

Incompatibilities of lornoxicam with 4 antiemetic medications in polyolefin bags during simulated intravenous administration

Bao-xia Fang (MD)^a, Peng Li (PhD)^a, Xiao-ya Shi (MD)^a, Fu-chao Chen (MD)^a, Lin-hai Wang (MD)^{b,*}

Abstract

The administration of drugs by patient-controlled analgesia (PCA) is routinely practiced for the management of postoperative pain. It is common for 2 or more drugs to be combined in PCA solutions. The combination of analgesics and antiemetic agents is frequently required. Unfortunately, the compatibility and stability of lornoxicam and antiemetic agents, such as droperidol, ondansetron, granisetron, and tropisetron, has not been determined. The aim of this study was to evaluate the compatibility and stability of solutions containing lornoxicam with the 4 antiemetic agents in combination for PCA administration.

In our study, test samples were prepared in triplicate by adding 40 mg lornoxicam and 5 mg droperidol, 8 mg ondansetron, 6 mg granisetron, or 5 mg tropisetron to 100-mL polyolefin bags of sodium chloride 0.9% and stored at 25 °C. The analgesic mixture samples were visually inspected for precipitation, cloudiness, and discoloration at each sampling interval. Drug concentrations were determined using high-performance liquid chromatographic (HPLC) analysis.

No loss of lornoxicam occurred with any of the 4 antiemetic agents tested for up to 48 hours. However, the contents of droperidol, ondansetron, granisetron, and tropisetron were significant loss >48 hours. After storage of 4.0 to 48.0 hours, the presence of a slight precipitate was observed in all the injection combinations.

The results indicate that combinations of lornoxicam with droperidol, ondansetron, granisetron, or tropisetron in infusion solution during simulated intravenous PCA administration were incompatibility when stored protected from light at 25 °C.

Abbreviations: 5-HT₃ = 5-hydroxytryptamine type 3, HPLC = high-pressure liquid chromatography, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting.

Keywords: antiemetic agents, incompatibility, lornoxicam, patient-controlled analgesia, postoperative pain

1. Introduction

Lornoxicam, a nonsteroidal anti-inflammatory drug with potent analgesic and anti-inflammatory activity and it belongs to the class of oxicams. The drug has a short plasma half-life, of ~4 to 6 hours. Due to this, lornoxicam is suitable in the postoperative period for acute pain.^[1] Intravenous patient-controlled analgesia

(PCA) with lornoxicam has reported to be as effective as morphine, tramadol, or fentanyl for postoperative pain management. However, it is associated with a high incidence of postoperative nausea and vomiting (PONV).^[2–6] PCA lornoxicam-induced PONV, such as postoperative pain, could reduce patients' postoperative satisfaction and cause severe complications such as prolongs hospital stays and economic loss.^[7,8]

Droperidol is a dopamine D₂ receptor antagonist that has been widely used for the prevention and treatment of PONV and analgesic-induced PONV during PCA over several decades. Three 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists, such as ondansetron, granisetron, and tropisetron, have been recommended by clinical practice guidelines for PONV prevention because they have fewer side effects than other antiemetics.^[9] Previous clinical studies demonstrated that antiemetics as an adjuvant to opioids PCA for postoperative pain and demonstrated mixing antiemetics with the PCA solution were suggested for the prevention of PCA opioids-induced PONV.^[10–12] For this reason, the combination of lornoxicam with antiemetics, such as droperidol, ondansetron, granisetron, and tropisetron in infusion solution for PCA administration for postoperative pain management, may be desirable.

Mixing of 2 or more drugs together in infusion solutions via intravenous PCA, drug incompatibility, or loss of stability can occur. Chemical incompatibility and instability of the drugs in the mixtures will result in an inadequate therapeutic outcome, and the degradation products may cause undesirable side effects.^[13] In the literature, the compatibility and stability of lornoxicam with the 4 antiemetic medications in infusion solutions for PCA

Editor: Somchai Amorniyotin.

Authorship: conceived and designed the experiments—BXF, LHW; performed the experiments—BXF, PL, LHW; analyzed the data—XYS, FCC; contributed reagents/materials/analysis tools—PL, XYS, FCC; write the paper—BXF, PL, LHW.

