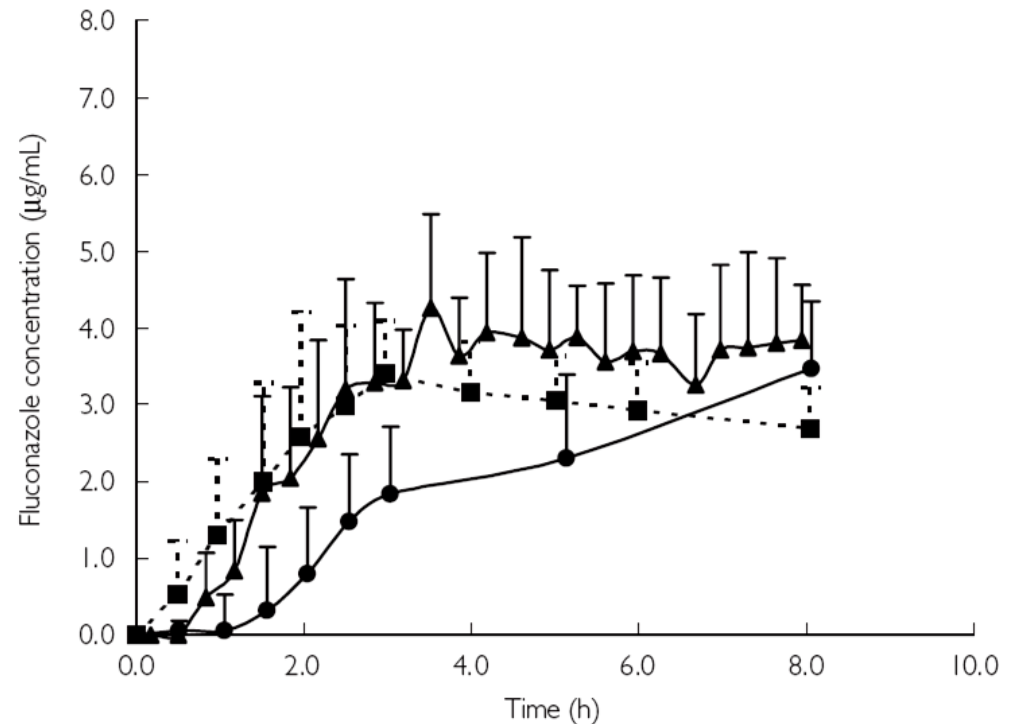
van der Voort et al. 2007 JAC 59, 952–956

Fluconazol in menschlichen Geweben

	n	Conc.	C_{Tis}/C_{PL}	Method	Reference
Brain	4	17.6 µg/g	1.33±0.74	TU Surgery	Thaler et al. 1995 AAC 39:1154
Sputum	11	3.71/2,23 4h/24h	1.05/0.94 4h/24h	Bronch- ectasis	Ebden et al. 1989 AAC 33: 963
Gyn. tissues	52	3.5-4.5 µg/ml	0.90-1.15	Hyster- ectomy	Mikamo et al. 1999 AAC 43:148
Prostate	8	1.9 ±1.2 µg/g	0.29±0.03	Transuretr. resection	Finley et a. 1995 AAC 39: 553
Pancreas	15	8.19 µg/g	0.96	Surgery Tu, pancreatitis	Shrikhande et al.2000 AAC 44;2569

Fluconazol-Pharmacokinetics im Subkutan-Gewebe

- 5 Probanden
- Einzel-Dosis
- FLU200 mg p.o.
- Blasen durch Ansaugen
- MD Sonde OA



Sasongko et al. 2003 BJCP 56:551

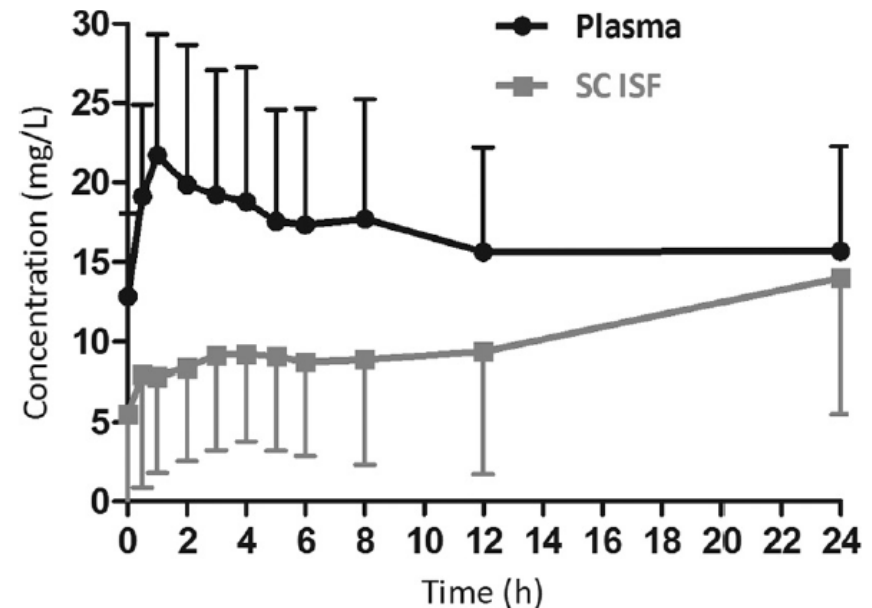
Unbound plasma (■); microdialysis (▲); and blister fluid (●)

Fluconazol in subkutaner interstitieller Flüssigkeit kritisch Kranker

- 12 kritisch Kranke mit Sepsis
- 400 mg i.v. ü. 1h d3-d5
- Mikrodialyse-Recovery $51 \pm 16\%$

Mediane $fAUC_{0-24}$ mg · h/l

- Plasma 340.4
- ISF 141.1



Dosis > 400 mg für therapeutische SC-ISF-Konzentrationen!

Freie FLU Konz. median (Interquartile-Range) i. Plasma und SC ISF n. 400 mg

Sinnollareddy et al. 2016 AAC 60:827-32

Fluconazol in Körperflüssigkeiten

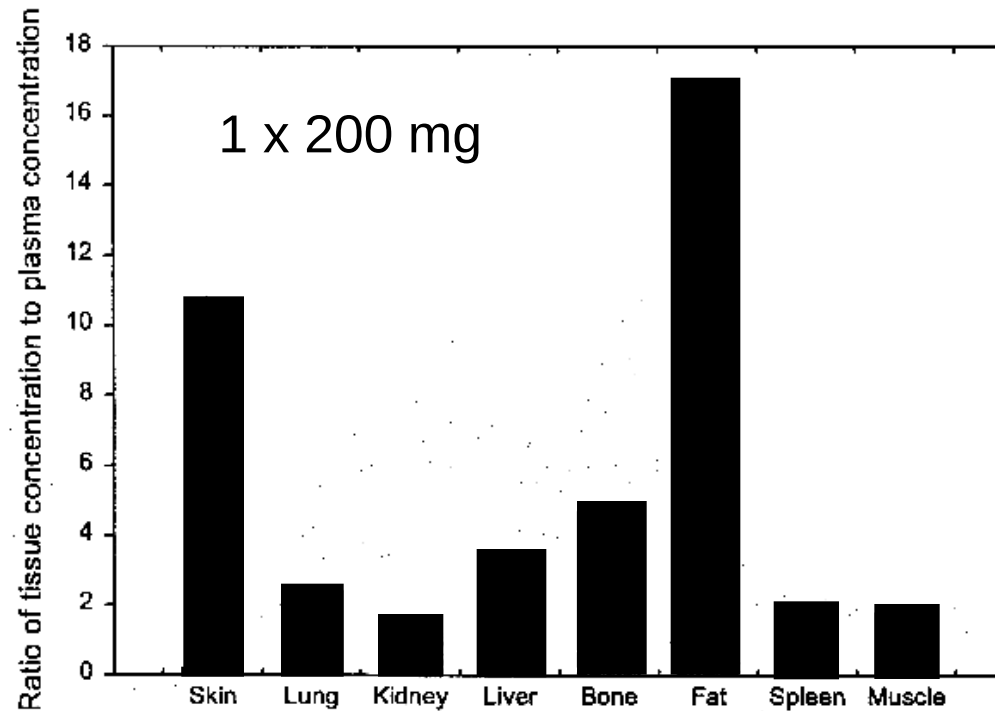
Tissue [reference]	No. of subjects	Fluconazole daily dose in mg (no. of doses)	Time after dose (h)	Penetration ratio	Fluconazole level in tissue or fluid ($\mu\text{g/mL}$)
Saliva [17]	8	50 (1)	1	1.0	1.2
Sputum [27]	11	150 (1)	4	1.06	3.7
	11	150 (1)	24	0.92	2.2
CSF [20]	6	50 (6)	1	0.52	1.26
CSF [20]	6	100 (7)	1	0.62	2.74
CSF [24]	3	50 (V*)	4-8	0.74	2.0-2.3
CSF [24]	8	100 (V)	4-12	0.88	3.4-6.2
Vagina [28]	27	150 (1)	2-72	1.0	2.95-0.61
Blister fluid [26]	12	50 (14)	3-144	1.04-1.14	2.96-0.32
Blister roof [26]	12	50 (14)	3-144	2.27-12.6	6.45-3.55
Skin scrapings [17]	9	50 (14)	2	11.4	24.16
Urine [29]	11	50-400 (V*)	0-24	~10	118
Brammer et al. 1990 Rev Infect Dis 12 Suppl 3:S318					
Bile	2 LTX	100-200	24	0.5	6.3-9.0
Ascites	1 LTX	150, 100	24	0.85	9.6

