

Nephrotoxicity of Amphotericin B in 10% Lipid Emulsion for Treatment of Invasive Fungal infections in Children.



Researchers:

Santimaleeworagun W *, Pruekprasert P **
Apiromrak P ***, Pattharachayakul S ****

* Department of Pharmacy, Faculty of Pharmacy, Silpakorn University
** Department of Pediatrics, Faculty of Medicine, Prince of Songkla University
*** Department of Pharmacy, Songklanagarind Hospital
**** Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University

Backgrounds:

- Amphotericin B (AmB) is one among therapeutic choices for fungal infections
- Its major adverse reaction, nephrotoxicity (incidence 30-80 %)
- Irreversible renal insufficiency

Harbarth S et al. *The American Journal of medicine*. 2001 Nov;111(7):528-34.

Benson, J. M. and Nahata, M. C. (1989), *Antimicrob Agents Chemother*, 33 (11), 1989-93.

Miller, R. P. and Bates, J. H. (1969), *Ann Intern Med*, 71 (6), 1089-95.

Bates DW et al. *Clin Infect Dis*. 2001 Mar 1;32(5):686-93.

Backgrounds:

- Result in early discontinue Amphotericin B
- Increase in length of stay
- Several strategies have been applied to reduce this problem

Harbarth S et al. *The American journal of medicine*. 2001 Nov;111(7):528-34.

Benson, J. M. and Nahata, M. C. (1989), *Antimicrob Agents Chemother*, 33 (11), 1989-93.

Miller, R. P. and Bates, J. H. (1969), *Ann Intern Med*, 71 (6), 1089-95.

Bates DW et al. *Clin Infect Dis*. 2001 Mar 1;32(5):686-93.

Backgrounds: (cont.)

- The dispersion of amphotericin B in 10% lipid emulsion
- However; the study in children was limited
- In Songklanagarind Hospital, a university-affiliated medical school, this preparation have been used since 2005, but its nephrotoxic outcome never been evaluated.



Amphotericin B
in 10 % lipid
emulsion

Objective:

To evaluate the prevalence of nephrotoxicity caused by AmB in 10% lipid emulsion experienced by pediatric patients with invasive fungal infections.

Method:

- Retrospective medical record review in pediatric patients with fungal infection (empiric or documented therapy) during November 2005-June 2007

- Age \leq 15 years old
- Received \geq 7 days



The medical records of patients were reviewed:

- Age
- Gender
- Hospital ward
- Presence of underlying diseases
- Scr, Electrolytes
- The source of infections
- Diagnosis of infections

Definition: Nephrotoxicity

Serum creatinine concentration \geq 2 times of baselines.

วันที่รับ	วันที่รับ-เวลา	วันที่	ตรวจพบ	ค่า	หน่วย	หมายเหตุ
1	03 มิ.ย. 50	2007-06-03/1/374	211	4		
2	06 มิ.ย. 50	2007-06-06/3/122	211	38		
3	06 มิ.ย. 50	2007-06-06/3/267	211	54		
				12.670		
1	03 มิ.ย. 50	2007-06-03/1/373	211	8		F3 ผลตรวจค่า
2	03 มิ.ย. 50	2007-06-03/1/373	211	-8		F4 ผลตรวจค่า
3	03 มิ.ย. 50	2007-06-03/1/374	211	4		F5 ผลตรวจค่า
4	03 มิ.ย. 50	2007-06-03/1/375	211	53		F6 ผลตรวจค่า
5	03 มิ.ย. 50	2007-06-03/1/375	211	-59		F7 ผลตรวจค่า
6	03 มิ.ย. 50	2007-06-03/1/376	211	471		F8 ผลตรวจค่า
				12.670		

Results:

- Nineteen patients received AmB in lipid emulsion
- Median age : 64.5 months (IQR = 6-135.5)
- Majority of the patients (63.2%) were female.
- Median duration of the AmB treatment: 12 days (IQR = 8-16)
- 31.6% of patients were admitted at ICU
- 42.1% of patients had hematologic malignancy and had neutropenia
- 68.4% were treated as empirical therapy

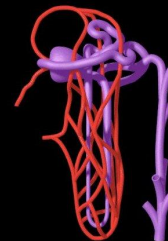
Results:

- 5.3 % of patients experienced nephrotoxicity
- Median serum creatinine at baseline and at the end of treatment

0.45 (IQR =0.27-0.51) and
0.39 (IQR =0.3-0.57) mg % ($p = 0.732$)

The baseline of serum potassium and bicarbonate were not significantly different between before and after of treatment

Median = 3.41 and 3.23 mEq/mL; $p = 0.398$
Median = 23.0 and 21.0 mEq/mL; $p = 0.173$



Conclusions & Discussions:

- In this study, the prevalence of nephrotoxicity was 5.3% in children
- The limitations of this study
 - Small sample size
 - No control gr. (AmB in D5W) to compare the findings
 - Efficacy of this regimen
 - The retrospective study

Thank you
for
Your Attention



AmB in 10 % Lipid emulsion

- 1 vial of AmB powder dissolved with 10 mL of steriled water for injection (concentration 5 mg/mL: Solⁿ A)

- To Aliquot the volume of Solⁿ A based on a requirement of AmB dosage (Dose of AmB is B mg)

- Disperse Solⁿ A with lipid emulsion in proportion (1:2) B mg (Solⁿ A) + Lipid emulsion 2 x B mL.