Funding: this work was supported in part by the Hubei Province health and family planning scientific research project (Number: WJ2015MB215 and WJ2015MB290) and Science and Technology Key Program of Shiyuan (Number: 14Y45).

The authors have no conflicts of interest to disclose.

^a Department of Pharmacy, Dongfeng Hospital, Hubei University of Medicine, Shiyuan, Hubei, P.R. China., ^b Department of Pharmacy, Renmin Hospital, Hubei University of Medicine, Shiyuan, Hubei, P.R. China.

* Correspondence: Lin-hai wang, Renming Hospital, Hubei University of Medicine Shiyuan, Hubei, China (e-mail: wanglhpharmacy@sina.com).

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Medicine (2016) 95:25(63824)

Received: 21 March 2016 / Received in final form: 4 May 2016 / Accepted: 10 May 2016

<http://dx.doi.org/10.1097/MD.0000000000003824>

has not yet been documented. Therefore, the objective of this study was to determine the compatibility and stability of lornoxicam with the 4 antiemetic medications in 0.9% sodium chloride injection when stored in polyolefin bags at room temperature for 48 hours.

2. Methods and materials

2.1. Materials and reagents

Reference standards for lornoxicam, granisetron hydrochloride, ondansetron hydrochloride, droperidol, and tropisetron hydrochloride were obtained from the National Institutes for food and drug Control (Beijing, China). Lornoxicam for injection 8 mg (Zhejiang Zhenyuan Pharmaceutical Co., Ltd, Shaoxing, China); ampules of 2 mg/mL ondansetron hydrochloride (Qilu pharmaceutical Co., Ltd. Shangdong, China); ampules of 1 mg/mL granisetron hydrochloride (Ningbo Team Pharm Co., Ltd. Zhejiang, China); ampules of 1 mg/mL tropisetron hydrochloride (Hengrui Medicine Co., Ltd. Jiangsu, China); and ampules of 1 mg/mL droperidol (Xiudong Pharmaceutical Co. Ltd. Shanghai, China) were obtained commercially. The infusion solution, 0.9 mg mL⁻¹ sodium chloride injection (Kelun Pharmaceutical Co., Ltd. Sichuang, China) in polyolefin bags, was also obtained commercially. The acetonitrile and other mobile-phase components were suitable for high-pressure liquid chromatography (HPLC) analysis. Ultrapure water was purified using a Milli-Q system (Millipore, Bedford, MA).

2.2. Analytical method

Drug concentrations of lornoxicam, granisetron, ondansetron, droperidol, or tropisetron were determined using a validated HPLC method. The details of the analytical methods used in our study are indicated in Table 1. The HPLC methods were adapted from previously published methods or were developed in our laboratory.^[14,15] The HPLC systems UltiMate-3000 from Dionex Corporation (Dionex, Sunnyvale, CA) were used for analysis of lornoxicam and the 4 antiemetic agents. The HPLC systems consisted of a quaternary-liquid gradient delivery pump, an auto-injector, a column oven, and a diode array detector. Chromatograms were recorded and integrated by a personal computer installed with Chromeleon version 6.8 (Dionex, Voisins-le-Bretonneux, France) chromatographic software. The phenomenex Luna C₁₈ (250 mm × 4.6 mm, 5 μm) (Phenomenex, Torrance, CA) was used as a stationary phase. The assay

was performed at room temperature and injection volume was 20 μL. The analytical methods for each of the drugs were validated as stable indicated by accelerated degradation. The sample solutions of lornoxicam with granisetron hydrochloride, ondansetron hydrochloride, droperidol, or tropisetron hydrochloride in 0.9% sodium chloride injection were degraded with 0.1 mol/L sodium hydroxide (acidified), 0.1 mol/L sodium hydroxide (alkaline degraded), and 3% hydrogen peroxide (oxidized) for 5 hours at 60 °C. The chromatogram obtained for the degraded preparation was compared with a chromatogram obtained from the standard curve to confirm separation of the parent molecule from its degradation products. Under extreme conditions, these 5 analytes were found to be stable with <3% decomposition compounds and baseline separated from all analytes.

