Stability of an epidural analgesic admixture containing butorphanol tartrate and ropivacaine hydrochloride

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ABSTRACT

Background Local anaesthetics and opioid mixtures are commonly used for the management of postoperative pain. The purpose of this study was to investigate the stability of butorphanol tartrate and ropivacaine hydrochloride in polyolefin bags over a period of 15 days, both at room temperature and at 4°C.

Methods Admixtures were assessed initially and for 15 days after preparation in polyolefin bags using 0.9% sodium chloride injection as diluents and stored at 4°C and 25°C. The initial concentrations were 50 µg/mL butorphanol and 1–2 mg/mL ropivacaine. The stabilities were determined by visual inspection, pH measurement and high-pressure liquid chromatography assay of drug concentrations.

Results The initial concentrations of butorphanol and ropivacaine were >97% after 15 days. The drug mixtures were clear in appearance and no colour change or precipitation was observed. Throughout this period, the pH value remained stable.

Conclusions Butorphanol and ropivacaine in 0.9% sodium chloride injection are stable for at least 15 days when stored in polyolefin bags at 4°C and 25°C.

INTRODUCTION

Combinations of local anaesthetics and opioids are often used in clinical practice for the management of moderately severe postoperative pain by patient-controlled epidural analgesia (PCEA) to ensure that a minimal dose of each is used.[1–3] One such drug mixture is a combination of butorphanol and ropivacaine. The structures of the drugs are shown in figure 1.

Butorphanol tartrate (figure 1A), morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (–)-, (*S*-(*R**,*R**))-2, 3-dihydroxybutanedioate (1 : 1) (salt), a synthetic opioid, is a µ-opioid antagonist and a κ-receptor agonist.[4–7] The WHO suggests that butorphanol use in humans is as an anaesthetic or pre-anaesthetic adjunct or a narcotic analgesic for postoperative pain. Ropivacaine hydrochloride (figure 1B), (-)-(2*S*)-*N*-(2,6-dimethyl phenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate, is a long-acting local anaesthetic agent mainly used in surgery and for postoperative pain relief.[8] Previous studies have shown that epidural butorphanol–ropivacaine combination via a patient-controlled anaesthesia pump provides better analgesia and reduces undesirable side effects.[9–13] However, there are no commercially available analgesic mixtures and they must be prepared in hospital pharmacy departments for clinical use. Mixing two or more drugs together in infusion solutions can lead to physical or chemical changes, or both, which may result in a variation in the therapeutic properties and unwanted side effects.[14] To our knowledge, the stability of butorphanol with ropivacaine in infusion solutions has not been reported in the literature. In the current study we determined the stability of butorphanol combined with ropivacaine in 0.9% sodium chloride stored in polyolefin bags over a period of 15 days at 4°C and 25°C in order to provide background information on the storage of a butorphanol–ropivacaine mixture.

METHODS

Materials and reagents

Butorphanol tartrate and ropivacaine hydrochloride reference standards were obtained from the National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China. Butorphanol tartrate injection (1 mg/mL, lot 121225) was obtained from Hengrui Medicine Co, Jiangsu, China; ropivacaine hydrochloride injection (75 mg/10 mL, lot 1211015) was supplied by Qilu Pharmaceutical Co, Shangdong, China; and the solution of 0.9% NaCl used to prepare the sample mixtures was obtained from Kelun Pharmaceutical Co, Sichuang, China. Acetonitrile was of high-pressure liquid chromatography (HPLC) grade purchased from Fisher Scientific International, St Louis, Missouri, USA. Distilled and deionised water were used throughout the study. Potassium dihydrogen phosphate (KH_2PO_4) was obtained from Xilong Chemical, Guangdong, China.

Equipment

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

Chromatographic conditions

A Hypersil C_{18} analytical column 250×4.6 mm, 5 µm particle size (Thermo Electron, USA) was used as a stationary phase. The mobile phase consisted of 0.05 mol/L KH_2PO_4 and acetonitrile in the proportion of 75:25 (v/v) with a flow rate of 1.0 mL/min. The selected detection wavelengths for butorphanol and ropivacaine were 280 and 263 nm, respectively. The column temperature was kept ambient and injection volume was 20 µL.

