Nephrotoxicity of once-daily dosing Gentamicin in Children

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Background/Objectives

- ✓ The aminoglycosides once-daily dosing (ODD) was increasingly reported in favor of efficacy and safety among adults and neonates compared to traditional three-times daily dosing. Experiences in aminoglycosides ODD are still limited in children outside of neonates.
- ✓ Our aim of the survey was to evaluate nephrotoxicity in children who were treated with gentamicin ODD.

Methods

- Design: A single-center, retrospective cohort
- Site: Tokyo Metropolitan Children's Medical Center, Tokyo, Japan.
- Period: April, 2010 - March, 2017
- Inclusion criteria: Patients who were hospitalized at our hospital and treated with gentamicin ODD.
- Primary outcome: **Nephrotoxicity during and after treatment with gentamicin**
 - Nephrotoxicity was evaluated according to the staging 1-3 of KDIGO guideline for acute kidney injury. (Table 3)

Results

A total of **268** cases with gentamicin ODD were observed.

Table 1: Demographic characteristics of patients at enrolment

N=268	
Age, month	21 [5-100]
Male	142 (53.0)
Reason for gentamicin	
Urinary tract infection	149 (55.6)
Bacteremia, Sepsis	31 (11.6)
Cholangitis	29 (10.8)
Prophylaxis in surgery of biliary atresia	16 (6.0)
Administration of gentamicin	
Duration, days	5 [3-7]
Trough initially tested, µg/mL	0.53 [0.33-0.76]

Data are presented as n (%) or median [interquartile range].
ODD=Once-daily dose, AKI=Acute kidney injury,
UTI=Urinary Tract Infection, ICU=Intensive care unit,
GP=General pediatrics

Trough level exceeded safe range of 1 µg/mL was observed in **25** cases (9.3%) . Among them, no patients remained the acute kidney injury.

Table 2: Patients whose initial trough was over safety range

N=25	
Age, month	8 [3-53]
Male	12 (48.0)
Underlying diagnosis	
Cardiac	14*
Neurological	6 (4 individuals)
Gastrointestinal	5*
Reason for gentamicin	
Urinary tract infection	14
Peritonitis, Ileus	5
Administration of gentamicin	
Duration, days	4 [2-6]
Trough initially tested, µg/mL	1.46 [1.10-2.46]

*One patient is overlapped.

A total of **12** cases with Stage 1 and 2 AKI during or after treatment were observed.

Table 3: AKI definition

Stage	Serum creatinine	
	Increase compared to baseline (within the prior 7 days)	Increase within 48 hours
1	1.5 ~ 1.9 times	≥0.3mg/dL
2	2.0 ~ 2.9 times	
3	3.0 times or initiation of renal replacement therapy	≥4.0mg/dL

Table 4: Patients with gentamicin-related nephrotoxicity

Ward	Age, month	Underlying diagnosis	Reason for gentamicin	Initial trough, µg/mL	Duration of gentamicin, days	Nephrotoxicity, Stage	
						During treatment	After treatment
ICU	1	Cardiac	UTI	1.02	5	1, Day7	0
	51	Cardiac	UTI	0.31	3	1, Day 4	0
	11	Cardiac	UTI	2.58	1	0	2, +7days
	1	Urological	UTI	0.51	4	1, Day8	0
	3	Cardiac	Bacteremia	1.31	16	0	2, +7days
	3	Cardiac	Bacteremia	0.45	40	1, Day7	0
	4	Cardiac	Peritonitis	0.91	7	1, Day5	1, +7days
	1	Malrotation	Peritonitis	1.08	3	1, Day3	1, +7days
	1	Biliary	Cholangitis	0.72	7	1, Day3	1, +7days
GP	143	Hematological	bacteremia	0.27	15	1, Day7	0
	3	Renal	bacteremia	0.24	13	2, Day 5	0
	166	Biliary	Cholangitis	0.53	14	1, Day 11	0

Discussion/Conclusions

Gentamicin ODD was safe in children regarding nephrotoxicity.

Only mild and transient nephrotoxicity was observed in minority of patients at equivalent rate of traditional three-times daily dosing.

ODD has advantages in theoretical efficacy and safety therefore ODD may be an option for children.

References:

- 1) Best EJ et al. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. *Pediatr Infect Dis J.* 2011;30(10):827-832.
- 2) Kellum JA et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* Vol 2.2012.

Limitations:

- We did not examine the efficacy.
- We evaluated nephrotoxicity using serum creatinine only.
- We did not investigate other drugs using concomitantly.
- The patients without renal impairment before using gentamicin might be selected.