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A Comparison of Amphotericin B Deoxycholate (D-AMB) versus Liposomal Amphotericin B (L-AMB) in Neonates: Is Newer Better?

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Abstract

Background:

Nephrotoxicity (NT) associated with D-AMB use is well documented in adults and occurs less frequently with the lipid formulations of amphotericin B (AMB). However, the incidence of NT associated with the various AMB products used in neonates (NEO) is poorly defined. The reported incidence of NT associated with AMB use in NEO ranges from 0-60%. The purpose of this study was to evaluate NT associated with D-AMB and L-AMB use in NEO.

Methods:

This is a retrospective analysis of NEO receiving at least one dose of either D-AMB or L-AMB at a single center between 1999 and 2010. Demographics including gestational age, birth weight, Apgar score at 1 min, and baseline Scr were evaluated. NEO with a baseline Scr > 1 mg/dL were excluded from this analysis. NT was defined as urine output < 1 mL/kg/hr, or an increase in SCr ≥ 0.3 mg/dL, or an increase in Scr ≥ 50% from baseline.

Results:

94 NEO received either D-AMB or L-AMB during the study period; 75 met the inclusion criteria. From 1999-2006, only 12/60 (20%) of all AMB products prescribed were L-AMB, whereas from 2006-2010, this had increased to 13/15 (87%). 54/75 (72%) NEO were premature with extremely low birth weight. Baseline characteristics were not different between D-AMB and L-AMB groups. No difference was found in NT defined by any of the previously described criteria. Incidence of NT ranged from 16% to 28%. Three NEO switched to L-AMB due to NT. All NEO had resolution of NT defined by returning to baseline renal function. No significant difference was found in daily fluid intake between D-AMB (141±16 ml/kg/day) and L-AMB (137±5ml/kg/day). *Candida* spp was isolated in 17/50 (34%) of the cases in D-AMB group and 10/25 (40%) of the cases in L-AMB group.

Conclusion:

Regardless of definition for renal dysfunction we did not find a difference in the incidence of NT between D-AMB and L-AMB in our population. Interestingly, similar to other recent reports in the US and Europe we noticed a trend for the increased use of the L-AMB compared to D-AMB. From previous reports and our data it would seem that increased L-AMB has occurred without evidence of increased efficacy or safety. The use of L-AMB instead of D-AMB to prevent NT in NEO seems unwarranted.

Introduction

- Amphotericin B (AMB) is a broad-spectrum agent that is associated with significant nephrotoxicity (NT) in adults.
- Liposomal formulations of AMB (L-AMB) was developed to address concerns of NT based mostly on evidence in adult population.
- The incidence of NT due to AMB may not be significant in pediatric patients.[1-2]
- Only two neonatal studies compared D-AMB and L-AMB nephrotoxicity which have revealed conflicting results.[3-4]

Acknowledgement

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References

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Objective

To evaluate nephrotoxicity associated with D-AMB and L-AMB use in neonates

Methods

- A retrospective analysis conducted between January 1999 and April 2011 at John H. Stroger Jr. Hospital of Cook County

- **Inclusion criteria:**
  - Neonates: <30 days old
  - Received at least one dose of amphotericin B
  - Survived ≥ 24 hours after initial AMB dose
- **Exclusion criteria:**
  - Baseline SCr > 1 mg/dL
- **Primary outcome:**
  - Nephrotoxicity defined as:
    - Urine output <1 ml/kg/day or
    - Absolute increase from baseline serum creatinine concentration of ≥0.3 mg/dL or
    - ≥50% increase in Scr from baseline
- **Statistical analysis**
  - Chi-squared and Fischer's exact tests (categorical data)
  - Student *t*-tests (continuous data).
  - *P* <0.05 was considered statistically significant.

Results

Figure 1: Enrollment

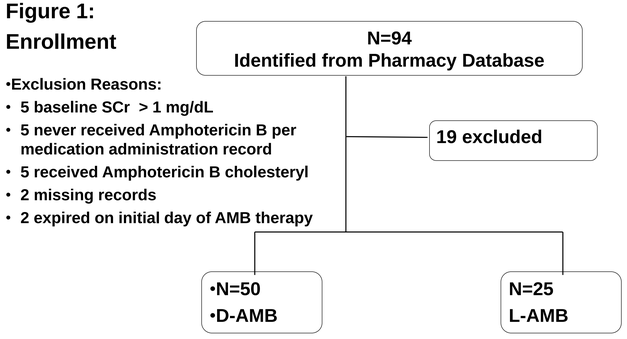
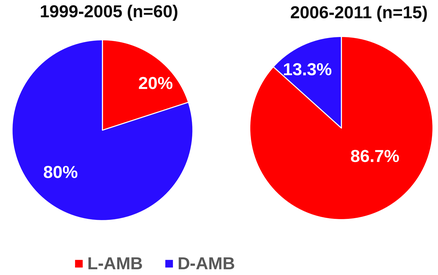