Preparation of stock and working solutions

Butorphanol tartrate 1.0 mg/mL and ropivacaine hydrochloride 4.0 mg/mL stock solutions were

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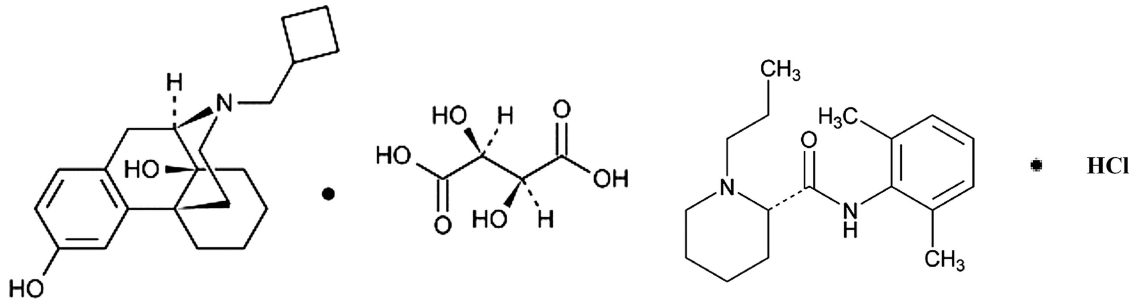

Figure 1 Structures of (A) butorphanol tartrate and (B) ropivacaine hydrochloride.

prepared in deionised water and frozen at −20°C. Fresh working standard solutions were prepared by diluting the stock solution with deionised water to the required concentrations before use.

Method validation

Validation of the method was made in terms of linearity, accuracy, intra- and inter-day precision and stability indication for each drug.

Linearity

The calibration curves were established by injecting six concentrations of butorphanol tartrate and ropivacaine hydrochloride in the concentration range 2.5–200.0 µg/mL and 0.1–2.0 mg/mL, respectively. Linear regression was calculated by the peak areas versus concentration of analytes.

Precision and accuracy

Assays of control solutions at three different concentrations of butorphanol tartrate and ropivacaine hydrochloride were undertaken to calculate the accuracy, intra-day and inter-day precisions. Accuracy and intra-day precision were estimated by means of the recovery value and relative SD (RSD, %) calculated from three quality control samples with five determinations per concentration at the same day. Inter-day precision (5 days) was also estimated as the RSD calculated from five replicate mixture samples prepared in the same way.

Stability indication

The stability-indicating capability of the chromatographic method was assessed using partially decomposed solutions of drug. The butorphanol tartrate and ropivacaine hydrochloride mixture degraded by heating at 60°C for 5 h under acidic (0.1 M hydrochloric acid), basic (0.1 M sodium hydroxide) and 3% hydrogen peroxide (H_2O_2) conditions was assayed to confirm separation of the parent molecule from its degradation products.

Preparation of analgesic mixture samples

Butorphanol tartrate injection and ropivacaine hydrochloride injection mixed together in a laminar airflow hood were added to commercial 100 mL polyolefin bags containing 0.9% sodium hydrochloride to produce solutions containing approximately 5 mg butorphanol tartrate and 100 or 200 mg ropivacaine hydrochloride. The butorphanol–ropivacaine admixture was filled in triplicate, protected from light and stored at 4°C and 25°C during a 15-day study period. These doses assayed in the study were chosen, taking into consideration those more frequently used for postoperative pain via PCEA.

Stability study of the analgesic mixtures

A 2 mL sample was removed from each admixture immediately after preparation and after 8, 24, 48, 72, 120, 168, 240 and 360 h. At each time point the solutions were examined for the development of colour, cloudiness, precipitation and gas production. Moreover, variations in the pH of the binary mixtures were also measured at 0 and 15 days using a pH meter. All samples were then frozen at −20°C until analysis. Samples were allowed to reach room temperature and diluted threefold in purified water before injection into a HPLC system. Each sample was assayed in triplicate by HPLC.