2.3. Preparation of injection combinations and storage conditions

The injection combinations were freshly prepared in polyolefin bags using volumes reflecting those of 2-day pumps (100 mL). The required contents of the ampoules were transferred to polyolefin bags (Kelun Pharmaceutical Co., Sichuang, China) and made up to volumes of 100 mL with 0.9% sodium chloride injection. The binary injection combinations of lornoxicam with ondansetron hydrochloride, granisetron hydrochloride, tropisetron hydrochloride, or droperidol were prepared with the following concentrations: 0.4 mg/mL lornoxicam with 0.08 mg/mL ondansetron hydrochloride, 0.06 mg/mL granisetron hydrochloride, 0.05 mg/mL tropisetron hydrochloride, or 0.05 mg/mL droperidol. These dose ranges were chosen according to daily practice. Three samples of each injection combinations were prepared under aseptic conditions in laminar flow hoods and kept in the dark at room temperature (25 ± 0.5°C). This study was approved by the Medical Ethics Committee of the Dongfeng Hospital, Hubei University of Medicine, China.

2.4. Physical compatibility of the injection combinations

In the physical compatibility study, 5-mL samples were removed from each injection combinations for analysis of appearance at predetermined times (0, 2, 4, 8, 24, and 48 hours). At the specified times, color change, cloudiness, and precipitation were evaluated against light and dark backgrounds. Moreover, the pH values of each samples was also determined at each time point by using a

Table 1
Chromatographic methods used for analysis of lornoxicam and 4 antiemetic medications.

Variable	Drug				
	Lornoxicam	Droperidol	Ondansetron	Granisetron	Tropisetron
Mobile phase	Acetonitrile:0.05 mol/L KH ₂ PO ₄ (pH 6.0) (35:65,v/v)	Acetonitrile:0.05 mol/L ammonium acetate (30:70,v/v)	Acetonitrile:0.05 mol/L KH ₂ PO ₄ (pH 6.0) (35:65,v/v)	Acetonitrile:0.05 mol/L KH ₂ PO ₄ (pH 6.0) (35:65,v/v)	Acetonitrile:0.05 mol/L KH ₂ PO ₄ (pH 6.0) (35:65,v/v)
Flow rate (mL/min)	1.0	1.0	0.8	1.0	0.8
Detection (nm)	380	246	306	302	284
Retention time (min)	10.6	6.5	7.6	6.2	4.9
Linear range (mg/L)	4.0–400	0.5–100	0.4–80.0	1.2–120.0	1.0–50.0
Linear equation	Y = 0.5477X - 0.4463	Y = 0.3097X + 0.1352	Y = 2.1704C - 6.575	Y = 3.0547X - 0.8225	Y = 4.1420C + 0.1895
Linearity (r)	0.9996	0.9997	0.9994	0.9996	0.9996
LOQ (mg/L)	2.0	0.25	0.06	0.18	0.6
LOD (mg/L)	0.8	0.1	0.02	0.06	0.2

LOQ = limit of quantification, LOD = limit of detection.

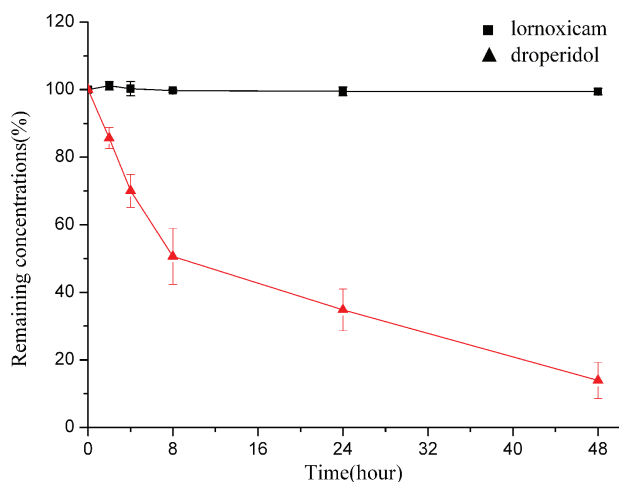


Figure 1. Drug concentrations (mean±SD [%]; n=3) of lornoxicam for injection and droperidol in PCA solution >48hours at 25°C. PCA=patient-controlled analgesia, SD=standard deviation.

