RENAL SAFETY OF SHORT TERM EMPIRIC GENTAMICIN THERAPY IN AGED PATIENTS

Authors: Christopher SB Sia¹, Michelle R Ananda-Rajah^{1,2,3}, Nikki R Adler^{1,4} Yi-Wei Baey¹, Danny Liew³, Erica Y Tong^{1,5}, Ar Kar Aung^{1,2,3}

1. Department of General Medicine, Alfred Hospital, Prahran, Victoria, Australia
2. Department of Infectious Diseases, Alfred Hospital, Prahran, Victoria, Australia
3. Monash University, Victoria, Australia
4. School of Public Health and Preventative Medicine, Monash University
5. Department of Pharmacy, Alfred Hospital, Prahran, Victoria, Australia

Corresponding author:

Dr. Ar Kar Aung
Department of General Medicine
Alfred Hospital
A.aung@alfred.org.au
P: 9076 2000
F: 9903 0843

Alternative corresponding author:

Dr. Christopher Sia
Department of General Medicine
Alfred Hospital
c.sia@hotmail.com
P: 9076 2000

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajag.12541](https://doi.org/10.1111/ajag.12541)

This article is protected by copyright. All rights reserved

M: 0401517657

F: 9903 0843

Funding: None received

The authors have no conflict of interests to declare.

Acknowledgements:

The authors would like to thank the members of Emergency and Pharmacy Departments (Cristina Roman, Caitlin Mulqueen, Nikki Cresswell, Carolyn Joyce) at the Alfred Hospital for provision of additional data and critically appraising this manuscript

DR. CHRISTOPHER SIA (Orcid ID : 0000-0002-8540-6813)

Article type : Brief Report

RENAL SAFETY OF SHORT TERM EMPIRIC GENTAMICIN THERAPY IN AGED PATIENTS

Abstract

Objective: To determine the incidence of acute kidney injury (AKI) in aged patients receiving empiric gentamicin therapy.

Methods : Patients aged ≥ 65 years receiving gentamicin upon admission between 2013-2015 at two Australian hospitals were retrospectively studied. AKI was defined as a rise in creatinine by $\geq 50\%$ and/or $\geq 26.5 \mu\text{mol/L}$.

Results: Most patients (95%) received a single dose of gentamicin. The incidence of AKI was 15% (36/242 patients). A composite outcome of persistent kidney injury, requirement for renal replacement therapy or inpatient death in a patient with AKI occurred in 10 (4%) patients. Patients who developed AKI were older (median 80.5 vs 78 years, $p=0.026$), had higher Charlson co-morbidity index (median 7 vs 5, $p=0.0004$) and had more advanced chronic kidney disease at baseline (Stage IV and V) (OR 4.38, 95% CI=1.45-13.2, $p=0.013$).

Conclusion: Empiric gentamicin use in patients with advancing age is associated with low rates of predominantly transient renal impairment.

Text

Introduction

Gentamicin is an aminoglycoside antibiotic effective against serious Gram negative bacterial infections. However, concerns regarding nephrotoxicity in patients with advanced age limit widespread use [1]. The Australian Therapeutic Guidelines recommend the empiric use of gentamicin for ≤ 48 hours against suspected Gram negative infections, before switching to a definitive therapy [2]. This study aimed to determine the incidence of acute kidney injury (AKI) in patients with advanced age who received empiric gentamicin upon presentation to the emergency department (ED), outcomes in these patients and risk factors for AKI.

Methods

Setting and study population

A retrospective cohort study was conducted at the Alfred and Sandringham Hospitals in Melbourne, Australia. These hospitals provide general and specialist medical and surgical services, including solid organ and bone-marrow transplantations. The Pyxis MedstationTM system (Becton, Dickinson and Company, New Jersey, USA) medication dispensary system was linked with hospital admission records to identify all admitted patients aged ≥ 65 years who were administered the first dose of empiric gentamicin in the EDs between April 2013 and March 2015. Patients were excluded if blood test results after the admission date were unavailable. Institutional ethics approval was obtained (457/15).

Data collection and definitions

All clinical data were manually extracted from medical records by the study clinicians (CS, AKA). Estimated glomerular filtration rate (eGFR) was reported using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [3], which compares favourably to other formulas used to estimate glomerular filtration rate in aged patients [4]. Admission serum creatinine (SCr) and eGFR at the first dose of gentamicin administration were regarded as the baseline values. The

daily dose, duration and total cumulative dose of gentamicin were recorded. Where synergistic gentamicin dosing was used, the daily total dose was taken as the equivalent of once daily dosing (e.g. 80mg tds = 240mg daily).