Analysis of data

The starting concentration of both drugs 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.[15]

Table 1 Validation of HPLC method

Compound	Concentration tested (mg/L)	Recovery (%)	Precision RSD (%)	
			Intra-day	Inter-day (5 days)
Butorphanol tartrate	5.0	100.2	1.3	2.4
	15.0	98.5	0.7	1.1
	50.0	99.7	1.2	1.6
Ropivacaine hydrochloride	200.0	100.3	0.9	1.2
	800.0	98.7	0.5	2.1
	1200.0	99.6	1.0	1.5

HPLC, high-pressure liquid chromatography; RSD, relative SD.

RESULTS

Validation of the HPLC method

Table 1 shows the results obtained for the accuracy, intra-day and inter-day RSD. The intra- and inter-day RSD% were below 2.5% for both drugs, with the recoveries obtained also being close to 100%. There was a good linear relationship between detector response and concentrations, with a correlation coefficient (r) better than 0.999 for both drugs. The degradation study results showed that the decomposition products were baseline separated from analytes and none would interfere with the quantification of butorphanol tartrate and ropivacaine hydrochloride (figure 2).

Stability of the infusions

No colour change, precipitation, turbidity or gas production was observed in the admixtures in polyolefin bags. Tables 2 and 3 show the percentages of the dose of butorphanol tartrate and ropivacaine hydrochloride remaining in the admixtures when stored in polyolefin bags over a period of 15 days at 4°C and 25°C. After 360 h of storage, the percentages of butorphanol and ropivacaine remaining in the drug mixtures were higher than 97% at both temperatures. Over the study period the pH value was close to 5 and changes were within 0.1 units of the initial pH for all drug mixtures.

DISCUSSION

Multimodal analgesia is currently recommended as an effective analgesia for moderate to severe postoperative pain control, which is achieved by combining different analgesics such as opioids, non-steroidal anti-inflammatory drugs and local anaesthetics in order to minimise individual doses and to reduce unwanted side effects.[2 16] However, when combinations of drugs are administered via PCEA infusion, drug incompatibility or loss of stability can occur. Previously, the physical compatibility and stability of butorphanol tartrate and ropivacaine alone or combined with other drugs in solution has been studied. Butorphanol tartrate was found to be stable for at least 1 week in 0.9% sodium chloride injection.[17] The combination of butorphanol tartrate with other drugs in solution has shown variable results. It is stable when combined with droperidol but unstable with lornoxicam in 0.9% sodium chloride injection.[18 19] Ropivacaine has been shown to remain stable in infusion solution when combined with morphine,[20] fentanyl,[20] sufentanil,[21–23] tramadol,[23] methylprednisolone acetate[24] or diamorphine[25] under normal conditions. Unfortunately, no published information is available on the compatibility and stability of butorphanol in combination with ropivacaine in PCEA solution. The aim of this study was therefore to fulfil this lack of information.

In this stability study the concentrations of butorphanol tartrate and ropivacaine hydrochloride chosen reflect the use of

