Tramadol use in pediatric sickle cell disease patients with vaso-occlusive crisis

Mary P Borgerding, Randall K Absher, Tsz-Yin So

Tramadol use in pediatric sickle cell disease patients with vaso-occlusive crisis

Mary P Borgerding, Randall K Absher, Department of Pharmacy, Wesley Long Hospital, Greensboro, NC 27401, United States
Tsz-Yin So, Department of Pharmacy, Moses H Cone Memorial Hospital, Greensboro, NC 27401, United States
Author contributions: Borgerding MP performed the majority of the research; Absher RK helped with the statistical analysis of the data; So TY helped with the design of the study and edited the manuscript.
Correspondence to: Tsz-Yin So, Pharm D, BCPS, Department of Pharmacy, Moses H. Cone Memorial Hospital, 1200 N. Elm St., Greensboro, NC 27401, United States. jeremy.so@conehealth.com
Telephone: +1-336-8327287
Received: March 28, 2013 Revised: May 30, 2013 Accepted: June 28, 2013 Published online: November 8, 2013

Abstract

AIM: To evaluate whether the addition of scheduled oral tramadol to intravenous morphine and intravenous ketorolac reduces morphine requirements.

METHODS: This single-centered, Institutional Review Board-approved, retrospective study at Moses Cone Memorial Hospital included pediatric patients who were ≥2 years old with vaso-occlusive crisis (VOC) caused by sickle cell disease (SCD), were on morphine patient-controlled analgesia (PCA), and had scheduled oral tramadol added to their standard pain regimen. The study population was admitted between March 2008 and March 2011. The data was collected from electronic records and included age, weight, morphine use, tramadol use, hemoglobin, pain scores, number of days on PCA, length of hospital stay, respiratory rate, and polyethylene glycol use. Thirty patients were analyzed as independent admissions and seven patients as paired admissions.

RESULTS: Eighteen pediatric SCD patients with VOC received morphine PCA and intravenous ketorolac and twelve patients received morphine PCA and intravenous ketorolac and scheduled oral tramadol. Baseline characteristics were similar between both groups with the exception of the average weight, which was greater in the tramadol group than in the morphine group. The average morphine requirements in patients with and without the use of tramadol were similar, both for the independent admissions [0.58 mg/kg per day vs 0.65 mg/kg per day (P = 0.31)] and the paired admissions [0.71 mg/kg per day vs 0.77 mg/kg per day (P = 0.5)]. The daily polyethylene glycol requirement was less in the tramadol group for both the independent [0.5 g/kg per day vs 0.6 g/kg per day (P = 0.64)] and paired admissions analyses [and 0.41 g/kg per day vs 0.55 g/kg per day (P = 0.67)].

CONCLUSION: The addition of scheduled tramadol in patients receiving concomitant morphine and ketorolac demonstrates a trend toward decreased morphine and polyethylene glycol use.

© 2013 Baishideng. All rights reserved.

Key words: Pediatrics; Sickle cell; Tramadol; Morphine; Vaso-occlusive crisis

Core tip: A small clinical study has shown that balanced analgesia using intravenous morphine, intravenous ketorolac, and intravenous tramadol followed by erythrocytapheresis was effective, as shown by pain relief and significant improvement in mood and sleep, in seven sickle cell disease patients aged three to twenty-eight years who presented with vaso-occlusive crisis. The objective of this study is to evaluate whether the addition of scheduled oral tramadol to intravenous morphine plus intravenous ketorolac provides adequate pain relief, and reduces morphine requirements, adverse effects, length of patient-controlled analgesia therapy, and length of hospital stay.

Borgerding MP, Absher RK, So TY. Tramadol use in pediatric sickle cell disease patients with vaso-occlusive crisis.

