Effect of pH on absorption of sufentanil citrate in a portable pump reservoir during storage and administration under simulated epidural conditions

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Introduction
The use of plastic components in parenteral delivery systems has gained widespread acceptance in clinical medicine. However, little is known about the magnitude of the problem in clinical practice of interaction between drugs and these plastic components. Despite the fact that several examples of such interactions are described in the literature [1], they are generally limited to information about specific drugs (e.g., morphine [2-4], fentanyl [5 6], methadone [7], heroin [8]).

In order to investigate this potential problem we started a series of studies on the interaction between sufentanil and the wall of a portable pump reservoir. In the first part of this series, the absorption of sufentanil in a portable pump reservoir with a polyvinyl chloride (PVC) wall, a glass container and a polyethylene container at -20°C, 4°C and 32°C was investigated. We found a loss of 12.8% of sufentanil during storage for 48 hours at 32°C in the portable pump reservoir [9]. Such a loss may result in reduced delivery of drug to the patient, with as a consequence diminished therapeutic response. In addition, this may provide a source of error in pharmacokinetic and pharmacologic studies where plastic infusion or perfusion systems are used. There was no change in the sufentanil concentration in the glass and polyethylene container stored at 32°C. But as glass and polyethylene are not flexible and are, therefore, not suitable for portable pump reservoirs, and as there is a widespread use in clinical practice of PVC reservoirs, we investigated the possibility to reduce the absorption problem with PVC.

The objectives of the present study were:
• to investigate the absorption of an unbuffered sufentanil solution in a portable pump reservoir under simulated epidural administration conditions (unbuffered administration: experiment 1);
• to investigate the absorption of a citrate-buffered sufentanil solution, alone and in combination with bupivacaine hydrochloride, in a portable pump reservoir under simulated epidural administration conditions (buffered administration: experiment 2A without and 2B with bupivacaine);
• to determine the effect of the pH on the absorption of sufentanil (pH effect: experiment 3).

The combination sufentanil with bupivacaine is used more and more in clinical practice and is based on the fact that the antinoceptive effects of an opioid when combined with bupivacaine were significantly greater than when an opioid or bupivacaine was injected alone [10-12].

Methods

Chemicals
Sufentanil citrate (Sufenta Forte®) (5 ml = 250 µg sufentanil) injection fluid (experiment 1: lot no. 90B15/859; experiment 2A: lot no. 91E06/568; experiment 2B: lot no. 90L10/564; experiment 3: lot no. 91K26/388; without preservative; pH 4.87-5.75) was obtained from Janssen Pharmaceutica (Beerse, Belgium).

Sodium citrate buffer 0.1 mol/l, pH 4.60, consisted of citric acid monohydrate 9.14 g, trisodium citrate dihydrate 16.62 g, demineralized water to 1,000 ml. Chemicals were obtained from OPG (Utrecht, the Netherlands).

Bupivacaine hydrochloride (Marcaine®) 20 ml = 100 mg injection fluid (lot no. 91D17/750; without preservative; pH 5.57) was obtained from Astra Pharmaceutica (Rijswijk, the Netherlands).

Sodium chloride 0.9% (wt/vol) solution for infusion was obtained from NPBI [Emmer-Compascuum, the Netherlands, experiment 1: lot no. BBW27A, pH 6.10; experiment 2A: lot no. 920504 1503, pH 6.25, experiment 3: lot no. 921012 1603; experiment 2B: lot no. 90L10/564; experiment 3: lot no. 91K26/388; without preservative; pH 4.87-5.75] was obtained from Janssen Pharmaceutica (Beerse, Belgium).

Storage
Stability
Sufentanil (5 µg/ml as citrate) was investigated for its stability when diluted with sodium chloride 0.9%, in 100 ml polyvinyl chloride portable pump reservoirs during administration under simulated epidural conditions at 32°C for 48 h. Sufentanil was absorbed into the polyvinyl chloride, resulting in a reduction of 10.9% of the concentration after 48 h. The absorption of sufentanil (5 µg/ml as citrate), alone and in combination with bupivacaine hydrochloride (2 mg/ml), was investigated when diluted with sodium chloride 0.9% in combination with a citrate buffer (pH 4.6), in the same reservoirs under similar conditions. There was no loss of sufentanil after 48 h in both experiments. The effect of the pH on the absorption of sufentanil in polyvinyl chloride was investigated at different pH values. After storage for 21 days at 32°C there was 5.1% loss of sufentanil at pH 4 and 80.6% loss at pH 6. The citrate buffer at the optimum pH (4.6) has a low, acceptable buffer capacity for epidural administration.

