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Review of Safety Outcomes of Multiple Daily Dosing of Amikacin in Paediatric Febrile Neutropenic Patients with Cancer

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Background

Paediatric oncology patients with febrile neutropenia (FN) are at high risk of developing life-threatening infections1. In KK Women's and Children's Hospital (KKH), they are empirically treated with amikacin 7.5 mg/kg/dose every 12 hours if persistently febrile after treatment with piperacillin-tazobactam2. With the aim of proposing evidence-based recommendations to optimize the dosing of amikacin in the paediatric FN population, we studied the safety and efficacy of amikacin in this population.

Objectives

Primary: Percentage of patients who achieved amikacin trough levels within acceptable range (< 10 mcg/mL) after the first dose.

Secondary:

- Documented toxicities during amikacin treatment
- Percentage of patients who achieve defervescence within 3 days of initiating amikacin
- Days of amikacin therapy (DOT)
- 30-day infection-related mortality
- Number of sets of amikacin levels taken for therapeutic drug monitoring (TDM)

Methods

A retrospective medical record review of patients admitted under the Haematology-Oncology service of KKH was conducted. Patients were enrolled more than once if they had a distinct episode of FN and prior antibiotic treatment that had been completed at least 2 weeks earlier.

Serum levels were drawn after the first dose. True peak (C_{max}) and trough (C_{min}) levels were extrapolated using APK©, a pharmacokinetics software. Amikacin were adjusted as necessary to achieve the following targets: C_{max} of 30 – 40 mcg/mL and C_{min} of < 10 mcg/mL.

Inclusion criteria	• Required amikacin for the empiric treatment of FN from January 2013 to December 2014. FN is defined by the KKH as follows: i. Absolute neutrophil count (ANC) < 1.0 x 10^9/L or in a patient whose ANC is expected to fall < 1.0 x 10^9/L in the next 48 hours and ii. Fever defined as a single temperature ≥ 38.5ºC or two episodes of ≥ 38ºC taken 30 minutes apart. • Patient's age was ≥ 1 year to < 18 years old • First-dose amikacin TDM was performed
Exclusion criteria	• Documented infection with positive culture and sensitivity results within the past 30 days • Critically ill patients • Unstable renal function or renal impairment • Received amikacin within the last 14 days

Results

Forty episodes in 26 patients were analyzed.

Table 1. Amikacin pharmacokinetic parameters after the first dose.

Parameter	
Median no. of pairs of serum amikacin levels taken per FN episode (range)	2 (1-5)
C_{min} (mcg/mL)	1.2 (0.57)
% C_{min} < 10 mcg/mL	100%
C_{max} (mcg/mL)	15.1 (5.0)
% C_{max} 30–40 mcg/mL	0%
Median time to achieve C_{max} 30–40 mcg/mL, days (range)	2 (1-4)
Achieved C_{max} 30–40 mcg/mL within 3 days (no. (%))	29 (72.5)

NOTE. Data are mean (±SD), unless otherwise indicated.

Table 2. Treatment outcomes.

Clinical characteristics	FN episodes
Documented nephrotoxicity/ototoxicity	0
Mean maximal percent increase in sCr from baseline over treatment course (±SD)	3.73 (6.25)
Reasons for discontinuation of amikacin (no. (%))	
Defervescence	39 (97.5)
No indication for antibiotics (non-bacterial)	1 (2.5)
Time to defervescence after initiating amikacin, days	1 (1-10)
Defervescence within 3 days (no. (%))	33 (82.5)
Duration of hospital stay, days	8 (5-47)
Duration of amikacin therapy, days	4 (2-9)
Thirty-day mortality rate since onset of FN	0

NOTE. Data are median (range), unless otherwise indicated. sCr, serum creatinine level.

Conclusion and Future Work

The use of multiple daily dosing of amikacin in combination with piperacillin-tazobactam was safe and effective for the treatment of paediatric oncology patients with febrile neutropenia, but the initial dose of IV amikacin 7.5 mg/kg was insufficient to achieve the target C_{max} of 30 – 40 mcg/mL. It is of utmost importance to derive an optimal starting dose of amikacin so as to achieve clinical outcomes more rapidly[3].

References

1. Etiology and clinical course of febrile neutropenia in children with cancer. *Journal of pediatric hematology/oncology*. 2009.
2. KKH. Fever in the Immunocompromised Child Guidelines. Singapore: KKH; 2014
3. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis.* 1987