

Chemical stability of a solution of bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 µg/mL for filling syringes using a repeater pump

Karin Janssen¹, PharmD; René Wisselo², B App Sci; Charles Geerlings², PharmD; Jan Pieter Schouten², PharmD, MBM

ABSTRACT

Study objective: In Sint Franciscus Gasthuis, Rotterdam, The Netherlands, syringes filled with bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 µg/mL are administered epidurally during post-operative analgesia. These syringes are filled in the pharmacy using a Baxa Repeater pump. The suitability of the filling method and the shelf-life of the solution in the syringes were investigated.

Methods: During the filling process six samples were taken. Three syringes were stored at room temperature and three in the refrigerator. Samples were taken on days 4, 7, 14 and 28. High performance liquid chromatographic (HPLC) methods were used to measure the concentrations of both drugs in the samples.

Results: No loss of drugs was observed during the filling process. After 28 days at room temperature and in the refrigerator, the concentration of bupivacaine hydrochloride was $97.4 \pm 0.9\%$ and $97.9 \pm 1.0\%$ respectively, and that of sufentanil citrate was $95.6 \pm 4.2\%$ and $99.2 \pm 1.4\%$.

Conclusion: The filling method used with a Baxa Repeater pump is acceptable. Bupivacaine/sufentanil solution in syringes is chemically stable for at least 28 days in the refrigerator.

KEYWORDS

Bupivacaine hydrochloride, drug stability, high-performance liquid chromatography, sufentanil citrate, syringes

INTRODUCTION

In Sint Franciscus Gasthuis, Rotterdam, The Netherlands, a solution of bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 µg/mL is given as an epidural post-operative analgesic.

For the past few years, a ready-to-use solution has been prepared in the hospital pharmacy for two reasons. First, from a microbiological point of view, a syringe has a smaller chance of contamination when it is filled by a pharmacy technician under aseptic conditions in the pharmacy than when it is filled by nursing staff on the ward [1]. Second, centralised production guarantees a standardised procedure and, because of an increased production scale, a more efficient working method.

The bupivacaine/sufentanil solution was filled directly into 50 mL syringes using a Baxa Repeater pump. The syringes were stored in the refrigerator (2-8°C) until use. During the filling process, the solution was transferred using a sterile tube set containing polyvinyl chloride (PVC). It is known that sufentanil citrate adsorbs on to PVC. However, the degree of adsorption decreases when bupivacaine is added [2, 3].

The aim of this study was to investigate the suitability of the filling method used and the shelf-life of bupivacaine/sufentanil solution in syringes.

METHODS

Drugs and syringes

Bupivacaine hydrochloride (Marcaïne, AstraZeneca BV, Zoetermeer, The Netherlands) solution for injection 5 mg/mL, 20 mL vial (batch number: 03A01B, expiry date: 01/2006), sufentanil citrate (Hameln, Bipharma BV, Weesp, The Netherlands) solution for injection 5 µg/mL, 10 mL ampoule (batch number: 306066, expiry date: 01/2006) and sodium chloride solution for infusion 0.9%, 250 mL vial (Fresenius Kabi BV (Schelle, Belgium) were used. Kendall Monoject 50 mL syringes (Tyco Healthcare Nederland BV, Zaltbommel, The Netherlands) were filled with the prepared solution.

Preparation

Depending on the number of patients who are given the solution at a given time, a routine preparation consists of 11,

Contact for correspondence: Karin Janssen, PharmD

Apotheek Zuwe Hofpoort Ziekenhuis

2 Polanerbaan

3447 GN Woerden, The Netherlands

Tel: +31 348 427385

Fax: +31 348 427489

kjanssen@zuwe.nl

¹ Apotheek Zuwe Hofpoort Ziekenhuis, Woerden, The Netherlands

² Apotheek Sint Franciscus Gasthuis, Rotterdam, The Netherlands

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22 or 33 syringes. For 11 syringes, 150 mL of bupivacaine hydrochloride 5 mg/mL, 60 mL of sufentanil citrate 5 µg/mL and 390 mL of sodium chloride 0.9% are mixed in a conical flask for five minutes and then the solution goes through a sterile transfer tube set (Baxa number 11), filtered through a sterile 0.2 µm membrane filter (Rotrand 25 mm Schleicher & Schuell FP030/3) before filling the syringes using a Baxa Repeater pump.

Suitability of the filling method

On three different days, a solution was prepared as described above. During the filling process, six 5 mL samples (S1 to S6) were taken (Table 1). After mixing the solution, one sample (S1) was taken from the flask and another sample (S2) was filled using the Baxa Repeater pump. For determining the shelf-life of the solution, at this point six 50 mL syringes were filled using the Baxa Repeater pump. Syringes 1, 2 and 3 were stored in the refrigerator; syringes 4, 5 and 6 were stored at room temperature. A 5 mL sample (S3) from syringe 1 was immediately taken and stored in a glass tube. The pump, the tube set and the flask, including the remainder of the solution, were left in place. Samples were taken after one hour (S4) and two hours (S5) of completing the filling process, out of the flask. Two hours after completing the filling process, another syringe was filled with the bupivacaine/sufentanil solution (S6) using the Baxa Repeater pump. Immediately after taking the samples, the concentrations of bupivacaine hydrochloride and sufentanil citrate were determined by HPLC in samples S1 to S6.

