Compatibility and Stability of Binary Mixtures of Ketorolac Tromethamine and Tramadol Hydrochloride Injection Concentrate and Diluted Infusion Solution

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1. Introduction

Recent guidelines for pain management suggest the use of multimodal analgesia to improve pain relief and to reduce analgesic-related side effects. Of the multimodal protocols, the practice of combining nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids is commonplace in the treatment of acute and chronic pain. By allowing a reduction in the individual drug dose and, in turn, a decrease in the risk of adverse effects from each drug, analgesic synergy between NSAIDs and opioids has reinforced

Objective: Ketorolac added to tramadol as an injection mixture convenient for clinical use has been shown to be an effective balanced analgesic regimen in alleviating moderate-to-severe pain. However, analytical confirmation of the compatibility and stability of this combination is not available. This study examined the compatibility and stability of this combination.

Methods: Two different mixtures containing ketorolac tromethamine and tramadol hydrochloride were examined: ketorolac (10 mg/mL) and tramadol (33.3 mg/mL) prepared as injection concentrate in ampoule mingled together in the ratio of one ampoule to one ampoule; diluted ketorolac (2 mg/mL) and tramadol (20 mg/mL) prepared in saline infusion solution, with or without pH adjustment. The mixtures were visually inspected for precipitation and color change. Quantitative chemical analysis was performed on days 0, 1, 3 and 7 by high-performance liquid chromatography.

Results: When stored at room temperature under ambient light, the ketorolac (10 mg/mL)−tramadol (33.3 mg/mL) injection concentrate and ketorolac (2 mg/mL)−tramadol (20 mg/mL) solution, without pH adjustment and adjusted to pH 5−8, were physico-chemically stable, and neither visible precipitation nor loss of concentration was found. With the ketorolac (2 mg/mL)−tramadol (20 mg/mL) solution adjusted to pH 9, however, precipitation occurred immediately, resulting in a significant loss of tramadol.

Conclusion: This study suggests that a ready-to-use ketorolac−tramadol mixture, either undiluted or diluted in physiological saline solution, can be prepared, with a shelf life of at least 7 days when stored at room temperature under ambient light.
the pharmacological basis for the clinical utility of NSAID–opioid combinations.\textsuperscript{2,3}

In the clinical setting, the use of a single syringe or infusion bag for systemic administration of a mixture of an NSAID and opioid is a very simple and convenient practice. Among the various NSAID–opioid analgesic mixtures used in clinical pain management, ketorolac–tramadol has been reported to be an excellent regimen of validity in postoperative pain\textsuperscript{4,5} and acute sickle cell pain.\textsuperscript{6} Although both ketorolac and tramadol remain a hot topic of discourse and discussion in the literature, the compatibility and stability of their combination have not been scientifically validated. Making use of clinically relevant concentrations of ketorolac tromethamine and tramadol hydrochloride, this study was conducted to determine the stability of ketorolac–tramadol mixtures at two different ratios: (1) ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) injection concentrate mixture, given as a convenient bolus for moderate acute pain; and (2) ketorolac (2 mg/mL)–tramadol (20 mg/mL) mixture diluted in 0.9% sodium chloride, as an infusion solution commonly utilized in our hospital for postoperative patient-controlled analgesia.

2. Methods

2.1. Reagents

The tested drugs used were ketorolac tromethamine (30 mg/mL; Yung Shin Pharm. Ind. Co. Ltd., Taichung, Taiwan), tramadol hydrochloride (100 mg/2 mL, prepared in ampoules; Grünenthal GmbH, Stolberg, Germany), 0.9% sodium chloride injection (Y.F. Chemical Corp., Hsin-Chuang, Taiwan), and the complementary reagents 0.5 N, 1 N and 5 N NaOH and 0.5 N HCl (Hwa Sin Biotech Ltd., Hsinchu, Taiwan).