Outcome definitions

Acute kidney injury was defined as an increase in SCr by $\geq 50\%$ and/or $\geq 26.5 \mu\text{mol/L}$ from baseline, within 14 days from the first gentamicin dose, in accordance with Kidney Disease Improving Global Outcomes (KDIGO) guidelines [5]. The duration of 14 days was taken as a conservative estimate of the period within which gentamicin-associated nephrotoxicity is likely to occur [6]. The severity of AKI was determined according to KDIGO guidelines [5] (KDIGO Stage I: SCr increase to 1.5-1.9 times baseline or by $\geq 26.5 \mu\text{mol/L}$, Stage II: SCr increase to 2.0-2.9 times baseline, KDIGO Stage III: SCr increase to 3.0 times baseline, SCr $\geq 353.6 \mu\text{mol/L}$ or initiation of renal replacement therapy [RRT]). Renal replacement therapy included the requirement for continuous veno-venous haemodiafiltration or acute intermittent haemodialysis (HD).

A number of secondary outcomes were studied. Persistent kidney injury in patients with AKI was defined as a serum creatinine value that remained elevated by $\geq 50\%$ and/or $\geq 26.5 \mu\text{mol/L}$ from baseline ≥ 1 month after the date of onset of AKI. A composite serious adverse renal outcome was defined as a persistent kidney injury, requirement for RRT or inpatient death in a patient with AKI. Outcomes relating to AKI examined included inpatient mortality and length of stay.

Statistical analysis

Non-parametric and descriptive statistics were employed. Wilcoxon rank sum tests were used to compare continuous variables. Categorical variables were analysed using 2x2 contingency tables and Fisher's exact tests or where there were more than 2 groups, Chi-square tests. For ordinal data, Chi-square test for trends was employed. All statistical analyses were performed using Stata version 14.2 (StataCorp LP, College Station, Texas, USA) statistical software and a two-sided p-value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression was used to assess associations between patients who developed AKI and various clinical and biochemical characteristics. Variables were selected for univariate analysis based on previous published risk factors [1,7] and biologic plausibility. Variables significantly associated with AKI on univariate analyses and gender were included in multivariate logistic regression analysis.

Results

A total of 242 patients aged ≥ 65 years were identified [median age 78 (IQR 72-84) years; 52% male]. The majority (99%) of patients received ≤ 48 hours of gentamicin. The median daily dose was 240 mg (IQR 240-320 mg). The most common clinical indications were urinary tract infection (55%), intra-abdominal infections (13%) and sepsis with unknown source or suspected Gram negative bacteremia (11%). Patient characteristics are summarised in **Table 1**.

The incidence of AKI was 15% (36/242). The median time to peak creatinine was 4 (IQR 2-7) days. Among the 36 patients experiencing AKI, 29 (81%), 3 (8%) and 4 (11%) had KDIGO stage I, II and III AKI, respectively. Four (2% of total 242) patients developed persistent kidney injury. Renal replacement therapy was required in 2 patients (1%), for 2 days each. Long term HD was avoided in both cases.

Overall inpatient mortality was 9% (22/242), with a higher rate among AKI patients (5, 14% AKI vs. 9, 4% non-AKI, $p=0.04$). The cause of death in patients with AKI was sepsis (80%, 4/5 cases). A composite serious adverse renal outcome occurred in 10 (4%) patients.

Patients with AKI had longer length of stay (median 9 days vs. 4 days, $p<0.001$) but not greater 30-day readmission compared to those without AKI (0 [0%] vs 2 [1%], $p=1.0$). Two patients without AKI at index admission were readmitted within 30 days; one with AKI occurring >14 days after gentamicin administration, unlikely to be a direct effect of gentamicin, and the other with antibiotic-associated diarrhoea, following a switch to broad-spectrum beta-lactam and quinolone antibiotics.

Comparisons of clinical characteristics between those with and without AKI are summarised in **Table 2**. Advanced age, higher Charlson comorbidity index (CCI) [8], baseline advanced stage CKD and diuretic administration in the first 72 hours of admission were significant univariate predictors of AKI. In multivariate logistic regression analyses, only Stage IV CKD or worse kidney function at presentation remained significant. A trend to a statistically significant association was noted with CCI (**Table 2**).