World J Clin Pediatr 2013 November 8; 2(4): 65-69
ISSN 2219-2808 (online) © 2013 Baishideng. All rights reserved.
sickle cell disease patients with vaso-occlusive crisis. World J Clin Pediatr 2013; 2(4): 65-69. Available from: URL: http://www.wjgnet.com/2219-2808/full/v2/i4/65.htm DOI: http://dx.doi.org/10.5409/wjcp.v2.i4.65

INTRODUCTION

One of the major causes of hospitalization for patients with sickle cell disease (SCD) is vaso-occlusive crises (VOC). The hallmark characteristics of VOC include organ damage and pain due to the presence of dense red blood cells. The pain is generated through multiple pathways including somatic, neuropathic, and vascular mechanisms.\[1-4\]

Balanced analgesia is a strategy based on the co-administration of drugs with different pharmacological mechanisms in order to control pain at different origins, improve the efficacy of treatment, and reduce adverse effects of each drug.\[5\]. The administration of ketorolac and tramadol has been proven as a form of effective balanced analgesia, particularly for post-operative pain and pain caused by trauma.\[6\]. Tramadol and its active metabolite (M1) work by binding to the mu-opioid receptors in the central nervous system (CNS) and inhibiting the reuptake of norepinephrine and serotonin, causing inhibition of the ascending pain pathway and altering the perception of and response to pain.\[7\]. Tramadol is clinically known to have a better safety profile than the other major opioids, causing less respiratory depression and constipation.

In 2005, de Franceschi et al\[8\] published a study evaluating balanced analgesia using intravenous (iv) morphine, iv ketorolac, and iv tramadol followed by erythrocytapheresis in seven SCD patients aged three to twenty-eight years who presented with VOC. The co-administration of tramadol and ketorolac was effective in all VOC, as shown by pain relief and significant improvement in mood and sleep. The use of erythrocytapheresis, which is not available at our hospital, Moses Cone Memorial Hospital (MCMH), likely contributed to pain relief in this study.

At MCMH pediatric patients who presented prior to August 2010 with VOC caused by SCD were routinely prescribed iv morphine and iv ketorolac for pain control. However, because of the high morphine requirement in this patient population, severe respiratory depression and constipation can occur. After August 2010, pediatric physicians began adding scheduled oral (po) tramadol to the standard regimen of iv morphine patient-controlled analgesia (PCA) and iv ketorolac in an attempt to reduce narcotic-induced side effects. The objective of this retrospective study is to evaluate whether the addition of scheduled po tramadol to iv morphine and iv ketorolac reduces morphine requirements, provides adequate pain relief, decreases length of hospital stay, and reduces severe respiratory depression, severe constipation, and length of PCA therapy.

MATERIALS AND METHODS

This single-centered, Institutional Review Board (IRB)-approved, retrospective study included pediatric patients who were ≥ 2 years old with VOC caused by SCD, were on PCA morphine and iv ketorolac and had scheduled po tramadol added to their regimen. Tramadol was dosed at 1-2 mg/kg per dose po every four to 6 h (max: 400 mg/d and 100 mg/dose) and ketorolac at 0.5 mg/kg per dose iv every 6 h (Max: 30 mg/dose). Morphine PCA orders included a basal rate, intermittent dose, lockout interval, and a 1-hour and 4-hour limit. Using the International Classification of Diseases (ICD)-9 code for SCD, all patients < 21 years old who were admitted between March 2008 and March 2011 were included in this retrospective review. Patients were excluded from the review if they did not have a diagnosis of VOC or did not receive morphine PCA. The data was collected from electronic records and included age, weight, morphine use, tramadol use, hemoglobin, pain scores, number of days on PCA, length of hospital stay, respiratory rate, and polyethylene glycol (PEG) use. All patients were analyzed as independent admissions. Additionally, patients with multiple admissions during the study period (at least one with morphine only and one with both morphine and tramadol) were analyzed as paired admissions, acting as their own controls.

The primary outcome of this study was average daily morphine requirement. Secondary outcomes included average pain scores, respiratory rate, PEG dose, length of PCA therapy and number of days in the hospital.

All patients were analyzed as independent admissions using the Wilcoxon Rank Sum test. Patients who had multiple admissions, one with tramadol use and one without were also analyzed as paired admissions using the Wilcoxon Signed Rank test. The statistical analysis was completed using Stata, Version 10.1 (Cary, NC).

RESULTS

Between March 2008 and March 2011 eighteen pediatric SCD patients with VOC received morphine PCA and iv ketorolac and twelve patients received morphine PCA plus iv ketorolac and scheduled po tramadol. Baseline characteristics were similar between both groups with the exception of the average weight, which was greater in the tramadol group than in the morphine group because the latter group had a younger sample (Table 1).