2.2. Experimental design

Mixtures were prepared in two different mixing ratios. First, ketorolac 30 mg and tramadol 100 mg (one ampoule of each) were mixed together without addition of any diluents in a 5-mL polypropylene syringe (Terumo Corporation Taipei Branch, Taipei, Taiwan) to produce the ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) injection concentrate. Second, six 50-mL aliquots of 0.9% sodium chloride injection were taken, of which five were adjusted with NaOH or HCl to pH 5, 6, 7, 8 and 9, and one was left without pH adjustment. Kotorolac 30 mg and tramadol 300 mg were then transferred into a 100-mL polyvinyl chloride infusion bag (Mini-Bag Plus; Baxter International Inc., Deerfield, IL, USA) to make up a volume of 15 mL, and mixed with each of the pH-adjusted saline solutions, to produce the ketorolac (2 mg/mL)–tramadol (20 mg/mL) mixture infusion solutions of different acidity. All mixtures were prepared in triplicate and stored at room temperature (25ºC) under fluorescent light until analysis.

Mixtures were visually examined for changes in color and/or signs of precipitation, and concentrations of ketorolac and tramadol were determined using high-performance liquid chromatography (HPLC) on the day of preparation, and 1, 3 and 7 days after preparation. The pH of both mixtures of the ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) injection concentrate and the non-pH-adjusted ketorolac (2 mg/mL)–tramadol (20 mg/mL) solution was measured on the first and last day of the study using a pH meter (MP225; Mettler-Toledo Pac Rim AG Taiwan Branch, Taipei, Taiwan). All assays were done in duplicate.

2.3. HPLC

The chromatography equipment included a Waters 600E delivery pump, a Waters 717 Plus autosampler, and a Waters 2487 Dual Absorbance UV Detector, all of which were obtained from GenTech Taiwan Scientific Co. Ltd. (Taipei, Taiwan). A Symmetry C18 (3.5 mm ID×150 mm) column (Waters Asia Ltd., Taiwan Branch, Taipei, Taiwan) was used with a mobile phase consisting of CH$_3$CN (Burdick & Jackson HPLC grade; Honeywell International Inc., Morristown, NJ, USA) and 0.2% trifluoroacetic acid (27/73, v/v; Acros Organics, part of Thermo Fisher Scientific Inc., Geel, Belgium). Chromatography was performed using a flow rate of 0.9 mL/min, with detection wavelength set at 254 nm. The injection volume was 20 μL. The temperature of the chromatographic system was 35ºC. Chromatographic peak integration was performed using Empower software (Waters Corp., Milford, MA, USA).

2.4. Method validation

In accordance with the guidelines for Validation of Chromatographic Methods,\textsuperscript{7} calibration curves were processed in triplicate on 3 consecutive days. Using a fixed concentration of ketorolac and tramadol, two standard calibration solutions were prepared in the mobile phase: ketorolac (0.04 mg/mL)–tramadol (0.15 mg/mL) and ketorolac (0.02 mg/mL)–tramadol (0.2 mg/mL). Retention times of 18.68 minutes and 2.42 minutes were obtained for ketorolac and tramadol, respectively. The relative standard deviations (%) of the results of within-day and between-day precision always remained <2% for both drugs.
2.5. Stability analysis

The relative standard deviations of duplicate HPLC determinations performed on all the triplicate samples were consistently less than 2%. Percentages of initial ketorolac and tramadol remaining at the designated testing time points were calculated and the mean percentage for triplicate samples was determined. A 5% loss of initial concentration of either ketorolac or tramadol was considered to be significant.8

