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Physico-chemical stability of butorphanol-tramadol and butorphanol-fentanyl patient-controlled analgesia infusion solutions over 168 hours

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This study was to investigate the physical and chemical compatibility of butorphanol with tramadol or fentanyl in 0.9% sodium chloride injections for patient controlled analgesia administration. The solutions were prepared in polyvinyl chloride (PVC) infusion bags and stored without protected from light exposure at room temperature (25 °C) or refrigerated (4 °C). Over a period of 168 hours, stabilities were determined by visual inspection, pH measurement, and high-pressure liquid chromatography (HPLC) assay of drug concentrations. At both temperatures, admixtures of butorphanol-tramadol and butorphanol-fentanyl were clear in appearance, and no color change or precipitation was observed during the study period. The maximum losses obtained were lower than 5% for the three drugs after 168 hours of storage. The results indicate that, at ambient or refrigerated storage conditions, the drug mixtures of butorphanol-tramadol and butorphanol-fentanyl in 0.9% sodium chloride injections were physically and chemically stable for at least 168 hours when stored in PVC syringes.

1. Introduction

For patient-controlled analgesia (PCA) drugs with different analgesics are commonly combined with the aim to provide more effective analgesia and to reduce the incidence of unwanted side-effects compared with a single drug (Jin and Chung 2001). For this reason, several of these drug mixtures used in clinical practice are composed of butorphanol with other drugs, such as tramadol and fentanyl (Wei et al. 2010; Huang et al. 2007).

Butorphanol tartrate (Fig. 1a), morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (–)-, [*S*- (*R**, *R**)]-2, 3-dihydroxybutanedioate (1:1) (salt), is a partial μ-opioid antagonist (Wang et al. 2009; Lee et al. 2007). The world health organization suggests that butorphanol use in humans is as an anaesthetic or pre-anaesthetic adjunct or a narcotic analgesic for postoperative pain. Tramadol hydrochloride (Fig. 1,b), (trans(±)-2- [(dimethylamino) methyl]-1-(3–methoxyphenyl) cyclohexanol), a synthetic opioid of the aminocyclohexanol group's μ-opioid receptor agonist-deriving part of its effect by inhibiting the reuptake of norepinephrine and 5-hydroxytryptamine in the central nervous system offers a similar analgesic potential to opioids (Budd and Langford 1999). Fentanyl citrate (Fig. 1, c), *N*- (1-phenyl-4-piperidyl) propionanilide citrate, is a potent synthetic (man-made) narcotic analgesic extensively used for anesthesia and analgesia in the operating room and against postoperative pain.

Because these drugs are widely used in the treatment of postoperative pain with PCA alone or in combination, some stability studies of butorphanol, tramadol and fentanyl single or combined with other drugs in solution have been reported in the literature (Kowalski and Gonrlay 1990; Xu et al. 1997; Shields et al. 2008; Chen et al. 2013). However, to our knowledge stability of butorphanol with tramadol or fentanyl in infusion solutions has not been studied. Thus, the purpose of this study was to determine the physico-chemical stability of combined butorphanol-tramadol and butorphanol-fentanyl admixtures in 0.9% sodium chloride stored in PVC bags over a period of 168 h at 4 °C and 25 °C.

2. Investigations and results

2.1. Chemical stability study of analgesic mixtures

The HPLC-DAD method described above was applied to study the chemical stability of the analgesic mixture in PCA solution. Figure 2 presents the results of this chemical stability study. As indicated, after 168 h of storage in PVC bags at 4 °C and 25 °C, the percentages of butorphanol, tramadol, and fentanyl remaining in the drug mixtures were higher than 95.0%. pH values are given in the Table 1. The pH of all infusions increased slightly over 168 h. However, the slight pH increase did not affect chromatographic parameters and remained in the acceptable range.

2.2. Physical compatibility study of the mixture samples

This study was carried out by visual observation of possible physical alterations, such as color changes and the appearance of precipitated or muddy samples. For the analgesic mixtures of butorphanol-tramadol and butorphanol-fentanyl, no instability signal was observed for any situation studied, for example no precipitation or color change was detected. At least after 168 h from its preparation, the physical compatibility of the drug mixture was confirmed.