Average morphine requirements with and without tramadol were similar in the independent admission analysis [0.58 mg/kg per day and 0.65 mg/kg per day, respectively (P = 0.31)]. Average morphine requirements with and without tramadol were also similar in the paired admissions analysis [0.71 mg/kg per day and 0.77 mg/kg per day, respectively (P = 0.5)]. Contradictory to what was expected, pain scores were higher when tramadol was added to the pain regimen for both the independent admissions (6.75 vs 5) and the paired admissions (6.5 vs 5.5). The daily
Polyethylene glycol requirement was less in the tramadol group for both the independent and paired admissions analyses (0.5 g/kg per day vs 0.6 g/kg per day and 0.41 g/kg per day vs 0.55 g/kg per day, respectively) but neither difference was statistically significant (P = 0.64 and 0.67, respectively). The paired admissions analysis demonstrated a greater difference in PEG requirements which, while not statistically significant, may provide a more accurate comparison. Furthermore, there was no difference in the length of stay, number of days on PCA, or respiratory rate between groups in either analysis (Tables 2 and 3).

**DISCUSSION**

The addition of scheduled oral tramadol in patients receiving concomitant morphine and ketorolac did result in numerically lower average daily morphine requirements (Figure 1A) and polyethylene glycol use; however, differences in these endpoints were not statistically significant (Table 2). In the paired admissions analysis, four of the six patients who received less than 1 mg/kg per day of morphine used less morphine when tramadol was added to their regimen (Figure 1B); however, pain scores did not correlate with the decreased morphine requirement.

The lack of correlation between pain scores and morphine requirement may be due to the subjectivity of pain. After completion of the study, a pediatric psychiatrist spoke with several patients in the study and found that many patients did not understand how to use the visual analogue pain scale or the numeric scale to rate their pain. When asked to rate their pain as red, yellow or green (red corresponding to the most pain and green the least), patients gave more accurate representations of their true pain level. Extensive education on rating pain would be required to provide a more precise representation of pain relief with and without the use of tramadol.

There were several limitations to this study. The retrospective nature of the study forced us to rely on electronic nursing documentation for all of our data collection, which may have resulted in some inaccurately charted data. Frequently, bowel movements were not documented. We therefore measured average daily polyethylene glycol use to assess constipation. Additionally, we were unable to stratify patients based on their basal morphine PCA rate and determine how much of their daily morphine requirement was due to demand dosing, as this information was not documented electronically. Patients with multiple admissions for VOC can develop tolerance to narcotics, resulting in an increased morphine basal rate requirement. Documentation of this may have provided a more accurate assessment of which analgesic regimen provided better pain control and fewer narcotic-induced side effects.

VOC most commonly involves the back, legs, knees, arms, chest and abdomen. The location of the vaso-occlusive crisis has a significant impact on the intensity of pain and the ability to control that pain; however, this study did not stratify patients based on VOC location or disease severity. Additionally, the disease severity has interpatient and intrapatient variability making it more difficult to compare patients. Also, one patient in this study had drug-seeking behavior, which may have skewed the results causing increased average morphine requirement and pain scores.

A larger, controlled study would be more likely to determine statistical difference in the primary and secondary endpoints. Pediatric physicians at MCMH no longer routinely prescribe tramadol in this population but con-
shown by pain relief and significant improvement in mood and sleep. The co-administration of tramadol and ketorolac was effective in all VOC, as in seven SCD patients aged three to twenty-eight who presented with VOC. In 2005, de Franceschi et al published a study evaluating balanced analgesia using iv morphine, iv ketorolac, and iv tramadol followed by erythrocytapheresis in seven SCD patients aged three to twenty-eight who presented with VOC. The co-administration of tramadol and ketorolac was effective in all VOC, as shown by pain relief and significant improvement in mood and sleep.