Pea et al. 2014 JAC 69: 2585-6

Fluconazol im Liquor

	n	Dose	C _{maxi} CSF	C _{min} CSF	t _{1/2} CSF	Reference
CSF of children with hydro- cephalus	2	12.5 mg/kg i.v. once daily	Not detected	Not detected	-	Bafeltowska & Buszman 2005 Chemother 51:370
		7.5 mg intra- ventricularly once daily	19.54 µg/ml	0-0.3 µg/ml	1.84 h	

Itraconazol-Gewebeverteilung



Willems et al. 2001 J Clin Pharm Ther 26:159

Itraconazol in der Lunge

- 26 Freiwillige 2 x 200 mg p.o. nüchtern für 5 Tage
- HPLC, Konzentration in ELF: HST-Dilutionsmethode

BAL group (h)	AC concn at the indicated BAL time ($\mu\text{g/ml}$) ^c		ELF concn at the indicated BAL time ($\mu\text{g/ml}$) ^c		Plasma concn at the indicated BAL time ($\mu\text{g/ml}$) ^c	
	ITRA	OH-IT	ITRA	OH-IT	ITRA	OH-IT
4	5.5 $\pm$ 2.9	6.3 $\pm$ 2.8	0.3 $\pm$ 0.3	0.8 $\pm$ 0.5	2.1 $\pm$ 0.8	3.3 $\pm$ 1.0
8	4.0 $\pm$ 1.4	4.9 $\pm$ 1.7	0.3 $\pm$ 0.3	0.8 $\pm$ 0.3	1.2 $\pm$ 0.3	2.5 $\pm$ 0.5
12	4.9 $\pm$ 2.0	6.6 $\pm$ 3.1	0.5 $\pm$ 0.7	1.0 $\pm$ 0.9	0.9 $\pm$ 0.3	2.0 $\pm$ 0.7
16	3.7 $\pm$ 2.7	5.4 $\pm$ 2.1	0.3 $\pm$ 0.3	0.8 $\pm$ 0.4	1.2 $\pm$ 0.4	2.0 $\pm$ 0.5
24	2.1 $\pm$ 1.0	4.3 $\pm$ 0.9	0.2 $\pm$ 0.1	0.6 $\pm$ 0.2	0.9 $\pm$ 0.4	2.2 $\pm$ 0.9

means $\pm$ 1 SD.

Akkumulation in Alveolarzellen, niedrige Konz. in ELF: AC > Plasma > ELF

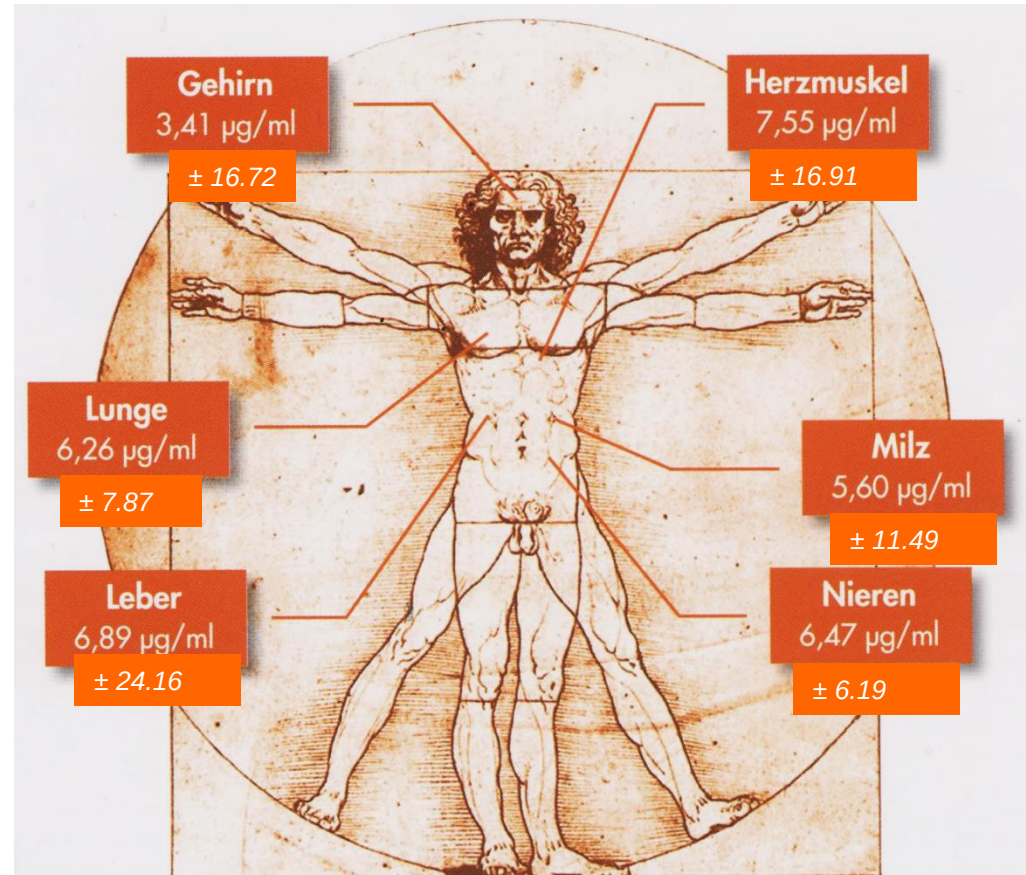
Conte et al.. 2004 AAC 48:3823-7.