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To simulate actual patient-use conditions pumps, reservoirs, extension sets and filters were stored at 32°C during the whole experiment and the pumps were run for 48 h at a flow rate of 2.0 ml/h. Prior to the 48 h pumping period the pumps were primed and 4 ml unbuffered and 5 ml buffered solution was collected separately for each pump. Total priming time was approximately 2 min for each pump.

During the 48 h pumping period samples were collected at intervals in air-tight containers. The end of the catheter was guided by a 16 gauge needle into a rubber-cap-sealed 50 ml glass container. There was no contact between the sufentanil admixture and the rubber cap. To decrease the workload the intervals for sampling during the buffered study were adapted based on the data of the unbuffered study. The samples were analysed for sufentanil and bupivacaine concentration and pH.

Study of the effect of pH on the absorption

Five 300 ml aliquots out of 1,500 ml of freshly prepared unbuffered sufentanil solution with a pH of 5.2 ± 0.1 were taken. The pH of these five portions of 300 ml was adjusted with sodium citrate buffer to pH 4.06, 4.57, 5.06, 5.62 and 6.16, respectively. Three 100 ml aliquots of each of the solutions were transferred into portable pump reservoirs as described above and stored at 32°C.

Samples of three ml were collected with a 5 ml syringe (Monoject, Sherwood), from each container immediately after preparation and after 1, 2, 7, 14 and 21 days of storage. Each container was weighed individually each time before and immediately after sampling to determine the loss of vehicle as well as the weight of the sample taken. The sufentanil concentration and pH of the samples were determined.

Colour, clarity and buffer capacity

Samples were inspected against a light and dark background in order to detect colour changes or particles according to the procedures described in the Ph.Ned. Ed. IX [14].

Admixture pH values were determined at room temperature by using a Consort PS14 pH analyser (Salm en Kipp, Breukelen, the Netherlands).

Buffer capacity of citrate-buffered solutions was determined by titrating 10.00 ml solution with 0.1 mol/l sodium hydroxide until pH 7.40.

HPLC analysis

All samples were collected into 2 ml air-tight glass containers and stored at 4°C. Before analysis samples were equilibrated at room temperature.

A 50 μl amount of undiluted sample was injected into a high pressure liquid chromatographic (HPLC) system. The HPLC system consisted of a pump (Spectra Physics SP 8800, Spectra Physics, Eindhoven, the Netherlands), an autosampler (Spectra Physics SP 8780) a fixed loop of 10 μl, and a variable ultraviolet absorbance detector (Spectra Physics SP 8450). For the analysis of sufentanil the detector was set at 225 nm and a column (Chromsep HPLC column, Chromspher C18 3.0 mm × 100 mm, Chrompack, Middelburg, the Netherlands) was used. The mobile phase (no. 1) was a mixture of 36.4% (vol/vol) methanol, 36.4% acetonitrile and 27.2% demineralized water containing 0.5% ammonium acetate. For the analysis of sufentanil in combination with bupivacaine the detector was set at 235 nm and a column (Chromsep HPLC column, Lichrosorb RP 8 3.0 mm × 100 mm, Chrompack, Middelburg, the Netherlands) was used. The mobile phase (no. 2) was a mixture of 36.4% (vol/vol) methanol, 36.4% acetonitrile and 27.2% demineralized water containing 0.5% ammonium acetate.

Absorption study with unbuffered and buffered sufentanil solution

For each study three portable pump reservoirs were filled with a 100 ml unbuffered or buffered sufentanil solution using a sterile disposable plastic syringe (Monoject, Sherwood, 's-Hertogenbosch, the Netherlands). Air was fully aspirated from the portable pump reservoirs with the sterile disposable plastic syringe which was used for filling. The portable pump reservoirs were attached to the pumps, the extension sets were connected to the reservoirs on one side and to the epidural filters on the opposite side. The epidural catheters were connected to the filters. To simulate actual patient-use conditions pumps, reservoirs, extension sets and filters were stored at 32°C [13] during the whole experiment and the pumps were run for 48 h at a flow rate of 2.0 ml/h.