Figure 2:Amphotericin B Product Use in Neonates



Results

Table 1. Baseline Characteristics

	D-AMB (n=50)	L-AMB (n=25)
Prematurity (Gestational age <37 weeks)	48(96%)	23 (92%)
Mean gestational Age (wks±SD)	27.5±3.3	27.4±4.1
Birth weight		
Normal weight (>2500g) (%)	3 (6%)	2 (8 %)
VLBW (<1500 g) (%)	15 (30 %)	2 (8%)
ELBW (<1000 g) (%)	32 (64%)	21 (84%)
Birth weight (kg±SD)	1.03±0.57	1.02±1.01
Male	33 (63%)	18 (72%)
Race/Ethnicity		
White	4	2
African American	23	14
Hispanic	11	2
Asian	1	0
Unknown	11	7
Apgar score at 1 min (mean±SD)	3.96 ± 0.31	3.16 ± 0.38
Medical History		
RDS	38	21
PDA	21	17
NEC	3	4
Thrombocytopenia	10	10
Suspected sepsis	21	12
IVH	8	9
Hyperbilirubenemia	32	23
Concomitant phototherapy	7 (14%)	2 (8%)
Concomitant TPN	31 (62%)	23 (92%) *
Daily fluid intake (ml/kg/day) (mean±SD)	141.1±15.6	137.5±15.5
SCr (mg/dL) (mean±SD)	0.65±0.24	0.75±0.17

RDS: Respiratory distress syndrome; PDA, Patent ductus arteriosus; NEC, Necrotizing enterocolitis; IVH, Intraventricular hemorrhage; TPN, Total parental nutrition, * P<0.05, comparing D-AMB versus L-AMB

Table 2: Pathogens Isolated

	D-AMB (50)	L-AMB (25)
Candida		
-albicans	14	6
-glabrata	0	1
-parapsilosis	3	2
-guilliermondii	0	1
-lucitaniae	1	0

Table 3: Amphotericn B products

Median, IQR	D-AMB		L-AMB	
	NT	No-NT	NT	No-NT
Starting dose (mg/kg/day)	1 (0.5, 1)	0.9(0.5, 1)	3 (1, 5)	4 (1.1, 5)
Duration (days)	7 (4, 10)	7 (5.8, 14)	7 (5.5, 9.25)	7 (5, 9.5)
Cumulative dose (mg)	4 (2, 6.5)	6.5 (3, 11.8)	13 (6.5, 18.7)	20 (6.7, 34)

NT: nephrotoxicity

Results

Figure 3: Incidence of Nephrotoxicity

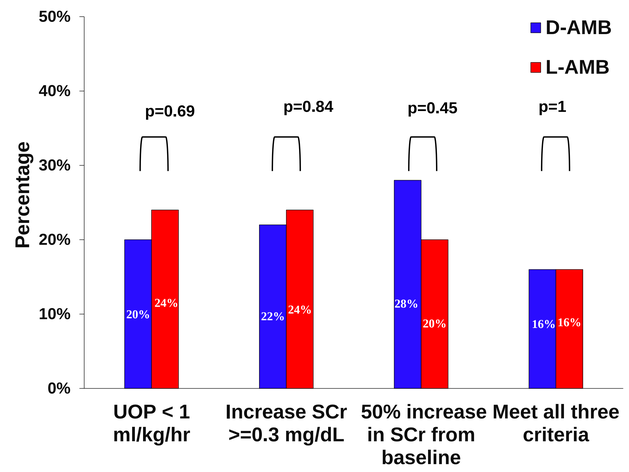


Table 4: Nephrotoxicity

	D-AMB (10)	L-AMB (6)
Baseline SCr (mg/dL) (mean±SD)	0.73±0.27	0.85±0.1
Daily fluid intake (mL/kg/day) (mean±SD)	142±24	137±11
Concomitant nephrotoxins		
Vancomycin	4	4
Gentamicin	1	2
Indomethacin	1	1
Time to nephrotoxicity (days) (median, IQR)	4 (3, 5.5)	4 (2.5, 5.5)
Resolution (%)	100%	100%
Time to resolution (days)(median, IQR)	4 (3.5, 4.5)	3.5 (2.25, 4)
D-AMB changed to L-AMB	3	--

Table 4 is generated based on the definition of UOP<1 ml/kg/hr

Summary and Conclusions

- No difference in the incidence of nephrotoxicity between D-AMB and L-AMB
- Majority of patients included were high risk premature neonates
- No difference in baseline serum creatinine, daily fluid intake and cumulative dose of amphotericin in neonates who developed nephrotoxicity
- Increased L-AMB use has occurred without evidence of increased safety
- The use of L-AMB instead of D-AMB to prevent nephrotoxicity in neonates seems unwarranted