Voriconazol in Autopsiematerial



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- Gewebeproben von 8 Patienten (6 m, 2 w), die unter Voriconazoltherapie verstorben sind
- kumulative Dosis 3,650 mg, QR 3,650 mg
- Gewebekonzentrationen in $\mu\text{g/g}$, Median, $\pm$ Interquartilrange



Weiler et al. 2011 AAC 55:925–928

Voriconazol im ZNS

Liquor von LP: 0.39-1.00 $\mu\text{g/mL}$ PI 1.36-2.65 $\mu\text{g/mL}$, n=1

Schwartz et al.1997 BJH 97:663-5

Liquor von LP: 0.08-3.93 $\mu\text{g/mL}$ mediane PR 0.46, n=14

Hirn (Autopsie) 11.8-58.5 $\mu\text{g/g}$ n=2

Lutsar et al.2003 CID 37:728;

Liquor aus Ventr.-Drainage 0.08-1.70 $\mu\text{g/mL}$ n=1, 6 Proben

Denes et al.2004 CID 39:603

Hirnabszess 1.2-1.4 $\mu\text{g/g}$ n=2

Elter et al. 2006 IJAA 28:262

Voriconazol in Patienten-Proben

Kammerwasser 3.47 $\mu\text{g/mL}$ n=1

Spriet et al. 2009 JAC 64:877–878

Pleura-Empyem 0.8-1.4 $\mu\text{g/mL}$ PR~1, n=1, 2 Proben

Stern et al. 2004 AAC 48:1065

Pleura-Empyem 2.2 $\mu\text{g/mL}$, PR 0.6, n=1

Perikard-Erguss 3.7 $\mu\text{g/mL}$, PR 0.6, n=1

Poupelin et al. 2006 ICM 32:936

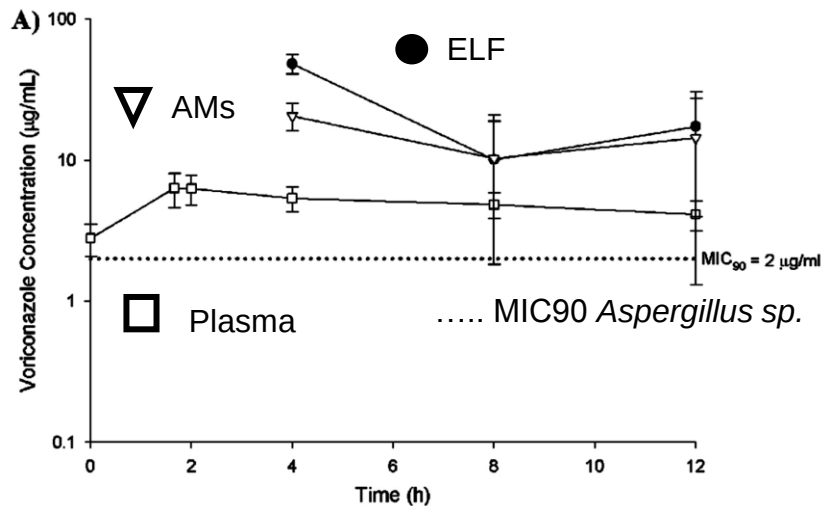
Voriconazol in alveolärer ELF

12 Pat. St.p. LuTX, VORI-Prophylaxe: LD 2 x 6 mg /kg iv. ED 2 x 200 mg po.

Subject	Type of lung transplant	No. of oral doses	Timing of dose prior to bronchoscopy (h)	Voriconazole concn ($\mu\text{g/ml}$)		ELF/plasma ratio
				Plasma	ELF	
1	Double	164	0.5	0.19	1.98	11
2	Single left	27	3.0	NA ^b	4.73	NA
3	Double	114	3.0	1.35	13.28	10
4	Single left	30	4.0	1.34	7.85	6
5	Single right	98	4.5	0.76	1.58	2
6	Single left	36	5.0	2.66	44.00	17
7	Single left	34	5.0	2.10	57.90	28
8	Single left	77	6.0	4.56	83.32	18
9	Double	38	6.5	0.05	0.29	6
10	Single left	27 ^c	6.5	1.16	13.27	11
11	Single left	47	12.0	0.15	0.73	5
12	Single left	99	13.5	0.43	2.16	5
Mean (SD)		66 (44)				11 (8)

Voriconazol in alveolärer ELF

- 20 Probanden VORI + ANID Standard-Dosis iv. über 3 Tage
- BAL 4, 8, 12 h nach Infusion



Time of BAL (h)	Concn ($\mu\text{g/ml}$)		
	Voriconazole		
	Plasma	ELF	AMs
4	5.3 (1.4)	48.3 (7.6)	20.6 (4.5)
8	1.7 (0.9)	10.1 (10.8)	10.3 (8.5)
12	2.2 (1.1)	17.2 (13.3)	14.4 (13.1)

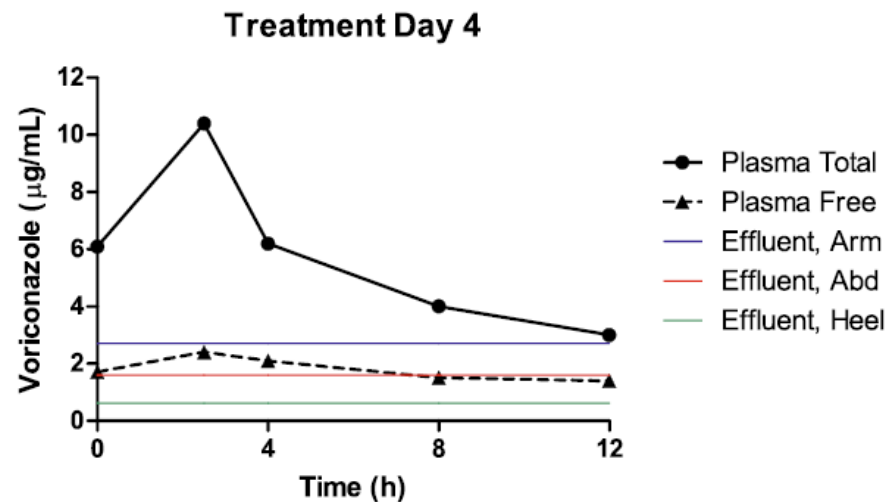
ELF > AMs > Plasma

Plasma-PK

Drug (dose)	$C_{\max}$ ($\mu\text{g/ml}$)	$T_{\max}$ (h)	$\text{AUC}_{0-\tau}$ ($\mu\text{g} \cdot \text{h/ml}$)	V_{ss} (liters)	CL (liters/h)	$t_{1/2}$ (h)
Voriconazole (4 mg/kg)	5.3 (1.8)	1.8 (0.2)	39.5 (19.8)	109.7 (33.9)	171.6 (86.2)	6.9 (2.1)

Voriconazol in Wundsekret

- Polytrauma-Patient n. Kriegsverletzungen: *A. flavus*
- LMAB 5 mg/kg, VRC 2 x 4 mg/kg
- 99 d stationäre Behandlung



Akers et al. 2015 BMC Infectious Diseases 15:184

Posaconazol in Autopsie-Proben

Pat. St.p. allo-HSCT letzte Dosis- † 4-196 h, 1 x 200 mg – 2 x 400 mg or. Susp.
Einnahme Plasma-Probe 9-57 h (Pt. 4 / Pt. 2)

Patient no.	Time from initiation of treatment to death (days)	Dose (mg) ^a	Patient no.	Plasma concn (ng/ml) ^a	Posaconazole concn (ng/g) in:				
					Brain	Kidney	Liver	Heart	Lung
1	5	200 (2 doses 5 days before death, 1 dose 3 days before death)	1	30	160	480	620	310	140
2	4	400 (2 doses 4 days before death), 200 (2 doses 1 day before death)	2	10	80	320	660	180	200
3	31	200 (q12h, every second day)	3	40	40	280	260	ND ^b	110
4	42	200 (q12h, every second day)	4	70	ND	510	1,000	510	550
5	196	200 (q12h, every second day)	5	50	60	330	500	260	670
6	19	200 (q12h, every second day)	6	330	260	4,600	7,460	1,790	4,530
7	22	200 (q8h), 200 (q12h the last 2 days before death)	7	390	320	1,550	2, 290	1, 730	890

- Subtherapeutische Plasma-Spiegel < 500 mg/ml
- niedrige Gewebespiegel im Gehirn unter oraler Suspension – variable enterale Resorption!

