Full Length Research Paper

Compatibility and stability of lornoxicam with morphine, tramadol or fentanyl in infusion solutions

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The administration of drugs via patient controlled intravenous analgesia (PCIA) is routinely practiced for the management of postoperative pain. A combination of lornoxicam and opioid analgesics such as morphine, tramadol, or fentanyl is often administered for the management of severe pain to ensure that a minimal dose of each is used. Unfortunately, no data are available about compatibility and stability of lornoxicam in combination with these opioid analgesics. The aim of this study was to evaluate the compatibility and stability of these mixtures in polypropylene syringes for up to 168 h. Admixtures were assessed for 168 h (7 days) after preparation stored at 25°C and protected from sunlight exposure. Samples were withdrawn from each bag immediately after preparation and at predetermined intervals (2, 4, 8, 24, 48, 72, 120, and 168 h after preparation). Admixtures were visually inspected for precipitation, cloudiness, and discoloration at each sampling interval. Drug concentration was determined using high performance liquid chromatographic analysis. At ambient temperature, the drug mixtures lornoxicam/morphine and lornoxicam/tramadol were clear in appearance and no color change or precipitation was observed during the study period. After 168 h of storage, the maximum losses obtained were lower than 10% for three drugs. On the contrary, fentanyl showed an evident decrease of its concentration in its mixture with lornoxicam. After 168 h, fentanyl concentration was less than 10% of the starting concentrations. The results indicate that, at ambient storage conditions, the drug mixtures lornoxicam/morphine and lornoxicam/tramadol in 0.9% sodium chloride injection were physically and chemically stable for at least 168 h when stored in polypropylene syringes. However, the lornoxicam/fentanyl mixture was physically incompatible.

Key words: Lornoxicam, tramadol, morphine, fentanyl, drug interactions, compatibility, patient controlled analgesia.

INTRODUCTION

Postoperative pain therapy is still a major challenge for clinicians. An effective analgesia can accelerate postoperative surgical recovery and improve the patient's quality of life (Kehlet and Holte, 2001). Opioid and non-opioid analgesics are widely used in the treatment of postoperative pain.

Lornoxicam is a potent nonsteroidal anti-inflammatory drug (NSAID). The drug has a short plasma elimination half-life, of approximately 4 to 6 h. Because of this, it is suitable in the postoperative period for acute pain (Balfour et al., 1996; Bianchi and Panerai, 2002). It has been reported that Intravenous Patient Controlled Analgesia (IV PCA), with lornoxicam is as effective as opioid analgesics for postoperative pain management (Rosenow et al., 1998; Staunstrup et al., 1999; Zhao et al., 2005).

The use of a single analgesic to treat moderate to severe postoperative pain has proven inadequate to ensure optimal analgesia. Multi-modal analgesia is currently recommended for effective postoperative pain control (Jin and Chung, 2001). Multi-modal analgesia is achieved by combining different analgesics such as opioid analgesics, NSAIDs and local anaesthetics in...
order to minimize individual doses and to reduce unwanted side-effects (Karaman et al., 2006). For this aim, a combination of lornoxicam and opioid analgesics (morphine, tramadol, or fentanyl) is often administered for the management of severe pain in our institution. Unfortunately, few data are available on compatibility and stability of lornoxicam in combination with other drugs. Injection of an admixture composed of incompatible drugs to patient could cause additional side-effects or could result in inappropriate or sub-therapeutic delivered dosage (Hamdi et al., 2009). Therefore, the objective of this study was to determine the compatibility and stability of these mixtures in polypropylene syringes for up to 168 h.

MATERIALS AND METHODS

This study was performed with the approval of the Medical Ethics Committee of Dongfeng Hospital Affiliated to Hubei University of Medicine (MEC-2011-013).

The pharmaceutical formulations used to prepare the mixtures were lornoxicam (8.0 mg/5 ml), Lifesline Pharmaceutical Co. Ltd. (China); Morphine hydrochloride injection (10 mg/2 ml), Humanwell Pharmaceutical Co. Ltd. (Yichang, China); Tramadol hydrochloride injection (100 mg/2 ml), Grunenthal Pharmaceutical Co. Ltd.; and Fentanyl citrate injection (0.1 mg/2 ml), Humanwell Pharmaceutical Co., Ltd. (China). The solution of 0.9% NaCl used to prepare the sample mixtures was from Sichuang Kelun Pharmaceutical Co., Ltd (China).