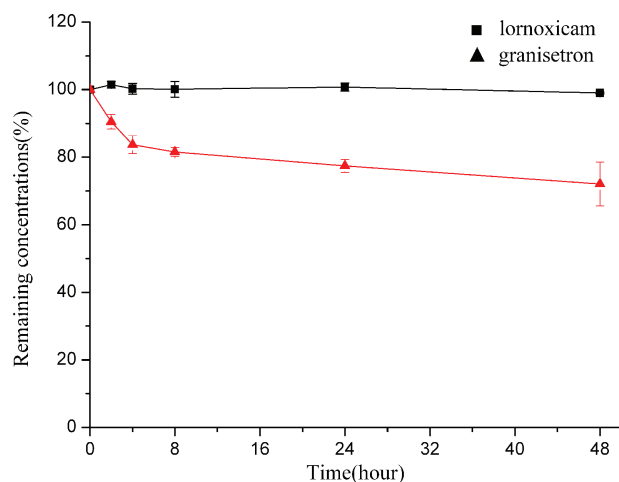


Figure 3. Drug concentrations (mean±SD [%]; n=3) of lornoxicam for injection and granisetron hydrochloride in PCA solution >48hours at 25°C. PCA=patient-controlled analgesia, SD=standard deviation.

phs-3c pH meter (Leici Instrument Co., Shanghai, China). PH value at the initial and 48-hour assessments had to be within 2.0 units to meet compatibility requirements.^[16]

2.5. Chemical stability of the injection combinations

At each time point, samples were analyzed for drug concentrations. Immediately after each sample was physical compatibility studied, a 2 mL portion was filtered through 0.45-µm filters and diluted to 10 mL with mobile phase. Dilutions were determined at each analysis by the above-described HPLC analytical method. In the concentrations analysis, determinations were performed in triplicate for each sample. The initial concentrations of lornoxicam, granisetron hydrochloride, ondansetron hydrochloride, droperidol, and tropisetron hydrochloride were defined as 100%, and subsequent sample concentrations for every drug in the mixtures were reported as the percentage of the initial concentration. The admixtures were considered chemically stable if they retained 90% of the initial concentrations.

3. Results

The chemical stability results of lornoxicam-droperidol, lornoxicam-ondansetron hydrochloride, lornoxicam-granisetron hydrochloride, and lornoxicam-tropisetron hydrochloride injection combinations simulated PCA administration stored at room temperature are presented in Figs. 1–4. As indicated in Figs. 1–4, the results obtained in our study showed that nonsignificant variation in lornoxicam concentration in all the injection combinations tested. At the end of the study period (48 hours), the percentages of lornoxicam remaining in the admixtures were higher than 98 %. On the contrary, the 4 antiemetic agents such as droperidol, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride showed an evident decrease of its concentration in its injection combinations with lornoxicam. In all injection combinations, the percentage of the remaining concentration for the 4 antiemetic agents after 48 hours of the sample preparation was <90.0%.

The average pH of the injection combinations stored in polyolefin bags at room temperature are given in Table 2. The

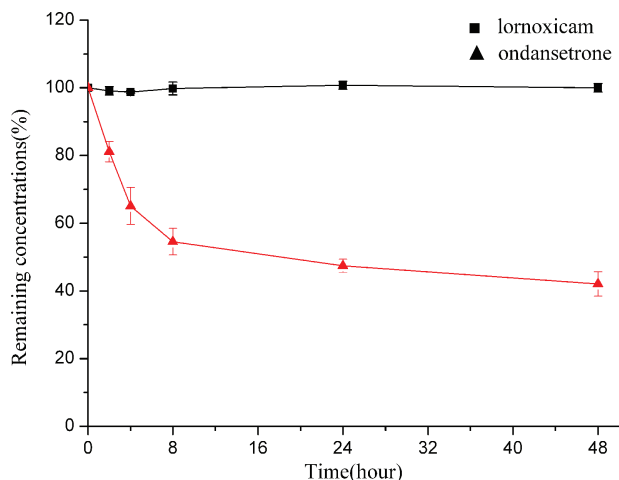


Figure 2. Drug concentrations (mean±SD [%]; n=3) of lornoxicam for injection and ondansetron hydrochloride in PCA solution >48hours at 25°C. PCA=patient-controlled analgesia, SD=standard deviation.