Posaconazol in ELF Gesunder

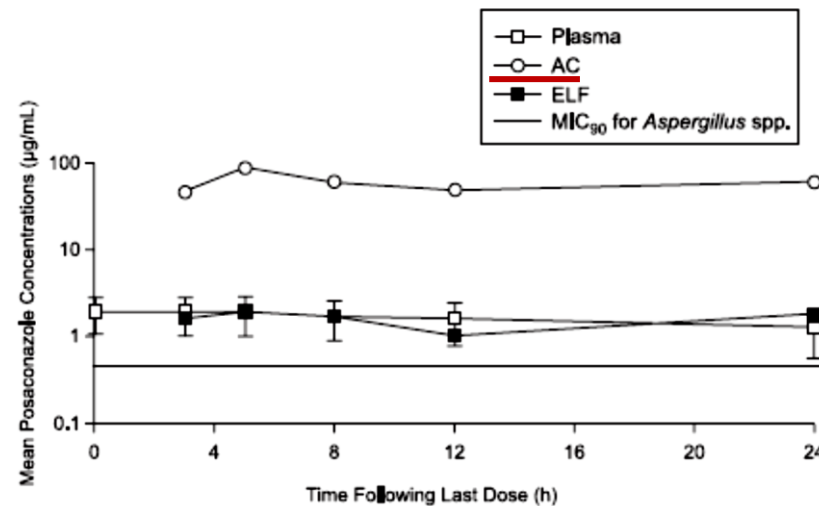
25 Probanden 2 x 400 mg für 8d, AE bei 36%

TABLE 1. POS concentrations in plasma, ACs, and ELF at the time of BAL

Time of BAL (h)	n	Plasma concn ^a (µg/ml)	AC concn ^b (µg/ml)	AC/plasma ratio	ELF concn ^b (µg/ml)	ELF/plasma ratio
3	3	1.93 (47)	46.2 ± 26.3	34.5 ± 25.8	1.66 ± 1.05	1.08 ± 0.47
5	4	1.93 (48)	87.7 ± 65.0	44.3 ± 44.2	1.86 ± 1.30	0.75 ± 0.38
8	4	1.73 (48)	60.9 ± 32.3	32.5 ± 14.0	1.69 ± 0.82	0.95 ± 0.20
12	5	1.62 (52)	49.0 ± 49.7	27.3 ± 18.0	1.02 ± 0.97	0.59 ± 0.35
24	5	1.28 (56)	60.7 ± 49.2	34.9 ± 18.6	1.80 ± 1.71	0.92 ± 0.65

^a Mean values (percent coefficient of variation) are shown

^b Mean values ± SD are shown.

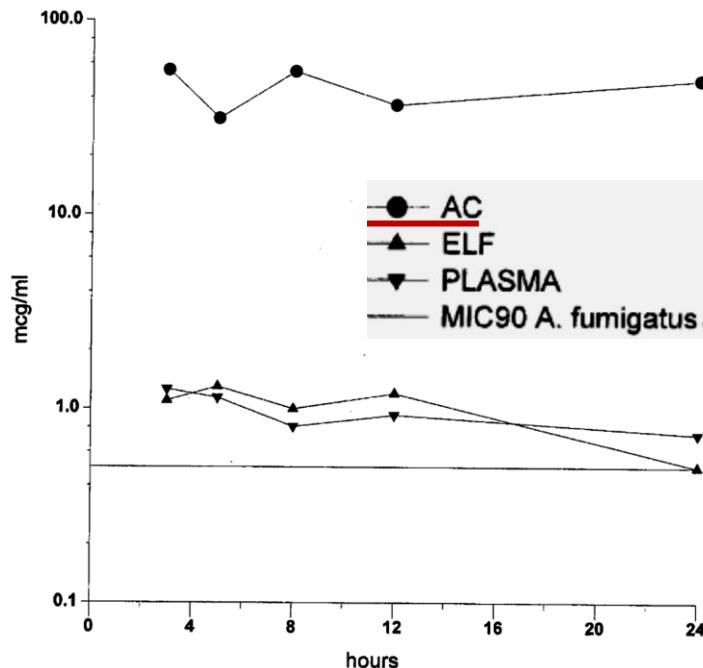


Anreicherung in
Alveolarzellen
AC > ELF ~ Plasma

Conte et al. 2009 AAC 53:703–7

Posaconazol in ELF n. LuTX

20 Erwachsene Lugentransplantierte, 2x400-mg POS orale Suspension mit fettreicher Mahlzeit für 7 d



Parameter	Value		
	Plasma	ELF	AC
$AUC_{0-12} (\mu\text{g/ml} \cdot \text{h}^{-1})$	10.99	11.21	530.2
AUC_{0-12}/MIC_{90}	19.95	18.42	1,162
$AUC_{0-24} (\mu\text{g/ml} \cdot \text{h}^{-1})$	21.98	22.42	1,060
AUC_{0-24}/MIC_{90}	39.90	36.84	2,324
12-h C_{max} ($\mu\text{g/ml}$)	1.3 ± 0.4	1.3 ± 1.7	55.4 ± 44.0
12-h C_{max}/MIC_{90}	2.5	2.6	110.8
12-h T_{max}	2.8 ± 0.6	5.3 ± 1.0	3.2 ± 0.7
12-h C_{min} ($\mu\text{g/ml}$)	0.81 ± 0.49	1.0 ± 0.8	31.3 ± 25.4
$T > MIC_{90}$ (h)	24	24	24

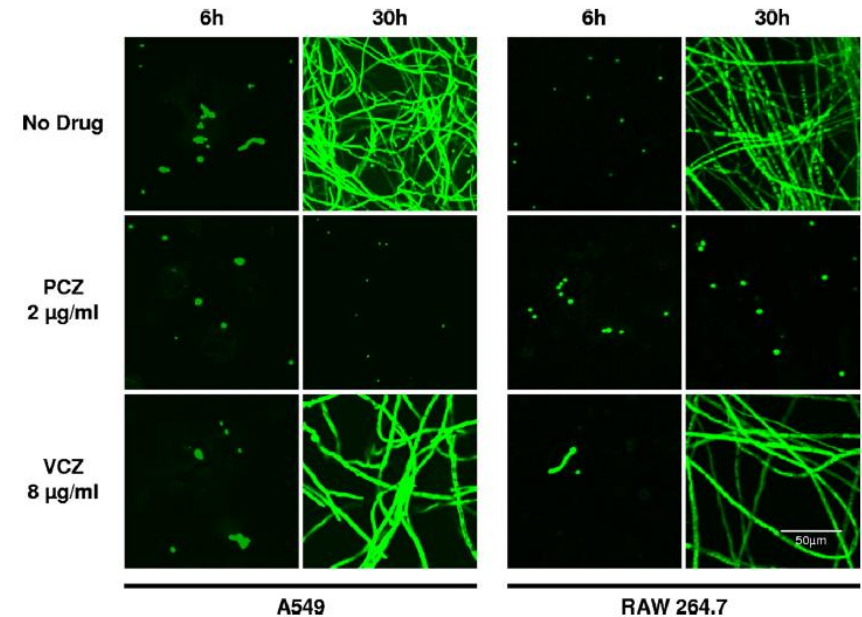
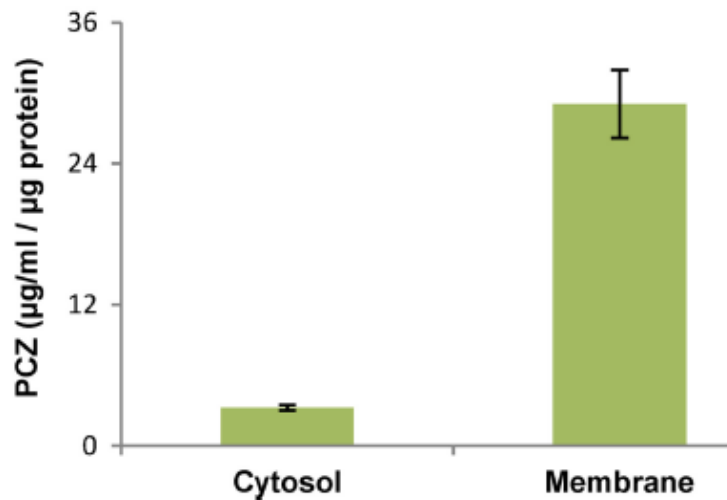
Anreicherung in Alveolarzellen
Resultate vergleichbar mit Probanden