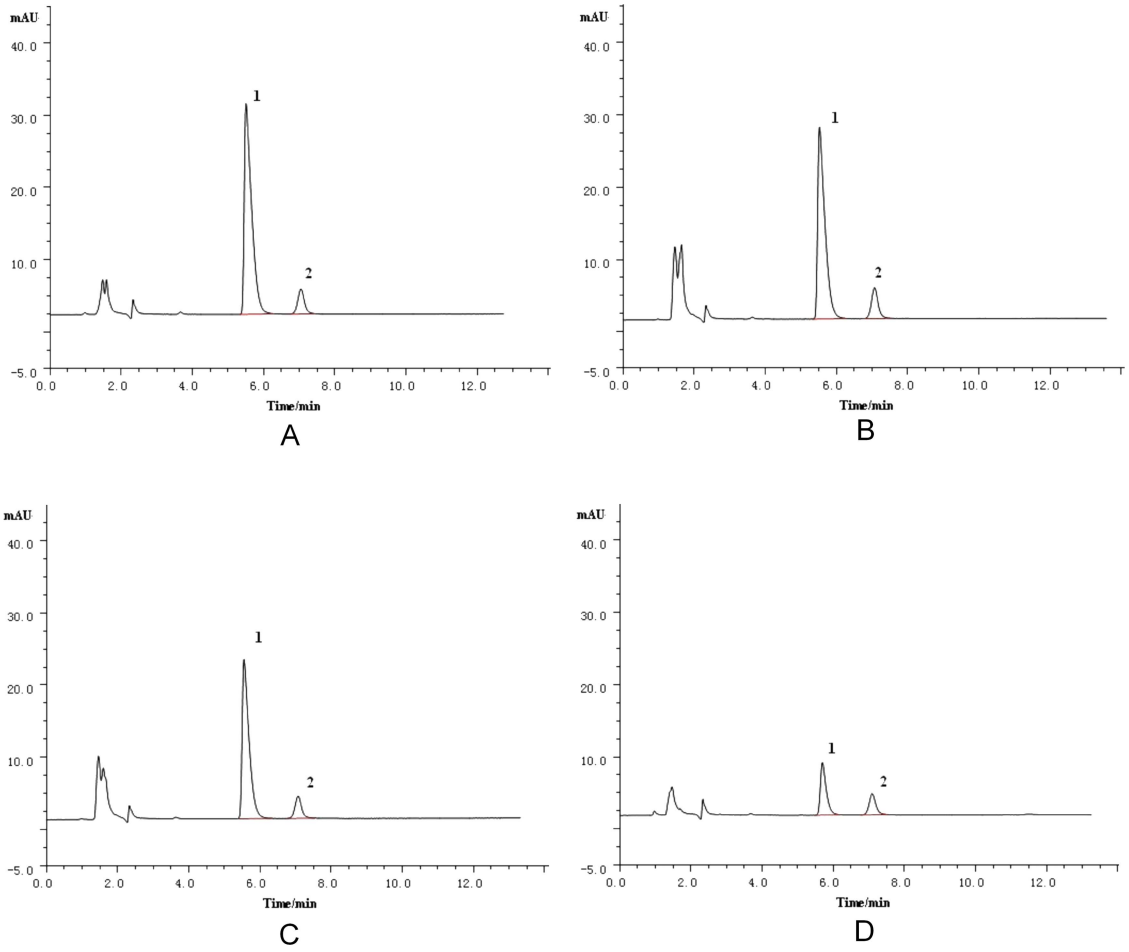

Figure 2 Chromatograms of butorphanol tartrate 0.015 mg/mL and ropivacaine hydrochloride 0.8 mg/mL admixtures that were freshly prepared (A), exposed to 0.1 M hydrochloric acid at 60°C for 5 hs (B), exposed to 0.1 M sodium hydroxide at 60°C for 5 h (C), and exposed to 3% hydrogen peroxide at 60°C for 5 h (D). Retention times were 5.6 min for ropivacaine hydrochloride (peak 1) and 7.1 min for butorphanol tartrate (peak 2). The other peaks were for degradation products.

Table 2 Drug concentrations (mean±SD (%); n=3) of butorphanol tartrate (50 μg/mL) and ropivacaine hydrochloride (1 mg/mL) in polyolefin bags at different storage conditions