Discussion

The incidence of AKI after empiric gentamicin use in patients with advanced age has not been previously described in an Australian setting. We observed a low rate of severe (KDIGO Stage II or III) AKI (7/242, 3%), persistent kidney injury (2%) or serious composite adverse renal outcomes (4%) amongst a cohort of patients aged ≥ 65 years who received empiric gentamicin.

While mortality was 14% among patients with AKI, it was predominantly attributable to sepsis. Overall, these findings support that Australian Therapeutic Guidelines recommendations for empiric gentamicin use in suspected serious Gram negative infections, even in patients with advancing age, is relatively safe from a renal perspective.

The incidence of nephrotoxicity in our study was 15%. Studies in younger cohorts reported incidences ranging from 10 to 25% [9,10] while those in older cohorts with a longer mean duration of treatment (mean 4.4-7.5 days) found the incidence of nephrotoxicity to be 12-22% [7,11,12]. Similar studies in consecutively admitted aged (≥ 60 years) patients (who did not receive gentamicin) found AKI was diagnosed in 14% of patients [13]. However, caution should be exercised in directly comparing these reported incidence rates due to varying definitions of AKI employed, some of which are no longer contemporary. The definition of AKI for the present study was based on a recently published KDIGO definition, which correlates closely with mortality data [14]. Given the descriptive nature of the study, causality for AKI cannot be determined and caution is suggested in attributing AKI entirely to gentamicin. Physician judgement is therefore required when selecting alternative antibiotics in patients whom clinicians determine to be at increased risk for aminoglycoside nephrotoxicity.

Gentamicin should be prescribed with caution in those who may be susceptible to poor renal outcomes, e.g., in those with advanced stage CKD and multiple co-morbidities. Concurrent diuretic administration within the first 72 hours of admission may also predispose to AKI. The association between diuretic administration and aminoglycoside nephrotoxicity has been reported in some [1,12] but not all [6,7] previous studies. Volume depletion from diuretics increases the risk of renal ischaemia, which may increase gentamicin uptake in the proximal tubules [15]. Gentamicin has been shown to exacerbate post-ischaemic AKI in animal models [16]. Therefore volume depletion increases gentamicin toxicity, which in turn potentiates ischaemic renal damage, creating a cycle of renal injury [15].

Our study has several limitations. The lack of a comparator control group comprising patients who received antibiotics other than gentamicin for similar clinical indications and also matched for baseline clinical and biochemical characteristics was a significant limitation. To adjust for potential confounders, we performed multivariate analyses and determined that advanced CKD remained significantly associated with AKI. ICU admission and nadir systolic blood pressure are crude markers of illness severity and we therefore cannot completely exclude severity of illness as a confounder. However, previous studies have found no increase in nephrotoxicity in patients with confounders such as severe sepsis who were prescribed gentamicin [6]. Lack of other significant

associations in multivariate models may have been due to a small number of patients with AKI. Larger studies with greater sample sizes are required to validate our findings and to further investigate these associations. We did not include patients in whom gentamicin was initiated after discharge from ED to the ward, limiting the generalisability of results to the population. The generalisability of the study is further limited by the high proportion of patients in this cohort with Stage II CKD or better. This may lead to underestimation of AKI rates in cohorts with higher Stages of CKD. Finally, the majority of patients in this study received a single dose of gentamicin and these findings may not apply to patients receiving prolonged courses.

Conclusion

In patients aged >65 years with predominantly Stage II CKD, in whom the majority received a single dose of gentamicin, the incidence of acute kidney injury was 15%. Kidney injury was transient in the overwhelming majority of patients. Severe AKI, persistent kidney injury or any serious adverse renal outcome was uncommon. Nevertheless, AKI was associated with increased unadjusted LOS and inpatient mortality. Caution should be exercised in administering gentamicin to patients with advanced CKD.

Impact Statement

The incidence of nephrotoxicity in aged patients receiving a short course of gentamicin (as recommended by the Australian therapeutic guidelines) is 15%. Renal replacement therapy or long term kidney injury was uncommon. This study identifies increasing age, comorbidity and chronic kidney disease as risk factors for acute kidney injury in patients receiving a short course gentamicin.