Conte et al. 2010 AAC 54:3609–13

Posaconazol in Alveolarzellen in-vitro

Alveolar-Epithel-Zellen A549 u. – Makrophagen RAW264.7

POSA-Exposition für 4 h -> Beimpfung mit *A. fumigatus* Conidien



- Anreicherung in der Membran im ER durch Diffusion
- Post-antimykotischer Effekt von POSA

Campoli et al. 2011 AAC 55:5732–9

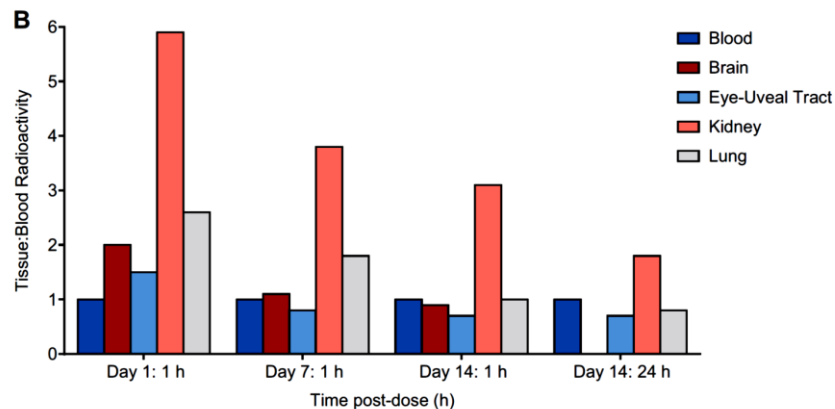
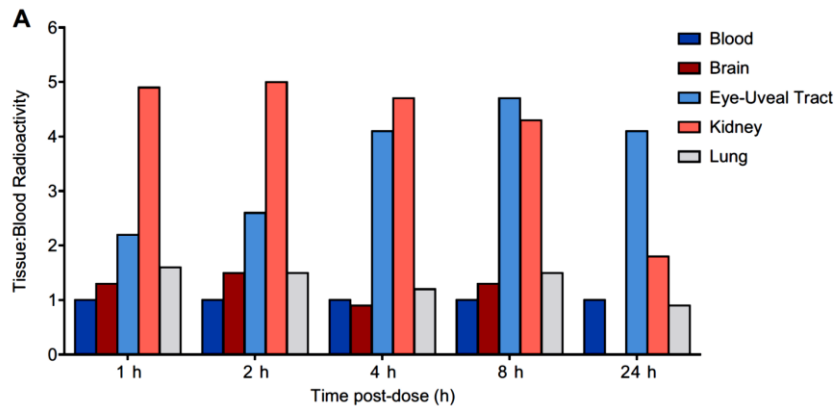
Posaconazol in diversen Kompartimenten *orale Suspension*

Kompartiment	n	POSA-Konzentration	
ELF „BAL F“ LuTX	24, 8 CF	0.64 µg/ml IQR 0.27-0.94 Serum CF 1.37 NCF 1.45	Thakuria et al. 2016 IJAA 47:69-76
Liquor	1	1.2–4.6 ng/ml, Median 1.5 Plasma 136 -989	Reinwald et al. 2009 BMT;44:269-70
	1 (HIV)	< 31 ng/ml (LLOD) Plasma 668	Calcagno et al. 2011 JAC 66:224-5
	2	<10 - 221 ng/ml Plasma 88-93	Rüping et al. 2008 JAC 62:1468-70
Hirnabszess	1	162/187 ng/ml Plasma 396	Rüping et al. 2008 JAC 62:1468-70
Muskel	1 Verbr. kont. HD	<0.1 µg/ml Plasma <0.1 µg/ml	Ressaire et al. 2015 ICM;41:948-9

Unzureichende Posaconazol-Resorption mit *oralen Suspension*

Isavuconazol im Gewebe

Ratte Isavuconazol $^{14}\text{C}/^3\text{H}$ markiert
D=3 mg/kg i.v. n=1 / Zeitpunkt



Patient mit rhinocerebraler
Rhizopus oryzae Mucormykose
refraktär gegenüber LAMB

Weichteilgewebe: 1.09–1.38 µg/g

Plasma 0.76–0.86 µg/mL

Caspofungin-Verteilung in Ratten

TABLE 3. Mean concentrations and amounts of radioactivity in the tissues of rats receiving a 2.0-mg/kg i.v. bolus of [³H]caspofungin^a

Tissue	Mean ± SD concn (µg eq/ml or µg eq/g) (mean amt as % of dose) at:			
	0.5 h	2.0 h	24 h	288 h
Plasma	11.0 ± 5.73 (24.6)	6.10 ± 0.596 (13.7)	1.74 ± 0.849 (3.91)	0.068 ± 0.040 (0.151)
Red blood cells	4.08 ± 2.57 (7.50)	1.93 ± 0.127 (3.54)	0.445 ± 0.219 (0.818)	0.132 ± 0.094 (0.243)
Skeletal muscle	0.305 ± 0.042 (7.63)	0.386 ± 0.096 (9.64)	0.103 ± 0.013 (2.58)	0.009 ± 0.002 (0.214)
Fat	0.431 ± 0.087 (0.862)	0.357 ± 0.073 (0.714)	0.358 ± 0.110 (0.715)	0.007 ± 0.000 (0.013)
Skin	1.60 ± 0.137 (14.0)	1.91 ± 0.043 (16.7)	0.959 ± 0.364 (8.38)	0.285 ± 0.128 (2.49)
Heart	2.31 ± 0.138 (0.382)	1.87 ± 0.045 (0.284)	0.642 ± 0.089 (0.097)	0.030 ± 0.004 (0.005)
Lung	5.12 ± 0.192 (1.10)	4.50 ± 0.601 (0.937)	2.44 ± 0.416 (0.531)	0.115 ± 0.022 (0.024)
Kidney	9.15 ± 1.30 (3.48)	10.6 ± 1.80 (3.91)	11.4 ± 1.64 (4.18)	0.789 ± 0.132 (0.282)
Spleen	4.37 ± 0.042 (0.606)	3.87 ± 0.491 (0.585)	3.62 ± 0.607 (0.472)	0.299 ± 0.035 (0.050)
Liver	5.03 ± 0.597 (8.37)	7.04 ± 1.34 (14.4)	22.2 ± 2.43 (35.2)	1.65 ± 0.530 (2.82)
Small intestine	3.94 ± 0.487 (2.42)	3.69 ± 0.076 (3.58)	2.27 ± 0.220 (1.30)	0.097 ± 0.004 (0.062)
Large intestine	2.25 ± 0.164 (0.402)	2.00 ± 0.388 (0.527)	1.38 ± 0.160 (0.216)	0.044 ± 0.002 (0.009)
Brain	0.127 ± 0.004 (0.045)	0.153 ± 0.021 (0.054)	0.164 ± 0.111 (0.057)	0.022 ± 0.002 (0.008)
Lymph nodes	1.93 ± 0.118 (0.544)	1.85 ± 0.527 (0.335)	1.56 ± 0.352 (0.256)	0.062 ± 0.008 (0.013)
Eye	0.516 ± 0.064 (0.025)	0.478 ± 0.081 (0.018)	0.295 ± 0.051 (0.012)	0.025 ± 0.002 (0.001)

^a n = 3 rats per time interval.