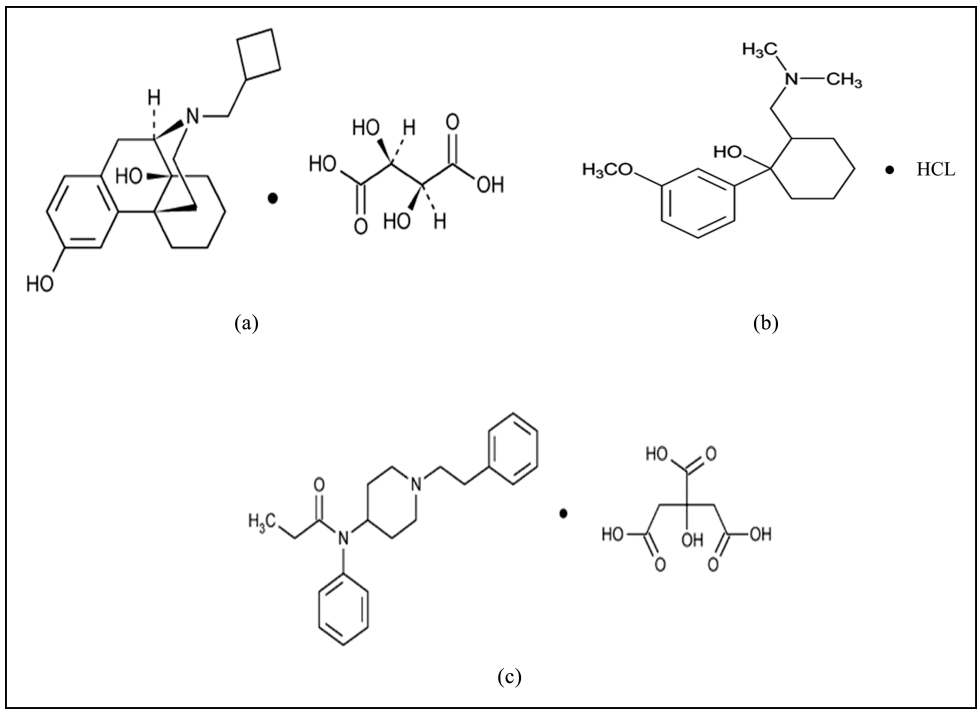

Fig. 1: Structures of (a) butorphanol tartrate, (b) tramadol hydrochloride, and (c) fentanyl citrate.

3. Discussion

Combinations of different drug solutions are often used in clinical practice to relieve post-operative pain using the PCA technique, although little or no information is available about the chemical stability and compatibility of these analgesic mixtures. Currently, there are no commercially available analgesic mixtures, and they must be prepared in the hospital pharmacy departments for clinical use. Thus, it is necessary to prove that drugs remain stable in the admixture.

The combination of butorphanol plus tramadol or fentanyl brings together two well-known analgesics that have different but complementary mechanisms of analgesic action. Laboratory studies have demonstrated that these agents interact to produce synergistic analgesia with a desirable safety/efficacy