References

- [1] Bertino JS Jr, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis*. 1993; 167(1):173-9.
- [2] Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Limited; 2014

- [3] Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med.* 2009; 150:604-612.
- [4] Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol.* 2010; 5(6): 1003–1009.
- [5] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter* 2012; 2 (Suppl): 1-138.
- [6] Picard W, Bazin F, Clouzeau B, et al. Propensity-Based Study of Aminoglycoside Nephrotoxicity in Patients with Severe Sepsis or Septic Shock. *Antimicrob Agents Chemother.* 2014; 58(12): 7468–7474.
- [7] Paterson DL, Robson JM, Wagener MM. Risk Factors for Toxicity in Elderly Patients Given Aminoglycosides Once Daily. *J Gen Intern Med.* 1998; 13(11):735-9.
- [8] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5):373-383.
- [9] Leehey DJ, Braun BI, Tholl DA, et al. Can pharmacokinetic dosing decrease nephrotoxicity associated with aminoglycoside therapy. *J Am Soc Nephrol.* 1993; 4(1):81-90.
- [10] Moore RD, Smith CR, Lipsky JJ, Mellits ED, Lietman PS. Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med.* 1994;100(3):352
- [11] Raveh D, Kopyt M, Hite Y, Rudensky B, Sonnenblick M, Yinnon A. Risk factors for nephrotoxicity in elderly patients receiving once-daily aminoglycosides. *QJM : An International Journal of Medicine*, 2002; 95(5):291-7
- [12] Fraisse T, Gras Aygon C, Paccalin M, et al. Aminoglycosides use in patients over 75 years old. *Age and Ageing* 2014; 43:676-681 doi:10.1093/ageing/afu023.
- [13] Soerjadi N, Srikusalanukul W, Fisher A. Acute Kidney Injury In Hospitalised Elderly Medical Patients: Types, Incidence, Risk Factors And Relation To Clinical Outcomes. *Intern Med J.* 2016; 46(S3):24-25

- [14] Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365–3370
- [15] Molitoris BA, Meyer C, Dahl R, Geerdes A. Mechanism of ischemia-enhanced aminoglycoside binding and uptake by proximal tubule cells. *Am J Physiol*. 1993;264:F907–916
- [16] Zager RA. Gentamicin effects on renal ischemia/reperfusion injury. *Circ Res*. 1992;70(1):20

Author Manuscript

Table 1. Clinical characteristics of patients who received gentamicin (N=242)

Clinical Characteristic	Number (%) or Median (IQR)
Age (years)	78 (72-84)
Male	126 (52%)
ICU Admission	17 (7%)
Long-term care facility resident	36 (15%)
Stage of CKD on admission	
Stage I CKD	38 (16%)
Stage II CKD	116 (48%)

Stage IIIa CKD	51 (21%)
Stage IIIb	22 (9%)
Stage IV CKD	9 (4%)
Stage V CKD	6 (3%)
Baseline creatinine ($\mu\text{mol/L}$)	83 (69.25-107.75)
Baseline eGFR (ml/min)	67 (52-82)
Other Comorbidities	
Charlson co-morbidity index	5 (4-7)
Cerebrovascular disease	40 (17%)
Chronic obstructive pulmonary disease	33 (14%)
Congestive cardiac failure	23 (10%)
Connective tissue disorder	18 (7%)
Dementia	36 (15%)
Diabetes	61 (25%)
Malignancy	59 (24%)
Indication for treatment	
Genito-urinary tract infection	134 (55%)
Intra-abdominal infection	31 (1%)
Sepsis unknown source or suspected Gram negative bacteremia	26 (11%)
Respiratory infection (non-tropical)	7 (3%)
Urinary retention	4 (2%)
Back pain	4 (2%)
Delirium	4 (2%)
Other infective syndromes	11 (5%)
Other non-infective syndromes	21 (9%)
Gentamicin Dosing	
Received 1 dose	230 (95%)
Received 2 doses	10 (4%)
Received 3 or more doses	2 (1%)
Median daily dose (mg)	240 (240-320)

IQR = interquartile range, CKD = chronic kidney disease, eGFR (estimated glomerular filtration rate). Stage I CKD = eGFR >90ml/min, Stage II CKD = eGFR 60-89ml/min, Stage IIIa CKD = eGFR 45-59ml/min, Stage IIIb CKD = eGFR 30-44ml/min, Stage IV CKD = eGFR 15-29ml/min, Stage V CKD = eGFR <15ml/min.