Table 2 Independent admissions statistical analysis

|                          | Morphine (n = 18) | Morphine + tramadol (n = 12) | *P*-value |
|--------------------------|-------------------|-------------------------------|-----------|
| Morphine requirement (mg/kg per day), mean ± SD | 0.65 ± 0.35        | 0.58 ± 0.48                   | 0.31      |
| Pain score, median (range) | 5 (0-8)           | 6.75 (3-9)                    | 0.07      |
| PCA duration (d), median (range) | 4.5 (0-13)       | 5 (3-14)                      | 0.33      |
| LOS (d), median (range)    | 7 (4-14)          | 7.5 (3-17)                    | 0.85      |
| Respiratory rate, mean (range) | 21 (14-29)        | 19 (16-23)                    | 0.28      |
| Polyethylene glycol dose (gm/kg per day), mean (range) | 0.6 (0-1.66)    | 0.5 (0-1.12)                  | 0.64      |

*P*-value calculated using Wilcoxon Rank Sum test. PCA: Patient-controlled analgesia; LOS: Length of stay.

Table 3 Paired admissions statistical analysis (n = 7)

|                          | Morphine | Morphine + tramadol | *P*-value |
|--------------------------|----------|---------------------|-----------|
| Morphine requirement (mg/kg per day), mean ± SD | 0.77 ± 0.44 | 0.71 ± 0.57       | 0.50      |
| Pain score, median (range) | 5.5 (2-8)   | 6.5 (3-8)          | 0.27      |
| PCA duration (d), median (range) | 6 (4-13)    | 7 (3-10)          | 0.35      |
| LOS (d), median (range)    | 7 (5-14)   | 9 (3-12)          | 0.61      |
| Respiratory rate, mean (range) | 19 (14-20)  | 19 (17-25)        | 0.87      |
| Polyethylene glycol dose (gm/kg per day), mean (range) | 0.55 (0.28-1.1) | 0.41 (0.28-0.98) | 0.67      |

*P*-value calculated using Wilcoxon Rank Sum test. PCA: Patient-controlled analgesia; LOS: Length of stay.

tinue to use it in patients who have clinically shown improved pain control with tramadol in the past. Tramadol use is appropriate in this population as it has proven safe, usually causing no additional side effects and potentially providing some benefit in controlling pain and reducing narcotic-induced constipation. If tramadol continues to be clinically beneficial for pain control in other patients in this population, it may be possible to review our primary and secondary endpoints on a larger scale to determine any true differences.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Ola Akintemi, Dr. Jackie Roh, Dr. Michelle Turner, and Dr. Alison Grimsley for their effort in evaluating the research. Without their help, this work would not have been accomplished.

REFERENCES

1 Platt OS, Thorton BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med* 1991; 325: 11-16 [PMID: 1710777 DOI: 10.1056/NEJM199107043250103]

2 Cluster S, Vichinsky EP. Managing sickle cell disease. *BMJ* 2003; 327: 1151-1155 [PMID: 14613434 DOI: 10.1136/bmj.327.7424.1151]

3 Rees DC, Olujohungbe AD, Parker NE, Stephens AD, Telfer P, Wright J. Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol* 2003; 120: 744-752 [PMID: 12614204 DOI: 10.1046/j.1365-2451.2003.04193.x]

4 Benjamin I. Nature and treatment of the acute painful episodes in sickle cell disease. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. Disorders of hemoglobin: genetics, pathophysiology and clinical management. cambridge. United Kingdom: Cambridge University Press, 2001: 671-710

5 Kehiet H, Dahi JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. *Anesth Analg* 1993; 77: 1048-1056 [PMID: 8105724 DOI: 10.1213/00000539-1
Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; 60: 139-176 [PMID: 10929933 DOI: 10.2165/00003495-200060010-00008]

Lexicomp 2011: Tramadol. [Lexi-Comp ONLINE web site]. Available from: URL: http://www.uptodate.com.libproxy.lib.unc.edu/contents/tramadol-pediatric-drug-information?detectedLanguage=en&source=search_result&search=tramadol&selectedTitle=2%7E86&provider=noProvider

de Franceschi L, Finco G, Vassanelli A, Zaia B, Ischia S, Corrocher R. A pilot study on the efficacy of ketorolac plus tramadol infusion combined with erythrocytapheresis in the management of acute severe vaso-occlusive crises and sickle cell pain. *Haematologica* 2004; 89: 1389-1391 [PMID: 15531461]

Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. *Am Fam Physician* 2000; 61: 1349-1356, 1349-1356 [PMID: 10735342]

P- Reviewer: Al-Haggar M  S- Editor: Wen LL  L- Editor: A  E- Editor: Lu Y