Ex: Patient weighs 30 kg. ; dose of AmB is 30 mg/day

AmB is 30 mg/day

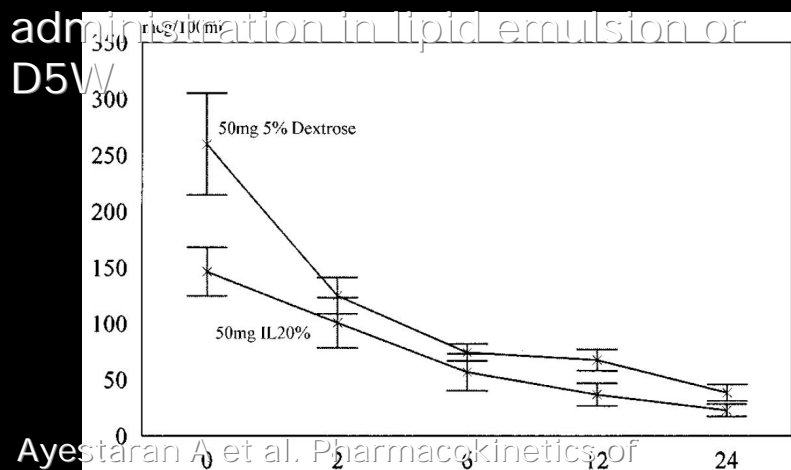
6 mL of Solⁿ A

AmB is 30 mg/day

60 mL of Lipid emulsion

6 mL of Solⁿ A mixed with 6 mL of Solⁿ A (~ 0.5 mg/mL)

Fig: Mean plasma amphotericin B concentration versus time after



Ayestaran A et al. Pharmacokinetics of conventional formulation versus fat emulsion formulation of amphotericin B in a group of patients with neutropenia. Antimicrobial agents and chemotherapy. 1996

Table: Comparative analysis of AmB

Formulation	C_{max} ($\mu\text{g/ml}$)	V (liters/kg)	Clearance (ml/min)	$t_{1/2\beta}$ (h)
AmB/G	2.94 ± 2.18	1.99 ± 1.41	0.88 ± 0.51	27.5 ± 17.7
AmB/L	1.30 ± 0.59	2.97 ± 2.78	1.49 ± 1.12	27.1 ± 21.0
<i>P</i> values	0.008	NS	NS	NS

The parameters were compared by use of the Wilcoxon test. Antimicrobial agents and chemotherapy. 1997 Apr;41(4):728-32.

Researcher	Description	Design	N (T/C)	Results
Pascual B et al. 1995	Amphotericin B 1 mg/kg/day in neutropenic patients.	RCT	10 / 10	Final Serum creatinine ($\mu\text{mol/L}$) 123.8 ± 34.4 VS 84.9 ± 23.9 (<i>p</i> -value = 0.047)
Nucci M et al. 1999	Amphotericin B patients.	RCT	33 / 28	Neutropenia (%) 50 VS 21 (<i>p</i> -value = 0.44)
Schoffski P et al. 1998	Amphotericin B 0.75 mg/kg/d	RCT	24 / 27	Creatinine clearance; ml/min (mean) (SD)

Researcher	Description	Design	N (T/ C)	Results
Moreau P et al. 1992	Amphotericin B 0.7-1 mg/kg/d	RCT	16	(Rising in 100%)
Caillot D et al. 1994	Amphotericin B 0.5 mg/kg/d	RCT	104 ± 49 (21)	106 ± 37 (21) 0.05
	Amphotericin B 1 mg/kg/d	RCT	62 ± 29 (19)	95 ± 46 (21) 0.01
	Amphotericin B 2 mg/kg/d	RCT	23 ± 6 (14)	40 ± 10 (19) 0.04
	Amphotericin B 4 mg/kg/d	RCT	24 ± 7 (12)	28 ± 8 (14) 0.00

Researcher	Description	Design	N (T/ C)	Results
Barquist E et al. 1999	0.5 mg/kg/d	RCT	18	Change in creatinine clearance (final / baseline):
	1.0 mg/kg/d	RCT	30	lipid VS dextrose
Sorkine P et al. 1996	Amphotericin B 0.5 mg/kg/d	RCT	30	Nephrotoxicity (p = 0.38)
	Amphotericin B 1 mg/kg/d	RCT	30	66.7 VS 20

Researcher	Description	Design	N (T/C)	Results
Friedlich et al. 1997	low-birth-weight (≤ 1250 g)	Cohort	23	1/23 (>0.4 mg/dL)
Nath CE et al. 1999	Amphotericin B in children with malignant disease.	RCT	20 / 15	Non significant of %changes in serum creatinine (final-baseline)
Nucci M et al.	Neutropenic	RCT	33 / 28	Rising in 50% (baseline) 3.32 VS 1.50