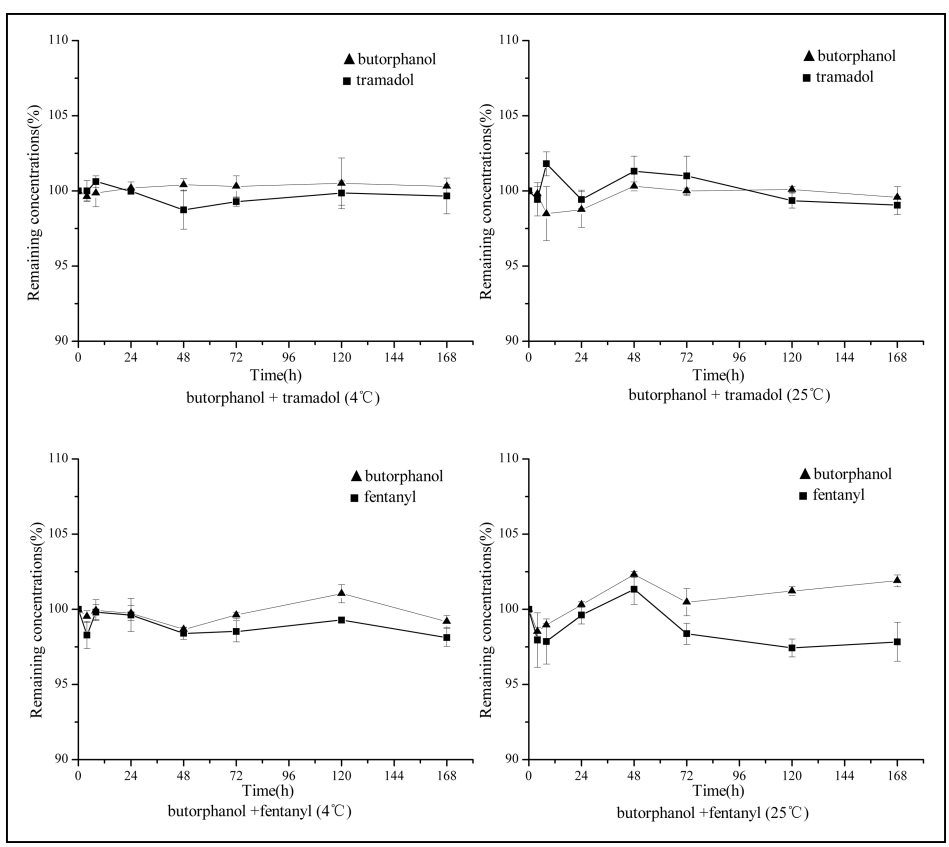

Fig. 2: Drug concentrations (mean ± SD [%]; n = 3) of butorphanol-tramadol and butorphanol-fentanyl in 0.9% sodium chloride injection over 168 h at 4 °C and 25 °C.

Table 1: pH values (mean ± SD [%]; n = 3) of butorphanol-tramadol and butorphanol-fentanyl admixtures in PVC infusion bags at different storage conditions

Time (h)	pH measurement after storage at:			
	Butorphanol-tramadol		Butorphanol-fentanyl	
	4 °C	25 °C	4 °C	25 °C
0	5.12 ± 0.2	5.18 ± 0.0	4.82 ± 0.5	4.94 ± 0.1
4	5.15 ± 0.2	5.08 ± 0.1	4.90 ± 0.8	4.92 ± 0.1
8	5.11 ± 0.5	5.14 ± 0.1	4.88 ± 0.0	4.97 ± 0.3
24	5.09 ± 0.1	5.16 ± 0.3	4.79 ± 0.4	5.02 ± 0.6
72	5.07 ± 0.3	5.25 ± 0.2	4.92 ± 0.7	5.11 ± 0.4
120	5.17 ± 0.6	5.19 ± 0.5	5.02 ± 0.1	5.05 ± 0.2
168	5.20 ± 0.1	5.26 ± 0.9	4.99 ± 1.0	5.15 ± 0.1

profile. Wei et al. (2010) administered fentanyl and combinations of butorphanol-fentanyl *via* PCA pump and found that butorphanol-fentanyl combinations produced the same good analgesia and few adverse effects than the single fentanyl group. Huang et al. (2007) have given tramadol, butorphanol, and combinations of butorphanol-tramadol after breast cancer operations and found that butorphanol combined with tramadol has a better effect of analgesia and fewer adverse reactions.

Mixing of two or more chemicals together can lead to physical, chemical or both changes, which may result in alteration of therapeutic properties and in having undesirable side effects (Gikic et al. 2000). Unfortunately, compatibility and stability of butorphanol with tramadol or fentanyl in infusion solutions for PCA has not yet been documented. Therefore, the aim of this study was to fill this lack of information.

The previous stability and compatibility tests of tramadol hydrochloride with a variety of parenteral medications (Cabrera et al. 2011; Lin et al. 2010; Athanasopoulos et al. 2010; Negro et al. 2010; Athanasopoulos et al. 2009; Lebitasy et al. 2009; Negro et al. 2007; Salmerón-García et al. 2009; Barcia et al. 2007; Negro et al. 2005; Abanmy et al. 2005) have demonstrated that tramadol hydrochloride is a very stable drug. None of the previous tests have found any loss of tramadol hydrochloride during the test period. On the contrary, combination of fentanyl with other drugs in solution has resulted in variable results. It is stable when combined with ondansetron hydrochloride (Trissel et al. 2007), bupivacaine hydrochloride (Sattler et al. 1998; Tu et al. 1990; Dawson et al. 1992; Kjønniksen et al. 2000; Priston et al. 2004; Jappinen et al. 2002), lidocaine (Sattler et al. 1998), midazolam (Wilson, et al. 1998), and ropivacaine (Oster Svedberg et al. 2002) but unstable with lornoxicam (Chen et al. 2012) in PVC containers. Moreover, an extremely rapid loss of fentanyl in alkaline solutions due to sorption by PVC was described by Xu et al. (1997) In the present study, the pH of butorphanol-fentanyl mixtures was acidic, with a pH close to 5.0. The stability and compatibility results showed that binary mixtures of butorphanol tartrate and fentanyl citrate in 0.9% sodium chloride injection were stable for at least 168 h when stored in PVC bags at both 4 °C and 25 °C.

When mixing drugs taken from ampoules of sterile solutions, there is also the potential issue of bacterial contamination. Here, we have only examined the physicochemical stability without taking into consideration microbial contamination. In clinic practice, we should follow the USP/NF Chapter 797. In this regulation, the preparation belongs to be low-risk compounding sterile product. In order to ensure the security, the preparation could be used at room temperature for 48 hours or at refrigerated temperatures for 14 days on the basic of USP specifies.