The doses assayed in the study were chosen and taking into consideration are those more frequently used in our institution of postoperative patients. The initial concentrations of the three analgesic mixtures were containing 40 mg/100 ml lornoxicam and 30 mg/100 ml morphine hydrochloride, 40 mg/100 ml lornoxicam and 40 mg/100 ml tramadol hydrochloride, and 40 mg/100 ml lornoxicam and 0.5 mg/100 ml fentanyl citrate. The mixtures were made up in volumes reflecting those used in 2-day infusion pumps (100 ml) and prepared by transferring the contents of the corresponding drug ampoules used in each mixture, and then adding 0.9% NaCl solution to give 100 ml. All the analgesic mixtures were prepared in commercial polypropylene syringes (Jierui, WeiGao Med., Shangdong, China) under aseptic conditions in laminar flow hoods and using sterile drug solutions.

The compatibility and stability studies were performed at 25 ± 0.5°C; all the analgesic mixtures were protected from light and dark backgrounds. Moreover, the pH values for each sample at each analysis were determined by using a pH meter (Leici Instrument Co., Shanghai, China).

Each sample was also analyzed by high-performance liquid chromatography (HPLC) to quantify for the components. HPLC system (UltiMate 3000, Dionex, GER) consisting of quaternary gradient pump, column oven and diode array detector (DAD, UltiMate 3000) was employed for analysis. Chromatographic data was acquired using Chromelone software version 6.80.

Lornoxicam and fentanyl citrate or tramadol hydrochloride were quantified by the same method. Lornoxicam was separated by HPLC from fentanyl citrate, tramadol hydrochloride on a Hypersil C18 column (150 mm × 4.6 mm, 5 μm) (Thermo Electron, USA). The mobile phase consisting of 0.05 mol/L potassium dihydrogen phosphate solution (Xilong Chemical Co. Ltd, Guangdong, China) and chromatographic grade methanol (Fisher Scientific, NJ, USA) in the ratio of 48:52 (v/v) was used throughout the analysis. The flow rate was 1.0 ml/min. The selected detection wavelengths for tramadol hydrochloride, fentanyl citrate, and lornoxicam were 272, 215, and 382 nm, respectively.

For the determination of morphine hydrochloride the method described in the USP 32 for the assay of morphine sulphate injections was used. A Hypersil C18 column (150 mm × 4.6 mm, 5 μm) (Thermo Electron, USA) was used with an isocratic mobile phase consisting of 720 ml of a solution of 0.73 g sodium 1-heptanesulfonate in water and 280 ml of methanol and 10 ml of glacial acetic acid. The flow rate was 1 ml/min and the detection wavelength was set at 284 nm.

Before use, both mobile phases were filtered through a 0.45 μm membrane filter (Jinteng Experiment Equipment Co., Ltd, Tianjin, China) and degassed by sonication for 10 min. Injection volumes of samples and standards were 20 μl. The temperature of the chromatographic system was 30°C.

The method was validated in accordance with the International Conference on Harmonization Guidelinelns (ICH, 1996; Balaji et al., 2008; Muhammad et al., 2011). Three determinations were carried out on each binary solution and at each time point. The starting concentration of each drug was designated as 100.0%; all subsequent concentrations were expressed as a percentage of the starting concentration. The drug was defined as stable if more than 90% of the starting concentration was retained. A 10% loss of starting concentration was considered to be significant. The changes with time of the concentrations of the drugs in solution were analysed using linear regression analysis. The study was considered significant at p < 0.05.

RESULTS

Figures 1, 2 and 3 show the percentages of dose remaining of lornoxicam with morphine, tramadol, or fentanyl in the admixtures when the tests were carried out at 25°C.

As indicated in Figures 1 and 2, the drug mixtures lornoxicam/morphine and lornoxicam/ tramadol maintained chemical stability for 168 h. Throughout these storage periods, the concentrations of lornoxicam, morphine and tramadol remained above 95% of the initial value, and most were near 100%. For the two samples, there was no visible evidence of precipitation or gas formation throughout the observation period.

