Clinical Trial/Experimental Study

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

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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 analytic 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 solutions 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
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. Shandong, 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. Sichuan, 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 Chromleon 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., Ltd., Sichuan, 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. |
|---------|----------------------------------------------------------------------------------|
| Drug    | Lornoxicam | Droperidol | Ondansetron | Granisetron | Tropisetron |
| Mobile phase | Acetonitrile:0.05 mol/L KH3PO4 (pH 6.0) | Acetonitrile:0.05 mol/L KH3PO4 (pH 6.0) | Acetonitrile:0.05 mol/L KH3PO4 (pH 6.0) | Acetonitrile:0.05 mol/L KH3PO4 (pH 6.0) | Acetonitrile:0.05 mol/L KH3PO4 (pH 6.0) |
| Flow rate (mL/min) | 1.0 | 1.0 | 0.8 | 1.0 | 0.8 |
| Detection (mm) | 380 | 2146 | 306 | 320 | 264 |
| Retention time (min) | 10.6 | 6.5 | 7.6 | 6.2 | 4.9 |
| Linear range (mg/L) | 0.4–80.0 | 1.0–50.0 | 1.2–120.0 | 2.1704C + 0.1895Y | 4.1200C + 1.0895Y |
| Linear equation | Y = 0.0577X – 0.4683 | Y = 0.325X + 1.352 | Y = 2.1704C – 6.075 | Y = 3.0547X – 0.8225 | Y = 4.1200C + 1.0895 |
| Linearity (r) | 0.9996 | 0.9997 | 0.9994 | 0.9996 | 0.9996 |
| LOD (μg/mL) | 2.0 | 0.25 | 0.06 | 0.18 | 0.6 |
| LOD (μg/mL) | 0.8 | 0.1 | 0.02 | 0.06 | 0.2 |

LOD = limit of quantification, LOD = limit of detection.
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
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, ansacrine, lansoprazole, or with sodium bicarbonate.[16–27] For tropisetron hydrochloride, Sun et al have revealed the instability of the drug mixture containing tropisetron hydrochloride with fosaprepitant, which seemed to precipitate because of pH modification.[28] Similar to the 3 S-H$_3$ 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.

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