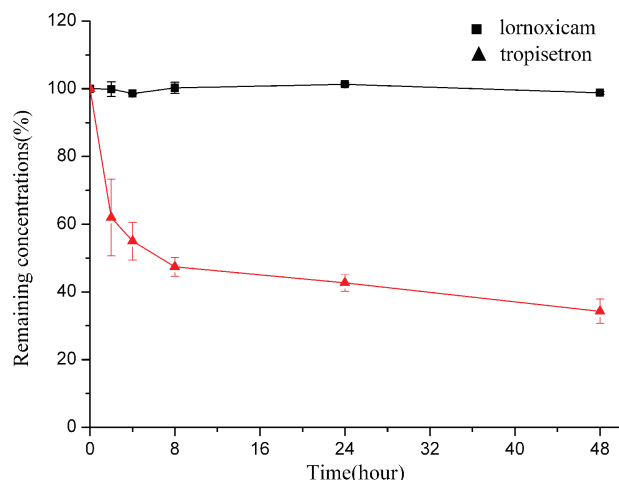


Figure 4. Drug concentrations (mean±SD [%]; n=3) of lornoxicam for injection and tropisetron hydrochloride in PCA solution >48hours at 25°C. PCA=patient-controlled analgesia, SD=standard deviation.

Table 2**pH values (mean \pm SD; n=3) of lornoxicam with the 4 antiemetic medications in PCA solution >48 hours at 25°C.**

Storage period (h)	pH values			
	Lornoxicam + Droperidol	Lornoxicam + Ondansetron	Lornoxicam + Granisetron	Lornoxicam + Tropisetron
0	9.02 \pm 0.15	8.61 \pm 0.11	8.84 \pm 0.02	8.56 \pm 0.04
2	8.96 \pm 0.06	8.65 \pm 0.14	8.90 \pm 0.12	8.61 \pm 0.06
4	8.84 \pm 0.11	8.68 \pm 0.06	8.85 \pm 0.05	8.58 \pm 0.03
8	8.88 \pm 0.04	8.72 \pm 0.21	8.84 \pm 0.02	8.63 \pm 0.10
24	8.86 \pm 0.08	8.64 \pm 0.08	8.87 \pm 0.06	8.71 \pm 0.05
48	8.72 \pm 0.20	8.70 \pm 0.12	8.81 \pm 0.13	8.67 \pm 0.09

PCA = patient-controlled analgesia, SD = standard deviation.

results show that the pH value of the injection combinations samples were alkalinity with pH values ranging from 8.8 to 9.0, which imply that no significant modifications occurred throughout the study.

All injection combinations were transparent and a little yellow without deposit, turbidity, or gas at time of preparation; however, after storage of 4 to 8 hours, the presence of a slight precipitate was observed in all 4 injection combinations. At the end of the study, the presence of a very significant precipitate was observed in all injection combinations. Results from this study indicate that injection combinations of lornoxicam with droperidol, ondansetron hydrochloride, granisetron hydrochloride, or tropisetron hydrochloride in 0.9% sodium chloride injection stored in polyolefin bags at room temperature were incompatibility.

4. Discussion

Postoperative pain and PONV are 2 of the major concerns for patients presenting for surgery. It is common practice in postoperative pain control to use combinations of drugs. The use of a combination of different drugs in postoperative analgesia aim to provide superior pain relief and to reduce the incidence of analgesic-related side effects compared with a single drug.^[17]

However, the injection combinations are not available commercially for clinical use, and they must be prepared in the hospital pharmacy departments under aseptic conditions. To our knowledge, no published information is available on the compatibility and stability of lornoxicam in combination with the 4 antiemetic agents, such as droperidol, ondansetron, granisetron, and tropisetron in infusion solution. Thus, the aim of this study was to fulfill this lack of information.