Stone et al.2003 AAC 48:815

Caspofungin in Patientenproben

Kompartiment	n	CAS-Konzentration	
Liquor	1	< LOD, Plasma 2.7/5.5 µg/ml	Hsue et al. 2004 JAC 54:292–294
Kammerwasser	1	d3: 0.28 µg/ml, Plasma 4.70 µg/ml	Spriet et al. 2009 JAC 64:877–878
Galle	1	0.8 µg/mL 1 h nach Infusion 1.0 mg/mL 2 h nach Infusion 0.6 mg/mL 3 h nach Infusion Serum 3.1 mg/ mL 1 h nach Infusion	Goicoechea et al. 2004 Clin Infect Dis 38:1040-1

Caspofungin in pulmonalen Alveolarzellen

Lungen-transplantierte Patientin CAS 50 mg, LD 70 mg d5

Time (h)	Concentration (mg/L)		AC/plasma ratio
	Plasma	ACs	
1	8.97	72.8	8.1
4	6.31	134.4	21.3
24	2.74	8.24	3.0

Burkhardt et al. 2009 IJAA 34:491–492

Lungenpenetration von Micafungin

Micafungin im alveolären Flüssigkeitsfilm von Probanden

Concentrations of micafungin in plasma, ELF, and AC
after three daily doses of 150 mg

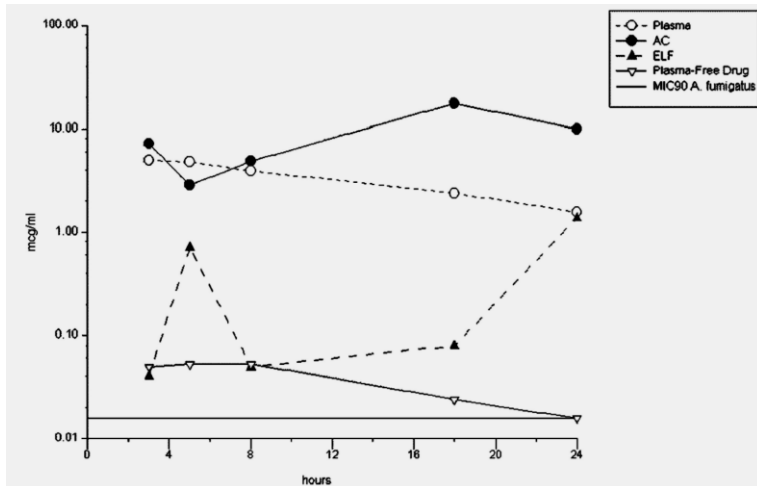
Collection time (h)	Concn ($\mu\text{g/ml}$) ^a in:			
	Plasma	ELF	AC	
4 ^b n=5	14.8 $\pm$ 1.6	0.52 $\pm$ 0.1	10.4 $\pm$ 5.6	n=4
12 ^c n=5	7.4 $\pm$ 1.4	0.44 $\pm$ 0.1	8.4 $\pm$ 5.5	
24 ^d n=5	4.8 $\pm$ 0.6	0.43 $\pm$ 0.2	14.6 $\pm$ 8.6	

ELF-Konzentration < Plasma-Konz., Anreicherung in Alveolarzellen

Nicasio et al. 2009 AAC 53:1218-1220.

Lungenpenetration von Micafungin

Micafungin im alveolären Flüssigkeitsfilm n. LuTX
150 mg Einzeldosis n=20



Für *A. fumigatus*,
MIC 90=0.0156 µg/ml

AUC₀₋₂₄ / MIC90 Ratios

Plasma	5,077
ELF	923
ACs	13,340

	Plasma	ACs	ELF
Day 1			
AUC _{0-24h} (mg.h.L ⁻¹)	79.2 ± 4.4*	208.1 ± 275.6	14.4 ± 18.4
AUC ratios**	NA	2.65 ± 3.51	0.18 ± 0.23

Micafungin in diversen Kompartimenten



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Kompartiment	n	MICA-Konzentration	
Pankreas-Pseudozyste	1	0.38 µg/ml	Lat et al. 2010 AAC 54:943-4
Liquor	7	1.9 µg/ml	Yamada et al. 2011 J Infect Chemother. 17:731-4
Pleuraerguss		0.7 µg/ml	
Aszites		1.0 µg/ml	
Wundsekret		4.4 µg/ml	
Wundkruste	1 Verbrennung 3	C _{min} SD 4 St.st. 14.8 µg/ml C _{min} SD 1.4 St.st. 6.7 µg/ml	Sasaki et al. 2012 AAC 56:1113-5 Sasaki et al. 2014 Eur J Drug Metab Pharmacokinet.;39:9 3-7
Galle	1	C _{min} 1.9 µg/ml	Maruyama et al. 2009 J Infect. 58:315-6

Micafungin im Auge

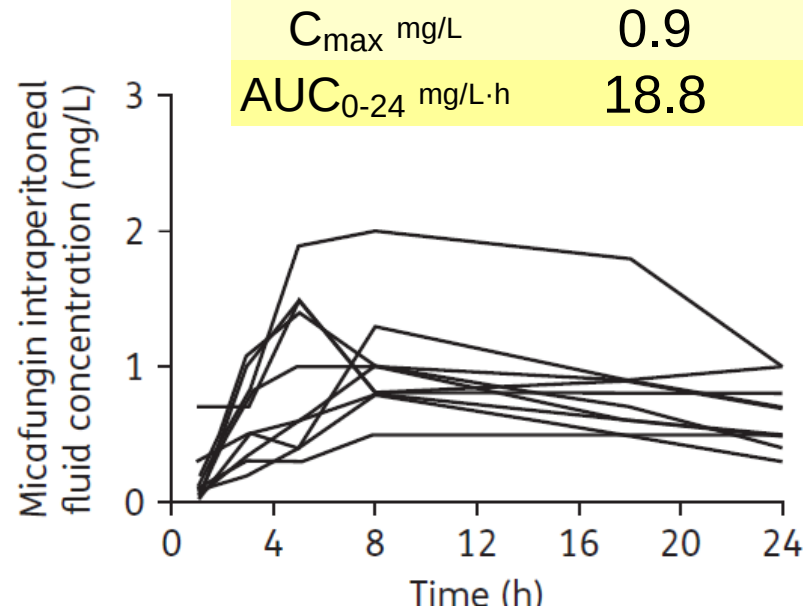
7 Patienten nach Vitrektomie, Dosis 150-300 mg

Kompartiment	n	MICA-Konzentration
Plasma	7	21.02 µg/ml
Glaskörper	7 / 1	0.10 µg/ml / 0.043
Kammerwasser	7 / 1	0.08 µg/ml / 0.026
Cornea	7	1.60-5.99 µg/ml
Iris	1	14.65 µg/ml
Retina	1	1.20 µg/ml
Choroidea	1	5.85 µg/ml

Mochizuki et al. 2011 J Ocul Pharmacol Ther. 27:531-3; Mochizuki et al. 2013 AAC57:4027-30