Table 2. Comparison of clinical characteristics between those who developed AKI and those who did not

	n=36	n=206	Univariate Analysis			Multivariate analysis		
Risk factor	AKI (n, %) or Median (IQR)	Non-AKI (n, %) or Median (IQR)	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	80.5 (76.8-86.3)	78 (71-84)			<0.05	1.02	0.97-1.08	0.37
Male	20 (56%)	106 (52%)	1.18	0.58 – 2.4	0.72	1.43	0.65-3.11	0.37
CCI	7 (5-8)	5 (4-6)			<0.05	2.71	0.94-7.76	0.06
ICU admission	4 (11%)	13 (6%)	1.86	0.57-6.05	0.31			
CKD								
Stage I	3 (8%)	35 (17%)						
Stage II	15 (42%)	101 (49%)						
Stage IIIa	10 (28%)	40 (19%)			<0.05*			
Stage IIIb	2 (6%)	20 (10%)						
Stage IV	4 (11%)	5 (2%)						
Stage V	2 (6%)	4 (2%)						
Stage IV or worse	6 (17%)	9 (4%)	4.38	1.45 – 13.2	<0.05	3.39	1.04-11.1	0.04
Adm. creatinine (umol/L)	91 (77.8-122.3)	80.5 (67-104.5)			<0.05			
Adm. eGFR (ml/min)	60 (49-68.5)	69 (53-83)			<0.05			
Vital Signs								
Nadir Systolic BP	110 (96.5-116.8)	105 (92.0-116.8)			0.60			
Temperature	37.3 (36.8-37.9)	37.4 (36.9-38.2)			0.54			
Pre-hospital nephrotoxins								
ACEi	6 (17%)	41 (20%)	0.81	0.31 – 2.06	0.82			
ARB	15 (42%)	57 (28%)	1.87	0.90 – 3.87	0.11			
Diuretics	11 (31%)	57 (28%)	1.15	0.53 – 2.49	0.69			
NSAIDs	1 (3%)	13 (6%)	0.42	0.05 – 3.35	0.70			
Others†	1 (3%)	1 (1%)	5.86	0.36 - 95.9	0.28			
Nephrotoxins <72 hours								
All nephrotoxins	23 (64%)	127 (62%)	1.10	0.527 – 2.30	0.86			

Diuretics	15 (42%)	48 (23%)	2.35	1.13 – 4.92	<0.05	1.91	0.86-4.24	0.11
ACEi	6 (17%)	27 (13%)	1.33	0.51 – 3.48	0.60			
ARB	9 (25%)	41 (20%)	1.34	0.59 – 3.07	0.51			
NSAID	1 (3%)	11 (5%)	0.51	0.06 – 4.05	1.0			
COX-2 inhibitor	1 (3%)	2 (1%)	2.91	0.26 – 33.0	0.39			
Vancomycin	3 (8%)	17 (8%)	1.01	0.28 – 3.64	1.0			
IV Radiocontrast	3 (8%)	21 (10%)	0.80	0.23 – 2.84	1.0			
Others‡	0 (0%)	2 (1%)	1.12	0.53-23.8	1.0			
Gentamicin dosing								
Single dose	35 (97%)	195 (5%)			0.28*			
2 doses or less	35 (97%)	205 (99%)						
≥ 3 doses	1 (3%)	1 (1%)						

RF = risk factor, AKI = acute kidney injury, OR = odds ratio, CI = confidence interval, IQR = interquartile range. CCI = Charlson Co-morbidity index, ICU = intensive care unit, , CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, Adm = admission, BP = blood pressure, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, NSAIDs = non-steroidal anti-inflammatory drug, COX-2 = cyclooxygenase-2, IV = intravenous

†Valaciclovir, lithium

‡ Intravenous acyclovir, lithium

*Chi-square test for trends

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Sia, CSB;Ananda-Rajah, MR;Adler, NR;Yi-Wei, B;Liew, D;Tong, EY;Aung, AK

Title:

Renal safety of short-term empiric gentamicin therapy in aged patients

Date:

2018-09-01

Citation:

Sia, C. S. B., Ananda-Rajah, M. R., Adler, N. R., Yi-Wei, B., Liew, D., Tong, E. Y. & Aung, A. K. (2018). Renal safety of short-term empiric gentamicin therapy in aged patients. AUSTRALASIAN JOURNAL ON AGEING, 37 (3), pp.227-231. <https://doi.org/10.1111/ajag.12541>.

Persistent Link:

<http://hdl.handle.net/11343/283919>