Austin Pediatrics

Open Access

Austin Publishing Group

Research Article

Assessment of Serum Creatinine in Adolescents Receiving Intravenous Ketorolac in the Emergency Department: A Retrospective Study

Poel KT[1]*, Santos M[1], Soranno DE[2], Brou L[3], Kane A[1], Ingram E[1], Faes N[1] and Gist KM[4]

[1]Department of Pharmacy, Children's Hospital Colorado, USA

[2]Department of Pediatrics, Section of Pediatric Nephrology, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, USA

[3]Department of Biostatistics and Informatics. University of Colorado, Anschutz Medical Campus, Aurora CO, USA

[4]Department of Pediatrics, Section of Cardiology, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, USA

***Corresponding author:** Poel KT, Department of Pharmacy, Children's Hospital Colorado, USA

Received: June 19, 2017; **Accepted:** July 20, 2017; **Published:** July 27, 2017

Abstract

Objective: To evaluate changes is serum creatinine in adolescent patients receiving intravenous ketorolac.

Methods: Retrospective chart review of 343 patient charts from January 2007 to August 2014. Patients were included if they were 12-18 years of age, received 2 or more doses of ketorolac and had at least one subsequent measure of serum creatinine after initiation of ketorolac. Patients were dichotomized into 2 groups based on ≥ 25% increase versus < 25% increase in serum creatinine. The predictors were evaluated as 1) total ketorolac dose in milligrams (mg), 2) total dose in mg/kilogram (kg) and 3) total doses received.

Results: One hundred and eleven patients were included in the analysis. There was no significant difference in baseline demographics. Baseline serum creatinine was significantly higher in the group with <25% increase in serum creatinine (p = 0.006). Serum creatinine increased by ≥ 25% in 11 patients. No patients developed acute kidney injury.

Conclusion: Use of ketorolac in the pediatric emergency room for the treatment of pain was not associated with a substantial increase in serum creatinine or acute kidney injury. Further studies assessing the concurrent use of ketorolac with other nephrotoxic medications are needed to determine if there is increased risk for acute kidney injury.

Keywords: Ketorolac; Serum Creatinine; Acute kidney Injury

Abbreviations

AKI: Acute Kidney Injury; NSAID: Non-Steroidal Anti-Inflammatory Drugs; SCr: Serum Creatinine; Mg: Milligrams; Kg: Kilograms

Introduction

Nephrotoxic medications are a major cause of Acute Kidney Injury (AKI), estimated to be causative in 25% of AKI cases [1]. The risk for nephrotoxic AKI increases with the use of multiple nephrotoxic medications [2]. AKI from other causes occurs in up to 30% of hospitalized critically ill children, and is associated with worse outcomes, including increased length of stay leading to increased hospital costs [3-6].

The most common medications known to cause AKI include chemotherapeutic agents, antimicrobials and non-steroidal anti-inflammatory drugs (NSAIDs) [1]. NSAIDs are a widely used class of medications in the pediatric population, and are known to cause AKI in approximately 3% of hospitalized pediatric patients [7]. There are two proposed mechanisms by which NSAIDs lead to AKI. The first is alteration of glomerular filtration rate by inhibiting the formation of prostaglandins, resulting in vasoconstriction of the afferent glomerular arteriole. The second mechanism, albeit more rare, results in interstitial nephritis, which is thought to be driven by leukotriene production involved in the inflammatory response [7]. In a study of adolescent patients admitted to the hospital, use of NSAIDs and subsequent development of AKI was associated with interstitial nephritis in 2.7% of patients [7]. The risk for NSAID related AKI can be exacerbated by intravascular volume depletion.

Ketorolac, an NSAID, is indicated for the treatment of moderate to severe pain. The typical dosing regimen at Children's Hospital Colorado is 0.5 mg per kilogram of total body weight every 6 hours with a maximum dose of 30 mg, and a maximum duration of 48 hours. Ketorolac has a notable adverse effect profile including hypertension, gastrointestinal hemorrhage, thrombocytopenia and AKI [7-10]. Despite this adverse effect profile, it is still widely used within this institution and hospitals across the country.The purpose of this study was to evaluate changes in serum creatinine (SCr) in adolescent patients receiving intravenous ketorolac presenting to the emergency department. We hypothesized that there is a dose-dependent increase in SCr from baseline associated with the use of higher dosing strategies.