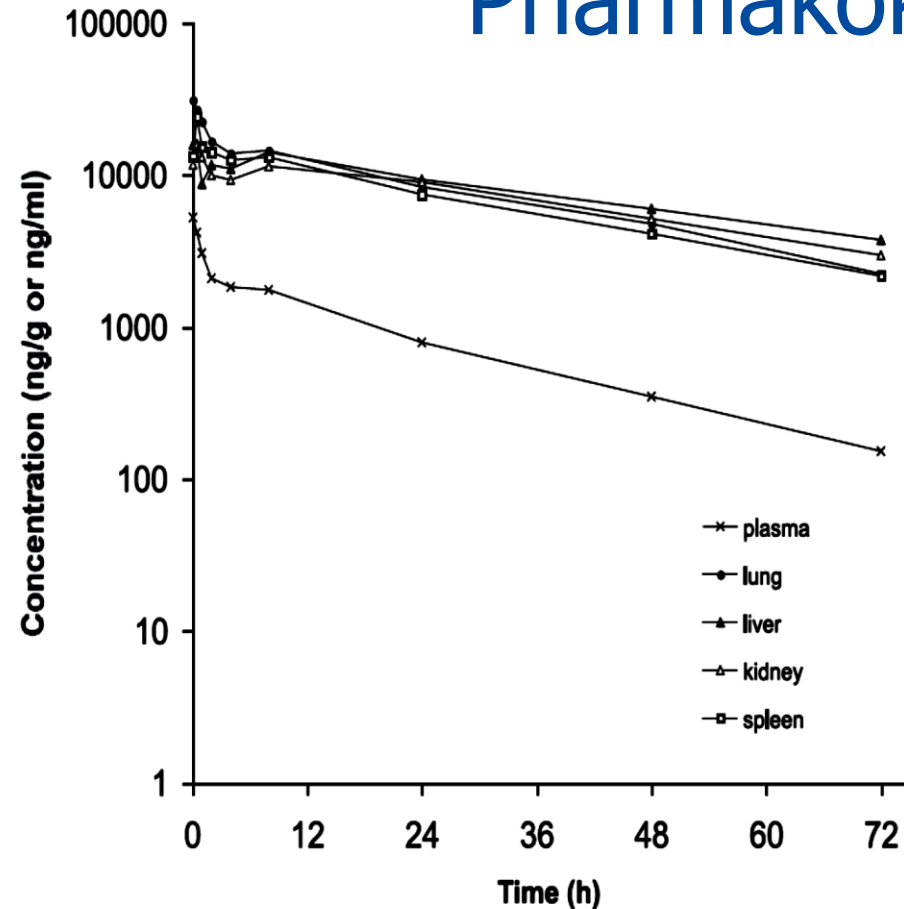
Micafungin in Peritoneal-Flüssigkeit

Micafungin in peritoneal fluid of
pts. with peritonitis, d 1.
Median, n=10



Grau et al. 2015 JAC.70:2854-61

Anidulafungin Gewebe- Pharmakokinetik in Ratten



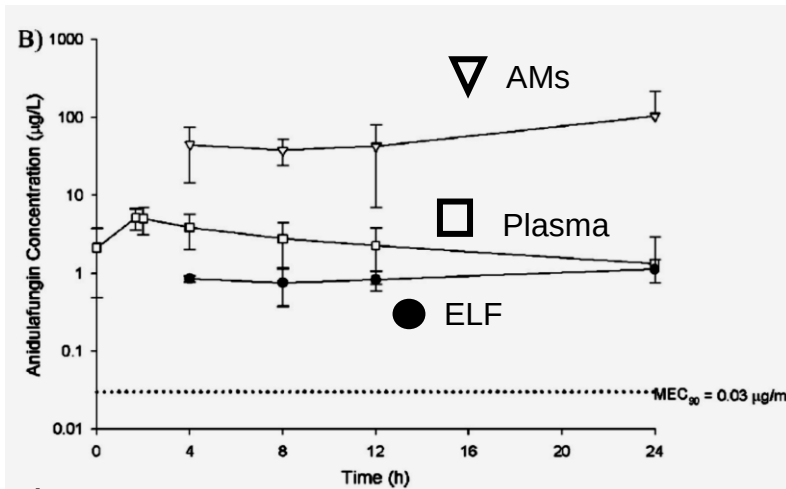
Tissue	$C_{\max}$ ($\mu\text{g/g}$ or $\mu\text{g/ml}$)	$t_{\max}$ (h)	AUC_{0-24} ($\mu\text{g} \cdot \text{h/g}$ or $\mu\text{g} \cdot \text{h/ml}$)	$AUC_{0-\infty}$ ($\mu\text{g} \cdot \text{h/g}$ or $\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2}$ (h)
Plasma	5.25	0.083	57.73	61.64	18.5
Liver	15.86	0.083	586.44	767.22	33.9
Lung	31.11	0.083	557.77	638.21	24.4
Kidney	16.09	0.5	517.32	658.93	32.3
Spleen	24.20	0.5	490.36	567.95	25.2
Skin	4.02	0.5	102.72	124.11	28.2
Muscle (quadriceps)	3.84	0.5	54.33	57.35	17.1

^a Parameters of anidulafungin were determined following a single intravenous bolus dose of 5 mg/kg of [^{14}C]anidulafungin in male F344 rats. Parameters were derived based on a composite, mean concentration-time profile with $n = 3$ rats per sampling time.

Damle et al. 2008 AAC 2008 52:2673-6.

Lungenpenetration von Anidulafungin

Anidulafungin-Steady-State-Konzentrationen (d3) im
alveolären Flüssigkeitsfilm von Probanden ($\mu\text{g/ml}$)
LD = 1 x 200 mg MD = 1 x 100 mg



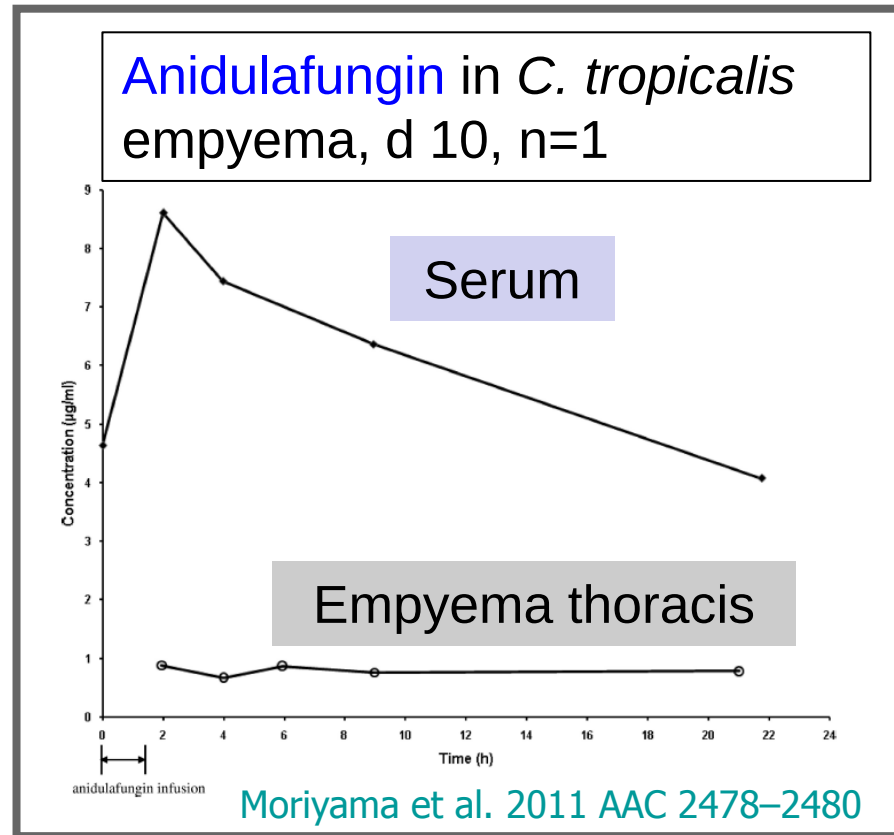
Time of BAL (h)	Anidulafungin ($\mu\text{g/ml}$) ^a		
	Plasma	ELF	AMs
4	6.0 (1.5)	0.9 (0.1)	44.6 (30.1)
8	5.1 (0.8)	0.8 (0.4)	37.9 (13.8)
12	4.4 (1.0)	0.8 (0.2)	42.7 (35.8)
24	3.0 (0.5)	1.1 (0.4)	103.1 (110.7)

n=5
n=5
n=5
n=5

Plasma-PK

$C_{\max}$ ($\mu\text{g/ml}$)	$T_{\max}$ (h)	$\text{AUC}_{0-\tau}$ ($\mu\text{g} \cdot \text{h/ml}$)	V_{ss} (liters)	CL (liters/h)	$t_{1/2}$ (h)
6.6 (1.6)	1.9 (0.2)	101.0 (21.8)	30.8 (6.8)	17.1 (3.1)	20.8 (3.1)

Anidulafungin in Pleuraempyem



In empyema and peritonitis, echinocandin concentrations were similar to those in un-inflamed body fluids.