Lornoxicam (6-chloro-4-hydroxy-2-methyl-N-pyridin-2-yl-2H-thieno [2, 3-e] [1, 2] thiazine-3-carboxamide-1,1-dioxide) is a monoprotic weak acid (pKa 4.7) and low solubility compounds. The drug is hardly soluble in water and acid. The solubility of lornoxicam showed strong pH dependence, as the solubility increased along with the pH step up.^[18] The stability of lornoxicam for injection in 0.9% sodium chloride injection prepared according to clinical regime showed that no significant change in 72 hours.^[19] However, drug incompatibility was occurred when lornoxicam combined with butorphanol tartrate or fentanyl citrate injection in 0.9% sodium chloride injection for PCA used.^[20,21]

As for the 4 antiemetic medications, ondansetron, granisetron, tropisetron, and droperidol are weak base (pKa were 7.4, 7.8, 8.9, and 7.64, respectively). The solubility of the 4 antiemetic medications showed strong pH dependence, which is stable in acid solution and may cause drug precipitation or crystallization in alkaline solution. Previously, ondansetron hydrochloride was

found to be incompatible when combined in infusion solutions with aciclovir sodium, aminophylline, amphotericin B, fluorouracil, furosemide, ganciclovir sodium, lansoprazole, parecoxib sodium, and sodium bicarbonate.^[22–25] Regarding granisetron hydrochloride, previous studies have demonstrated that incompatibility occurred in solution when combined with aciclovir sodium, amphotericin B, amsacrine, lansoprazole, or with sodium bicarbonate.^[26,27] For tropisetron hydrochloride, Sun et al have revealed the instability of the drug mixtures containing tropisetron hydrochloride with fosaprepitant, which seemed to precipitate because of pH modification.^[28] Similar to the 3 5-HT₃ receptor antagonists, droperidol was demonstrated to be incompatible when combined with allopurinol sodium, amphotericin B cholesteryl sulfate complex, fluorouracil, furosemide, lansoprazole, methotrexate sodium, and pemetrexed disodium.^[23,29–31]

In the present study, pH values of the 4 injection combinations of lornoxicam were alkaline, with pH among 8.6 to 9.0. According to these alkaline mixtures, the presences of precipitate were observed in all of the injection combinations during the study. Results from this study indicate that injection combinations of lornoxicam with ondansetron hydrochloride, granisetron hydrochloride, tropisetron hydrochloride, or droperidol during simulated PCA administration were incompatibility. This visual and chemical incompatibility could be attributed to an acid-base reaction.

5. Conclusion

Regarding this compatibility and stability study, injection combinations of lornoxicam with ondansetron hydrochloride, granisetron hydrochloride, tropisetron hydrochloride, or droperidol according to clinical regime in 0.9% sodium chloride injection and at room temperature are incompatibility. Clinicians should be aware that combinations of lornoxicam with the 4 antiemetic agents in 0.9% sodium chloride injection stored in polyolefin bags at room temperature should be avoided.

References

- [1] Hillstrom C, Jakobsson JG. Lornoxicam: pharmacology and usefulness to treat acute postoperative and musculoskeletal pain a narrative review. *Expert Opin Pharmacother* 2013;14:1679–94.
- [2] Karaca M, Kocoglu H, Gocmen A. Comparison of lornoxicam with tramadol in patient-controlled analgesia after gynecological surgery. *Eur J Gynaecol Oncol* 2006;27:78–80.
- [3] Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. *Anesth Analg* 1998;86:1045–50.
- [4] Zhao H, Ye TH, Gong ZY, et al. Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin Med Sci J* 2005;20:59–62.