4. Experimental

4.1. Chemicals and reagents

Butorphanol tartrate, tramadol hydrochloride, and fentanyl citrate reference standards were obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Butorphanol tartrate injection (1 mg/1 mL, lot 10122534) was obtained from Hengrui Medicine Co., Ltd., (Jiangsu, China); Tramadol hydrochloride injection (100 mg/2 mL, lot 879B01) was supplied by Grunenthal Pharmaceutical Co., Ltd; Fentanyl citrate injection (0.1 mg/2 mL, lot 110902) was obtained from Humanwell Pharmaceutical Co., Ltd. (Yichang, China). The solution of 0.9% NaCl used to prepare the sample mixtures was from Kelun Pharmaceutical Co., Ltd. (Sichuang, China). Methanol was of HPLC-grade and purchased from Fisher Scientific International (St Louis, MO, USA). Distilled and deionised water were used throughout the study. Potassium dihydrogen phosphate KH_2PO_4 was from Xilong Chemical (Guangdong, China).

4.2. Instrumentation

A modular Dionex HPLC system equipped with a UltiMate 3000 quaternary gradient pump, a ASI- 100 autosampler, a TCC-100 thermostat column oven, an ultraviolet detector (DAD) and a data system (Chromeleon ® version 6.80). Measurements of pH were determined with a precision pH meter (Model pHS-3C, Leici Instrument Co., Shanghai, China).

4.3. HPLC assays

HPLC column: Hypersil C_{18} 150mm × 4.6 mm × 5 μm (supplied by Thermo Electron, USA). The mobile phase was 0.05 M potassium dihydrogen phosphate solution: acetonitrile, 75:25 (v/v) at a flow rate of 1.0 mL/min. The selected detection wavelengths for butorphanol tartrate, tramadol hydrochloride, and fentanyl citrate were 280 nm, 272 nm, and 210 nm, respectively. The column temperature was kept ambient and injection volume was 20 μL. Under the current chromatographic conditions, retention times for tramadol hydrochloride, butorphanol tartrate, and fentanyl citrate were 4.3, 7.5 and 15.2 min, respectively, and baseline separation was achieved in all components.

Six-point calibration curves ranged from 8.0 to 80.0 μg/ml for butorphanol tartrate, 0.02 to 0.8 mg/ml for tramadol hydrochloride and 0.25 to 50.0 μg/ml for fentanyl citrate. The correlation coefficients for these curves were higher than 0.999 for three components. The precision of the method for butorphanol tartrate, tramadol hydrochloride, and fentanyl citrate for both intraday and interday analyses were all less than 2.0% for RSD.

The butorphanol-tramadol and butorphanol-fentanyl admixtures degraded by heating at 60 °C for 5 h under acidic (0.1 N HCl), basic (0.1 N NaOH) and 3% hydrogen peroxide (H_2O_2) conditions was assayed to confirm separation of the parent molecule from its degradation products. Under all conditions, loss of the intact drugs was observed, and there was no interference of the degradation product peaks or other drug peaks with the peak of the three components.

4.4. Preparation of analgesic mixture samples

Butorphanol tartrate-tramadol hydrochloride samples were prepared by adding 4 mg butorphanol tartrate and 400 mg tramadol hydrochloride to 100 mL bags of sodium chloride 0.9%. Six bags were prepared and stored under the following conditions: Three under refrigeration (4 °C) and Three at room temperature (25 °C). Six butorphanol tartrate-fentanyl citrate samples were prepared by adding 5 mg butorphanol tartrate and 0.5 mg fentanyl citrate to 100 mL bags of sodium chloride 0.9%. Three bags were prepared and stored at each of 4 °C and 25 °C. A rotary shaker was used to agitate the solution after each addition of fluid. The solutions were prepared using an aseptic technique in a laminar-airflow hood. The doses assayed in the study were chosen as those frequently used against postoperative pain *via* intravenous-PCA.

4.5. Physical and chemical stability of the analgesic mixtures

At predetermined times (0, 4, 8, 24, 72, 120, and 168 h), the solutions were examined for the development of color changes, cloudiness (turbidity), and/or precipitation. The pH of each solution was also determined at each analysis by a digital pH meter. Each sample was also analyzed by HPLC in triplicate to quantify the components. In the chemical stability study, the concentrations of the drugs were expressed as the percentage of the remaining drug concentration at different times for every drug in the mixtures.

4.6. Analysis of data

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. The changes with time of the concentrations of the drugs in solution were analyzed using one factor ANOVA. A P-value of less than 0.05 was considered to be significant.

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