ANID in Aszites und in Pleuraerguss

Pharmakokinetik

Sample	Patient	$C_{\max}$ ($\mu\text{g/ml}$)	$T_{\max}$ (h)	AUC_{0-24} ($\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2}$ (h)	PR
Ascites fluid	2	0.98	4	17.5	26	0.37
	3	0.34	12	7.0	162	0.07
Pleural effusion	9	0.99	4	21.4	362	0.18
Sample	Patient	$C_{\max}$ ($\mu\text{g/ml}$)	$T_{\max}$ (h)	AUC_{0-n} ($\mu\text{g} \cdot \text{h/ml}$)	Sampling period (h)	PR
Ascites fluid	1	0.58	4	5.6	12	0.12
	4	0.99	4	12.1	18	0.20
Pleural effusion	8	2.02	14	16.8	14	0.17

R. Welte et al. 2018 AAC Feb 12. [Epub ahead of print]

ANID in Aszites und in Pleuraerguss

Einzelpatienten

Patient	Concn of anidulafungin ($\mu\text{g/ml}$) in:			Time from infusion (h)	Day of anidulafungin treatment	PR
	Ascites fluid	Pleural effusion	Plasma			
4	0.28		2.88	8.0	3	0.10
5	0.30	R. Welte et al. 2018 AAC Feb 12. [Epub ahead of print]	5.39	5.5	5	0.06
6	0.32		4.69	8.8	2	0.07
7	0.45		2.15	18.0	7	0.21
7		0.45	2.48	20.0	21	0.18
9		0.88	4.50	9.5	4	0.20
10		0.32	4.18	4.0	12	0.08

ANID Konzentrationen im Aszites $< 1 \mu\text{g/ml}$, 6-37% des Plasmaspiegels, im Pleuraerguss $\leq 2.02 \mu\text{g/ml}$, 8-20% des Plasmaspiegels

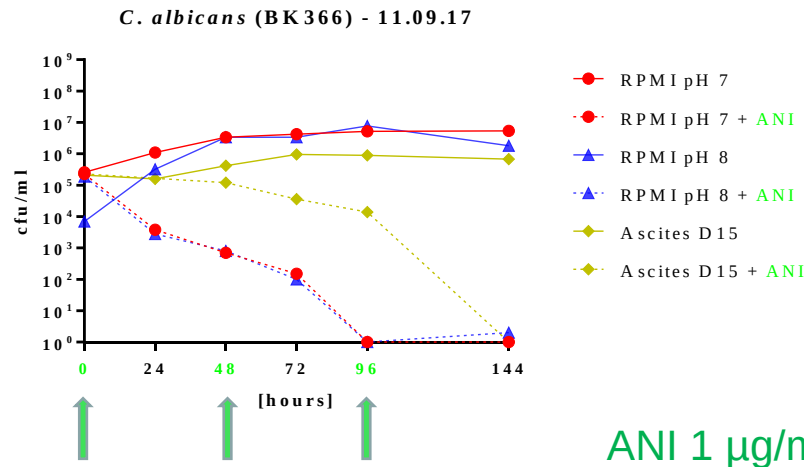
R. Welte et al. 2018 AAC Feb 12. [Epub ahead of print]

Anidulafungin-Pharmakodynamik in Aszites: *in-vitro* Simulation

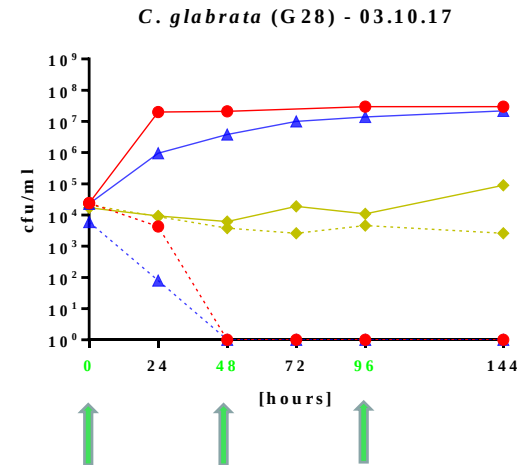


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Candida-Wachstum in Medium und in Aszites



Verzögertes Absterben in Aszites unter ANI



Geringes Wachstum in Aszites, geringer Effekt von ANI

Anidulafungin im Gehirn: *Autopsie-Proben*



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Pt.	Alter, Geschl.	Gewicht	Therapie- dauer	kum. Dosis mg	Intervall letzte Dosis - Tod	Intervall Tod – Autopsie	ANID Konz. µg/g
1	74 J, w	135 kg	6 d	700	32 h	14 h	0.29
2	68 J, w	85 kg	17 d	1800	313 h	24.5 h	0.05
3	45 J, w	43 kg	14 d	1500	11.5 h	15 h	1.90
4	70 J, w	50 kg	11 d	1200	29 h	21 h	1.55

Marx et al. 2017 Intrinsic Activity 5, Suppl A2.5

Gewebepermeation von Antimykotika

Compound	Eye			Skin			Vagina		Heart		Liver	Pancreas	Kidney	Bone		Prostate	Brain		Lung			Spleen	Muscle
	Aqueous	Vitreous	Cornea	Tissue	Interstitial fluid	Nail	Tissue	Fluid	Tissue	Pericardial fluid				Tissue	Synovial fluid		Tissue	CSF	Tissue	Alveolar cells	ELF		
Fluconazole	X	X	O	X	X	X	X	X	X	X	X	X	X	X	O	X	X	X	X		O	X	X
Itraconazole	O X	O ² X	O	X	X	X	X	X	X		X	O	X	X	X	X	O	X	X	X ⁸	X	X	X
Voriconazole	X	X		O	O				X	X ⁰	X	X	X	X	X		X	X	X	X	X ⁸	X	O
Posaconazole		X		X		X											O	X		X	X		
AmBd	X	X	X						O X ⁰		X	X	X	O	X		X	X	O	O ⁴	X ³	O	X
ABLC	O ²	O ²							X		X		X	O			O	X	X ⁰		X ⁸	X	X ²
L-AMB	O ²	O ²	O ²	X ⁰					O	X	X ⁰		X ⁰	O			X	X	X		X ⁸	X	X ²
5-FC	O	X		O					O		O		O	O	O		O	X	X	O ⁴		O ³	O
Anidulafungin	O	O		O					O		O		O	O			O	O	O	O	X	X	O
Caspofungin	X	O ²	X	O ²					O		O		O				O	X	O	X		O	O
Micafungin	O ²	O ²		X ⁰							O	O	X ⁸	O	O		X	X	X	O	X	X ⁸	O

$C_{Tiss} > 5 \times C_{PI}$

$5 \times \geq C_{Tiss} > 0.5 \times C_{PI}$

$C_{Tiss} \leq 0.5 \times C_{PI}$

Zusammenfassung

- Die höchsten AMB Spiegel finden sich in Leber u. Milz, mittlere in Lunge u. Niere, niedrige in Myokard und Gehirn, ELF, Aszites u. Pleuraerguss, nur mit AMBdc ausreichende Spiegel in Harn u. Galle
- 5-FC penetriert gut in die meisten Gewebe inkl. Knochen, Harn u. Hirn
- Ebenso FLU u. VORI, FLU auch in Harn u. Galle, variabel in den Liquor
- ITRA u. POSA akkumulieren in Alveolarzellen, POSA in Zellmembranen, erreichen niedrige Spiegel in Hirn u. Liquor, or. Susp. wenig resorbiert
- ECHI erreichen hohe Spiegel in Leber, Lunge u. Niere, geringe in Hirn, Auge, Aszites, Galle, Harn, Pleuraerguss u. ELF, Anreicherung in Alveolarzellen
- „Problem-Kompartimente“ sind ZNS, Auge, Aszites, Pleuraflüssigkeit, Galle, Harn, Knochen u. Wunden.
- Methodische Limitationen sind bei der Interpretation von Gewebe-Penetrationsdaten zu berücksichtigen.