	Solution stored at 4°C		Solution stored at 25°C	
Time (h)	Butorphanol	Ropivacaine	Butorphanol	Ropivacaine
0	100.0	100.0	100.0	100.0
8	98.7±1.7	101.1±0.1	98.7±0.5	99.1±1.8
24	100.2±1.1	102.5±1.3	98.3±1.2	100.4±0.5
48	99.2±0.3	99.8±0.7	102.2±2.1	97.7±2.4
72	100.6±0.4	102.1±1.6	101.8±0.9	98.3±0.2
120	100.9±1.0	97.5±2.2	100.3±2.0	102.2±0.3
168	101.3±1.3	100.4±0.7	99.9±1.1	99.2±1.9
240	99.6±0.1	101.2±1.0	100.4±0.2	98.9±0.6
360	99.8±1.5	102.1±0.9	98.5±0.7	100.3±0.5

the combinations by specialist analgesic treatment teams, expert consensus[26] and clinical research[9–13] in order to ensure that the results will have clinical utility. Administration of butorphanol in combination with ropivacaine via PCEA has been shown to improve postoperative pain with no serious side effects after surgery.[9–13] However, the elimination half-life of butorphanol is nearly 18 h but, in patients with renal or hepatic impairment, it is approximately doubled or tripled. Due to the pharmacokinetic data, it is not recommended for the treatment of postoperative pain over a long period. In addition, the dosage should be adjusted and drug monitoring should be carried out if treatment is given to older patients or those with excretion problems.

When mixing drugs taken from ampoules of sterile solutions there is also the potential issue of bacterial contamination. We have examined the physicochemical stability without taking microbial contamination into consideration. In clinical practice it is necessary to follow Chapter 797 of the USP/NF.[27] In this regulation the preparation belongs to low-risk compounding sterile products.[28] In order to ensure its safety, the preparation should not be used for more than 48 h after the date at room temperature or 14 days at refrigerated temperatures on the basis of USP specifications.

The results of our stability studies show that binary mixtures of butorphanol tartrate and ropivacaine hydrochloride in 0.9% sodium chloride injection are stable for at least 15 days when stored in polyolefin bags at 4°C and 25°C and protected from light. Moreover, there were no significant differences between steady storage at room temperature and in the refrigerator. We therefore conclude that this solution can be safely prepared and stored out of light for up to 14 days by licensed Central Intravenous Additive services.

Table 3 Drug concentrations (mean±SD (%); n=3) of butorphanol tartrate (50 μg/mL) and ropivacaine hydrochloride (2 mg/mL) in polyolefin bags at different storage conditions

	Solution stored at 4°C		Solution stored at 25°C	
Time (h)	Butorphanol	Ropivacaine	Butorphanol	Ropivacaine
0	100.0	100.0	100.0	100.0
8	100.1±0.5	100.9±0.2	100.6±0.7	100.7±0.6
24	100.9±2.0	99.9±1.6	99.7±1.1	99.6±0.2
48	101.8±1.0	100.0±0.5	101.1±0.9	102.5±1.3
72	102.1±1.9	99.3±1.0	102.6±0.8	101.4±2.1
120	99.5±0.2	99.6±1.2	99.4±0.7	99.7±1.6
168	100.5±0.8	100.2±0.8	98.5±1.3	101.0±1.4
240	101.0±1.3	101.5±0.3	100.3±1.1	99.6±0.8
360	99.2±0.4	100.1±1.1	97.7±0.5	101.8±0.9

CONCLUSION

A new and validated analytical HPLC method for the simultaneous determination of butorphanol tartrate and ropivacaine hydrochloride in analgesic mixture samples used in PCEA has been successfully developed. The method was successfully used to study the stability of the binary mixture of butorphanol and ropivacaine at the usual concentration levels used in clinical practice. The results show that the mixture of butorphanol (50 μg/mL) and ropivacaine (1–2 mg/mL) prepared in 0.9% sodium chloride injections and stored at ambient or refrigerated storage conditions for 360 h is compatible and stable.

Key messages

What is already known on this subject

Butorphanol combined with ropivacaine patient-controlled epidural analgesia regimen is useful for successful postoperative analgesia and allows a balance of pain control, proper sedation and fewer side effects.

What this study adds

The epidural drug solution can be safely prepared by the pharmacist and can be stored in a refrigerator for up to 14 days at 4°C.

Contributors FC and PL conceived and designed the experiments. FC, PL, BZ and JY performed the experiments. BF and JY analysed the data. PL, BZ and BF contributed reagents/materials/analysis tools. FC, PL and BZ wrote the paper.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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