Materials and Methods

We performed a retrospective chart review of patient's who presented to the emergency department, and received intravenous ketorolac between January 2007 and August 2014. The Colorado Multiple Institutional Review Board approved the study with a waiver of informed consent. Patients were included if they were 12-18 years

Citation: Poel KT, Santos M, Soranno DE, Brou L, Kane A, Ingram E, et al. Assessment of Serum Creatinine in Adolescents Receiving Intravenous Ketorolac in the Emergency Department: A Retrospective Study. Austin Pediatr. 2017; 4(3): 1059.

Table 1: Comparison of demographics and baseline serum creatinine values (SCr); IQR: Interquartile Range.

	<25% increase in SCr (n=100)	≥25% increase in SCr (n=11)	p-value
Age (Median (IQR))	14.5 (13.1, 16.5)	15.5 (14.8, 16.7)	0.12
Male: n (%)	50 (50.5)	7 (63.6)	0.53
Weight (Median (IQR))	49.0 (40.7, 63.2)	48.5 (36.6, 62.1)	0.96
Indication for ketorolac			
Surgical,n (%)	41 (41.8)	5 (45.4)	0.82
Medical, N (%)	57 (58.2)	6 (54.6)	
Baseline SCr (Median (IQR))	0.62 (0.46, 0.76)	0.40 (0.11, 0.60)	**0.006**
Peak SCr (Median (IQR))	0.65 (0.49, 0.76)	0.49 (0.19, 0.73)	0.12

Scr = serum creatinine, IQR = inter quartile range, n = number, % = percent.

of age, received 2 or more doses of ketorolac and had at least one measure of serum creatinine (SCr) after initiation of ketorolac in a single hospital encounter. Patients were excluded if a diagnosis of AKI was made on current admission prior to receiving ketorolac.

Patient demographics included gender, height (cm), weight (kg), baseline SCr as well as the highest SCr within 5 days of the last ketorolac dose. Baseline SCr was the lowest value in the medical record in the preceding 3 months prior to presentation [11]. If no baseline SCr was available, one was assumed using an estimated glomerular filtration rate of 120mL/minute/1.73m^2 using the Cockgroft Gault equation. We assessed for differences in SCr across 3 different dosing strategies: ≤ 15mg *vs.* > 15mg per dose, ≤ 0.5mg/kg/dose *vs.* > 0.5mg/kg/dose and ≤ 4 doses *vs.* > 4 doses.

Patients were dichotomized into 2 groups based on ≥ 25% increase versus < 25% increase in SCr Categorical variables were compared using Fisher's exact tests. Due to the non-normal distribution of the continuous variables, Wilcoxon rank-sum tests were performed to assess differences in the outcome groups. To determine a correlation between the change in SCr from baseline and the 3 different dosing strategies, Spearman's correlation testing was performed. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Three hundred and forty-three adolescent patients presented to the emergency department and received intravenous ketorolac during the study period. Two hundred and thirty-two patients did not meet inclusion criteria. Two hundred and twenty-six patients lacked follow up labs, three patients lacked a baseline SCr and one could not be estimated using the Cockgroft Gault equation and 3 patients were excluded due to poor records. One hundred and eleven patients were included in the final analysis. One hundred (90%) patients had a SCr that increased by < 25%. Eleven (10%) patients had a ≥ 25% increase in SCr from baseline. There were no significant differences in patient demographics, which are described in Table 1. The indication for ketorolac administration was more likely medical compared to surgical for both groups, although this difference was not significant (54.6% in ≥ 25% group; 58.2% in < 25% group; p=0.82).

Eight (7%) patients did not have a baseline SCr and thus the baseline value was estimated. Median baseline SCr was significantly higher in the < 25% group, which included the eight patients with no baseline SCr (0.62 *vs.* 0.40; p=0.006) (Table 1). There was no significant difference in peak SCr between the 2 groups (0.65 ± 0.27 *vs.* 0.49 ± 0.54;p=0.12) (Table 1). There was no significant difference in the change in SCr from baseline based on dosing strategy (Table 2). We also found no significant difference in SCr when patients were dichotomized by < 25% *vs.* a ≥ 25% increase in SCr when evaluated by dosing strategy (Table 3). There was no significant correlation between base SCr and peak SCr among the three different dosing strategies described above: ≤ 15mg *vs.* > 15mg per dose (ρ= -0.12, p= 0.2); ≤ 0.5mg/kg/dose *vs.* > 0.5 mg/kg/dose (ρ= 0.17, p=0.07); ≤ 4 doses *vs.* > 4 doses (ρ= -0.08, p= 0.39).