- [5] Staunstrup H, Ovesen J, Larsen UT, et al. Efficacy and tolerability of lornoxicam versus tramadol in postoperative pain. *J Clin Pharmacol* 1999;39:834–41.
- [6] Nørholt SE, Sindet-Pedersen S, Larsen U, et al. Pain control after dental surgery: a double-blind, randomised trial of lornoxicam versus morphine. *Pain* 1996;67:335–43.
- [7] Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006;19:CD004125.
- [8] Tramèr MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. *Anesth Analg* 1999;88:1354–61.
- [9] Tricco AC, Soobiah C, Blondal E, et al. Comparative efficacy of serotonin (5-HT₃) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med* 2015;13:136.
- [10] Moon YE, Joo J, Kim JE, et al. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *Br J Anaesth* 2012;108:417–22.
- [11] Kim YY, Moon SY, Song DU, et al. Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery. *Korean J Anesthesiol* 2013;64:122–6.
- [12] Kuo YM, Tsou MY, Chang WK, et al. To add or not to add? An empirical study on droperidol and intravenous patient-controlled analgesia. *J Chin Med Assoc* 2012;75:227–33.
- [13] Longfield V. Compatibility and stability of 5-HT₃ receptor antagonists: a pharmacology review. *Oncol Nurs Forum* 2002;29:1469–82.
- [14] Chen FC, Xiong H, Liu HM, et al. Compatibility of butorphanol with granisetron in 0.9% sodium chloride injection packaged in glass bottles or polyolefin bags. *Am J Health Syst Pharm* 2015;72:1374–8.
- [15] Chen FC, Shi XY, Li P, et al. Stability of butorphanol-tropisetron mixtures in 0.9% sodium chloride injection for patient-controlled analgesia use. *Medicine* 2015;94:e432.
- [16] Kanji S, Lam J, Johanson C, et al. Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. *Crit Care Med* 2010;38:1890–8.
- [17] Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. *Br J Anaesth* 2011;107:i27–40.
- [18] Zhang J, Tan X, Gao J, et al. Characterization of two polymorphs of lornoxicam. *J Pharm Pharmacol* 2013;65:44–52.
- [19] Fang BX, Ding J, Chen FC, et al. Stability of lornoxicam in 0.9% sodium chloride injection with different pH values. *Pract Pharm Clin Remed* 2011;14:494–5.
- [20] Chen FC, Fang BX, Li P, et al. Compatibility and stability of lornoxicam with morphine, tramadol or fentanyl in infusion solutions. *Afr J Pharm Pharmacol* 2012;6:2055–60.
- [21] Friedman B, Jiang HJ. Stability of butorphanol tartrate injection with lornoxicam injection in patient controlled analgesia pump. *Int J Health Care Fi* 2013;10:171–85.
- [22] Trissel LA, Tramonte SM, Grilley BJ. Visual compatibility of ondansetron hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991;48:988–92.
- [23] Trissel LA, Saenz C, Williams YW, et al. Incompatibilities of lansoprazole injection with other drugs during simulated Y-site coadministration. *Int J Pharm Compound* 2001;5:314–21.
- [24] Hauser AR, Trissel LA, Martinez JF. Ondansetron compatible with sodium acetate. *J Clin Oncol* 1993;11:197.
- [25] Canann D, Tyler LS, Barker B, et al. Visual compatibility of i.v. medications routinely used in bone marrow transplant recipients. *Am J Health-Syst Pharm* 2009;66:727–9.
- [26] Trissel LA, Gilbert DL, Martinez JF. Compatibility of granisetron hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997;54:56–60.
- [27] Mayron D, Gennaro AR. Stability and compatibility of granisetron hydrochloride in IV solutions and oral liquids and during simulated Y-site injection with selected drugs. *Am J Health-Syst Pharm* 1996;53:294–304.
- [28] Sun S, Schaller J, Placek J, et al. Compatibility of intravenous fosaprepitant with intravenous 5-HT₃ antagonists and corticosteroids. *Cancer Chemother Pharmacol* 2013;72:509–13.
- [29] Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994;51:1792–9.
- [30] Trissel LA, Gilbert DL, Martinez JF. Incompatibility and compatibility of amphotericin B cholesteryl sulfate complex with selected other drugs during simulated Y-site administration. *Hosp Pharm* 1998;33:284–92.
- [31] Trissel LA, Saenz CA, Ogundele AB, et al. Physical compatibility of pemetrexed disodium with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004;61:2289–93.