For the lornoxicam mixtures with fentanyl, the results obtained in our study showed no significant variation in lornoxicam concentration in the admixtures tested (P>0.05). On the contrary, fentanyl showed an evident decrease of its concentration in its mixture with lornoxicam. At room temperature and with protection from daylight, the remaining fentanyl concentration was less than 75%, 2 h after its preparation. At the end of the study period (168 h), the percentage of the remaining concentration of the sample prepared was less than 10.0% (Figures 3).

The pH of the mixture samples was also tested during the study (Table 1). Mixtures of lornoxicam with morphine, tramadol, or fentanyl showed a similar behavior, with the pH value close to 8.5, it implies that no statistically significant modifications occurred throughout
the study. No correlation was observed between pH value and time for any of the drug combinations ($P>0.05$).

**DISCUSSION**

Multi-modal approach to anaesthesia is a familiar concept that offers important benefits in the management of moderate to severe postoperative pain (Schug, 2005). The combination of lornoxicam with morphine, tramadol, or fentanyl brings together two well known analgesics that have different but complementary mechanisms of analgesic action. Laboratory studies have demonstrated that combination of lornoxicam with opioid analgesics via
Figure 3. Percentages of fentanyl citrate and lornoxicam remaining in the admixtures after storage at 25°C for 168 h.

### Table 1. Results of pH determinations for three analgesic mixtures.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Lornoxicam/morphine</th>
<th>Lornoxicam/tramadol</th>
<th>Lornoxicam/fentanyl</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>8.52</td>
<td>8.53</td>
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<td>8.53</td>
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<td>8.62</td>
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PCIA can be a means of reducing the doses of individual drugs, in providing superior pain relief and in reducing analgesic-related side effects (Wang et al., 2006; Kemal et al., 2007; Karaman et al., 2006; Kocaayan et al., 2007; Zhou et al., 2005).

Mixing of two or more chemicals together can lead to physical, chemical or both changes, which may result in an inadequate therapeutic outcome and the degradation products, may cause additional side effects. Unfortunately, no published information is available on the compatibility and stability of lornoxicam in combination with these opioid analgesics in solution for intravenous infusion. Therefore, the aim of this study was to fulfill this lack of information.

Previously, the physical compatibility and/or stability of morphine, tramadol, or fentanyl combined with other drugs in solution have been widely studied. Morphine chlorhydrate was found to be compatible when combined in infusion solutions with haloperidol (Negro et al., 2006), hyoscine N-butyl bromide (Barcia et al., 2005), clonidine (Hildebrand et al., 2003), ropivacaine (Oster Svedberg et al., 2002), ketamine (Lau et al., 1998) and bupivacaine (Johnson et al., 1997). Tramadol chlorhydrate has been reported to be a stable drug in infusion solution when combined with haloperidol (Negro et al., 2005), dexamethasone (Negro et al., 2007), hyoscine N-butyl bromide (Negro et al., 2010; Barcia et al., 2007), ropivacaine, bupivacaine, or metamizole (Salmerón-García et al., 2009). Combination of fentanyl with other drugs in solution has resulted in variable results. It is
Table 2. Compatibility of lornoxicam and morphine, tramadol, or fentanyl combination.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Lornoxicam</th>
<th>Morphine</th>
<th>Lornoxicam</th>
<th>Tramadol</th>
<th>Lornoxicam</th>
<th>Fentanyl</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<td>100.0</td>
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<td>100.3</td>
<td>98.8</td>
<td>8.3</td>
</tr>
</tbody>
</table>

stable when combined with palonosetron (Trissel et al., 2007), ketamine, droperidol (Lee et al., 2005), and ropivacaine (Oster et al., 2002) but unstable with fluorouracil in polyvinyl chloride containers (Xu et al., 1997).

On the basis of our stability study, the results showed that the drug mixtures lornoxicam/morphine and lornoxicam/tramadol both prepared in 0.9% NaCl and stored at ambient temperature for 168 h were chemically stable and physically compatible (Table 2). Therefore, it can be concluded that these drug mixtures are pharmaceutically stable in 0.9% NaCl and suitable for use in PCA for at least 168 h after their preparation. The mixture of lornoxicam with fentanyl citrate in 0.9% NaCl solution at room temperature was incompatibility. Based on this finding, it is suggested that, whenever possible, combinations of lornoxicam with fentanyl citrate in the same syringe should be avoided.

ACKNOWLEDGEMENT

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REFERENCES