Table 2: Change in serum creatinine (SCr) from baseline to peak between different dosing strategies; IQR: Inter quartile Range.

Dosing Strategy	Change in SCR from baseline	P-value
	Median (IQR)	
≤ 15mg	0.0 (0.0, 0.02)	0.55
> 15mg	0.0 (0.0, 0.05)	
≤ 0.5mg/kg/dose	0.0 (0.0, 0.04)	0.19
> 0.5mg/kg/dose	0.01 (0.0, 0.05)	
≤ 4 doses	0.01 (0.0, 0.05)	0.79
> 4 doses	0.0 (0.0, 0.04)	

Mg = milligrams, kg = kilograms, IQR = interquartile range.

Table 3: Comparison of the number of patients in each group and the dosing strategy received.

Dosing regimens: n (%)	<25% increase in SCr (n=100)	≥ 25% increase in SCr (n=11)	P-value
≤15mg	10 (10.0)	1 (9.1)	1
> 15mg	90 (90.0)	10 (90.9)	
≤ 0.5 mg/kg/dose	56 (56.0)	6 (54.5)	1
> 0.5 mg/kg/dose	44 (44.0)	5 (45.5)	
≤ 4 doses	31 (31.0)	4 (36.4)	0.74
> 4 doses	69 (69.0)	7 (63.6)	

N = number, % = percent, mg = milligrams, kg = kilograms, SCr = serum creatinine.

Discussion

We were not able to identify any significant changes in SCr in the presence of different dosing strategies in patients who presented to the emergency department for treatment of pain and were subsequently admitted. One important finding is that patients in the < 25% change in SCr group had higher baseline SCr levels. This higher baseline value

may be due to intravascular volume depletion/dehydration, and the minimal change in creatinine following rehydration could possibly suggest early renal injury. Importantly SCr has known limitations, and is affected by factors unrelated to renal disease. Some of these factors include muscle mass, hydration status, and liver dysfunction with hyperbilirubinemia [12,13]. In addition, SCr is a late marker of AKI, only rising more than 24 hours after injury has occurred, at which time there may already be significant reduction in renal function.

While there were no patients who met the Kidney Injury and Disease: Improving Global Outcome (KDIGO) criteria for AKI, even small increases in SCr in children may be clinically significant [14]. Routine surveillance of SCr should is considered in those deemed at highest risk, and who receive additional nephrotoxic medications during their hospital admission. A study in adult patients evaluated the risk of AKI in patients who received one to three courses of ketorolac compared to those who were treated with opioids. The authors found a low rate of AKI in their population. They did report an association between AKI and patients receiving > 5 days of ketorolac exposure [15].

At Children's Hospital Colorado, the pediatric nephrology section provides wallet-warning cards counseling against nephrotoxic medication use to those with known chronic kidney disease, and is in the process of including other vulnerable populations at risk for AKI and chronic kidney disease in this group. We are in the process of incorporating a nephrotoxic medication alert system detailed by Goldstein et al to reduce the risk of nephrotoxic AKI in exposed patients starting in the emergency department and who are admitted to the hospital for routine SCr surveillance [16]. In addition, the implementation of a clinically available biomarker of AKI has the potential to be used in the emergency department in patients with specific AKI risk factors, and could differentiate functional from tubular injury. SCr only provides an assessment of functional injury, and biomarkers, provide assessments of injury to sites where they are expressed [17]. One biomarker, namely Neutrophil Gelatinase Associated Lipocalin (NGAL), is a small protein expressed in the distal nephron epithelium and secreted into the tubular lumen very early after acute kidney injury, and is a sign of tubular injury when present in the urine. The use of NGAL in the clinical setting was recently described by Varnell et al. [18], and its future use could certainly include patients in the emergency department who are exposed to one or more nephrotoxic medications, especially if their baseline SCr is abnormal, and there is uncertainty as to whether the abnormal SCr represents more than functional injury or a pre-renal state.