3. Results

The percentages of initial ketorolac and tramadol concentrations (mean of triplicate samples) following mixture preparation are presented in Table 1. With the ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) mixture, there were no discernible changes in color throughout the study. No visible precipitation was observed. Initial mean pH was 7.25, and this did not change significantly after 7 days (mean pH at 7 days, 7.24). Neither ketorolac nor tramadol concentration varied appreciably, and all values were within 5% of baseline. With the ketorolac (2 mg/mL)–tramadol (20 mg/mL) mixture, there was also no color change, no visible precipitation and no loss of drugs throughout the study, when prepared in non-pH-adjusted saline or in saline adjusted to pH 5–8. Initial mean pH of the ketorolac (2 mg/mL)–tramadol (20 mg/mL) mixture in non-pH-adjusted saline was 7.19, and this did not change significantly after 7 days (mean pH at 7 days, 7.18). At pH 9, however, turbulent precipitation was observed immediately after drug mixing, and needle-like crystals were found from day 1 onwards to day 7. While the concentration of ketorolac remained unchanged over the test period, the tramadol concentration significantly decreased immediately after drug mixing (% remaining = 70.4%) and further decreased onwards to day 7 (% remaining = 56%).

4. Discussion

Our study demonstrates that both the ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) injection concentrate and the ketorolac (2 mg/mL)–tramadol (20 mg/mL) infusion solution diluted with 0.9% sodium chloride at pH 5–8 were stable at room temperature under ambient light for at least 7 days.

The practice of mixing two or more parenteral analgesics with synergistic mechanisms of action to produce an analgesic formulation convenient to use is widespread in the clinical setting. Although this practice is concordant with the concept of
multimodal analgesia advocated in pain management guidelines, potential drug incompatibility continues to be a matter of concern. Incompatible interactions may produce a number of adverse effects, including alteration in therapeutic properties, blockage of the cannula, and inflamed injection sites. Therefore, potential drug incompatibility issues with analgesic mixtures should be detected before implementing any combination analgesic therapy into clinical practice. Although ketorolac stability and tramadol stability in solution have been studied, no HPLC quantification and stability studies of ketorolac and tramadol mixture are available. Based on our findings, there was no evidence of drug interaction or degradation products for the ketorolac–tramadol mixture, and chromatography did not reveal any other substances. We believe that this information has clinical utility in facilitating the preparation and dispensing of the ketorolac–tramadol mixture.

In our work, raising the pH to 9 resulted in significant loss of tramadol but not ketorolac. This physicochemical behavior can be readily inferred from differences in the acid-base nature of the two drug molecules. As tramadol is a weak base with a pKa of 9.41, alkalinization will decrease its extent of ionization and solubility. In contrast, weakly acidic ketorolac (pKa, 3.54) will exist primarily in an ionized water-soluble form in an alkalinized environment.

Combination of tramadol hydrochloride with other drugs in solution has resulted in variable results. It is stable when combined with dexamethasone, haloperidol, and ondansetron in saline, but precipitates with acyclovir and clindamycin. Ketorolac tromethamine is stable when combined with morphine hydrochloride in saline at certain concentrations.

Guidelines for mixture preparation are empirical in nature. In our study, clinically relevant combination doses were used. In doses normally used for adults, ketorolac 30 mg (in 1-mL ampoule) and tramadol 100 mg (in 2-mL ampoule) are often given consecutively in our institute by bolus injection for the treatment of moderate-to-severe acute pain. When these two analgesics are mixed in the same syringe, a 3-mL ketorolac (10 mg/mL)–tramadol (33.3 mg/mL) injection concentrate is produced. In the form of a diluted solution, concentrations of 2 mg/mL for ketorolac and 20 mg/mL for tramadol were used in our study. These concentrations selected for combination are close to the 1.2–1.5 mg/mL and 10–20 mg/mL for ketorolac and tramadol, respectively, used for patient-controlled analgesia in other clinical studies. Such a ready-to-use formulation, either in the form of a bolus injection or an infusion solution, suits the needs of the clinical setting and will likely reduce the workload of nurses by simplifying their tasks.

One limitation of the study is that we did not examine any of our solutions for the potential issue of bacterial contamination. It is strongly recommended that preparation of the solution must take place under strict aseptic conditions within a laminar-airflow hood to reduce the chances of bacterial growth.

In conclusion, the clinical implications of our results are that injection concentrate and diluted infusion solution containing ketorolac tromethamine and tramadol hydrochloride may be pre-prepared and used with confidence up to 7 days following preparation when stored at room temperature under ambient light.

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References