Therapeutic drug monitoring is not available for ketorolac, and at our institution, ketorolac use is contraindicated in patients with known renal disease, and in those who have undergone organ transplant (heart, kidney, bone marrow). It is possible that target analgesia could be accomplished with a lower prescribed dose of ketorolac because of a dose-dependent analgesic effect that has been described in adults [19]. This may in fact decrease the risk of AKI, especially when there is concurrent use of other nephrotoxic medications. Additional pediatric pharmacokinetic studies to assess the possibility of a ceiling effect and the development of AKI in children receiving ketorolac are necessary.

Although this study provides insight into changes in SCr and ketorolac dosing, there are several important limitations. The study is a retrospective review at a single institution and is subject to the limitations associated with retrospective studies, including no baseline SCr in 8 patients, and no routine surveillance of SCr, with most patients only having 1 additional SCr measure after initiation of therapy. There were possibly missed cases of acute kidney injury without routine surveillance of SCr in the two hundred and twenty-six patients that had to be excluded. Hydration status and fluid resuscitation were not assessed as part of the data collection. We did not perform a power analysis, and thus our results may be influenced by insufficient power.

Conclusion

Use of ketorolac in the pediatric emergency room for the treatment of pain was not associated with an increase in SCr in those admitted to the hospital. Concurrent use of other nephrotoxic medications may increase patient risk for AKI, and consideration of dosing strategies similar to those described in adults should be explored to minimize the possibility of side effects, including the development of AKI.

References

1. Faught LN, Greff MJ, Rieder MJ, Koren G. Drug-induced acute kidney injury in children. Br J Clin Pharmacol. 2015; 80: 901-909.

2. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clinical journal of the American Society of Nephrology: CJASN. 2011; 6: 856-863.

3. Assadi F, Sharbaf FG. Practical considerations to drug dosing in children with acute kidney injury. Journal of clinical pharmacology. 2016; 56: 399-407.

4. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, et al. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2016; 67: 384-390.

5. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. New England Journal of Medicine. 2016.

6. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. Journal of the American Society of Nephrology: JASN. 2005; 16: 3365-3370.

7. Misurac JM, Knoderer CA, Leiser JD, Nailescu C, Wilson AC, Andreoli SP. Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. The Journal of pediatrics. 2013; 162: 1153-1159.

8. DRUGDEX System (Micromedex 2.0). 2014 August 2014. Truven Health Analytics; [c1974-2013].

9. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2012; 32:1491-1502.

10. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med. 1998; 158: 33-39.

11. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. Clinical journal of the American Society of Nephrology: CJASN. 2008; 3: 948-954.

12. Abrahamsson K, Jodal U, Sillen U. Reference interval for serum creatinine in children and adolescents with myelomeningocele. Scand J Urol Nephrol. 2009; 43: 233-235.

13. Askenazi D, Saeidi B, Koralkar R, Ambalavanan N, Griffin RL. Acute changes

in fluid status affect the incidence, associative clinical outcomes, and urine biomarker performance in premature infants with acute kidney injury. Pediatric nephrology. 2016; 31: 843-851.

14. Zappitelli M, Bernier PL, Saczkowski RS, Tchervenkov CI, Gottesman R, Dancea A, et al. A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. Kidney international. 2009; 76: 885-892.

15. Feldman HI, Kinman JL, Berlin JA, Hennessy S, Kimmel SE, Farrar J, et al. Parenteral ketorolac: the risk for acute renal failure. Annals of internal medicine. 1997; 126: 193-199.

16. Goldstein SL, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. Pediatrics. 2013; 132: 756-767.

17. Basu RK, Gist K, Wheeler DS. Improving acute kidney injury diagnostics using predictive analytics. Curr Opin Crit Care. 2015; 21: 473-478.

18. Varnell CD, Goldstein SL, Devarajan P, Basu RK. Near Real-time Urine NGAL Assessment and Impact on Clinical Practice: a Single Center Clinical Experience with an AKI biomarker. Kidney International Reports. 2017.

19. Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesthesia and analgesia. 1998; 87: 98-102.

Austin Pediatr - Volume 4 Issue 3 - 2017
ISSN : 2381-8999 | www.austinpublishinggroup.com

Citation: Poel KT, Santos M, Soranno DE, Brou L, Kane A, Ingram E, et al. Assessment of Serum Creatinine in Adolescents Receiving Intravenous Ketorolac in the Emergency Department: A Retrospective Study. Austin Pediatr. 2017; 4(3): 1059.