Table 1: Concentrations (mean ± standard deviation; n = 3) of bupivacaine hydrochloride and sufentanil citrate in samples taken during the filling process

Sample	Time of sampling	Bupivacaine HCl	Sufentanil citrate
S1	Immediately after mixing bupivacaine HCl, sufentanil citrate and sodium chloride	98.6% ± 0.7%	100.1% ± 0.9%
S2	From the first filtrate (after rejection)	98.1% ± 0.9%	99.0% ± 0.5%
S3	From the first syringe filled	98.3% ± 0.8%	99.6% ± 1.3%
S4	From the flask (one hour after finishing the filling process)	98.4% ± 0.8%	99.3% ± 0.4%
S5	From the flask (two hours after finishing the filling process)	99.2% ± 0.9%	99.3% ± 0.3%
S6	From the tube set (two hours after finishing the filling process)	98.2% ± 0.6%	94.8% ± 0.5%

Shelf-life

On days 4, 7, 14 and 28, 5 mL samples were taken from a syringe stored in the refrigerator and a syringe stored at room temperature. Immediately after taking the samples, the concentrations of bupivacaine hydrochloride and sufentanil citrate were determined by HPLC in both samples.

HPLC method

The concentrations of bupivacaine hydrochloride and sufentanil citrate were determined by HPLC. The HPLC system consisted of a SIL-10AD auto injector, a LC-10AT pump, a 5-µm Nucleosil column 100 C18 150 mm × 4.6 mm (Varian, Bergen op Zoom, The Netherlands), a SPD-10A variable UV detector (Shimadzu Benelux, 's Hertogenbosch, The Netherlands) and Shimadzu CLASS-VP 6.12 software. The concentration of bupivacaine hydrochloride was determined by a different HPLC method than the one used to determine the concentration of sufentanil citrate. The specifications of both methods are shown in Table 2. Both methods were adapted to the local situation and validated.

Linearity, trueness (closeness of agreement between the average value of the determined concentrations and the known concentration), precision (repeatability and reproducibility), selectivity, specificity and robustness were determined for both the methods of HPLC [4]. Selectivity and specificity were demonstrated by analysing forced degradation samples which were obtained by exposing the solution for four hours to acid (hydrochloride 2M), base (sodium hydroxide 2M) or oxidation (hydrogen peroxide 30%) and heat (105°C). The robustness was determined by making small variations in the detection wavelength (standard wavelength ± 5 nm), flow-rate (1.5 mL/min ± 0.1 mL/min), ratio buffer/acetonitrile (standard amount of buffer ± 25 mL) and the degree of acidity of the buffer (standard pH ± 0.15 pH unit).

Table 2: Specifications of the HPLC methods used for the determination of bupivacaine hydrochloride and sufentanil citrate concentrations

	HPLC method bupivacaine hydrochloride [5]	HPLC method sufentanil citrate [3]
Mobile phase	Buffer pH 3.35: acetonitrile = 675:325	Buffer pH 3.0: acetonitrile = 750:250
Flow rate	1.5 mL/min	1.5 mL/min
Injection volume	20 µL	50 µL
Detection wavelength	263 nm	235 nm
Concentration calculated with	Peak area ratios	Peak heights

Table 3: Parameters found during the validation of the HPLC method of bupivacaine hydrochloride (concentration 0.125%) and the HPLC method of sufentanil citrate (concentration 0.5 µg/mL) [4]

Item	Parameter	Bupivacaine HCl	Sufentanil citrate
Linearity ¹	Correlation coefficient	0.9998	0.9993
Trueness	Recovery	100.5%	100.6%
Repeatability	Concentration Variation coefficient	100.2 ± 0.2% ² 0.25%	101.0 ± 0.3% ² 0.43%
Reproducibility	Concentration Variation coefficient	100.2 ± 0.3% ² 0.32%	100.4 ± 1.0% ² 1.29%
Robustness	Concentration Variation coefficient	99.3 ± 0.6% ² 0.62%	105.7 ± 1.24% ² 1.17%

¹ Linearity was determined in the range of 75% to 125% of the declared concentrations; ² Percentage of the declared concentration

Standard solutions of bupivacaine hydrochloride and sufentanil citrate were prepared from Marcaine solution for injection 5 mg/mL and sufentanil solution for injection 5 µg/mL (Hameln) respectively, with the same batches as those used for preparation of the syringes. The concentrations of bupivacaine hydrochloride and sufentanil citrate were determined in triplicate in each standard solution and sample.

RESULTS

Validation of HPLC methods

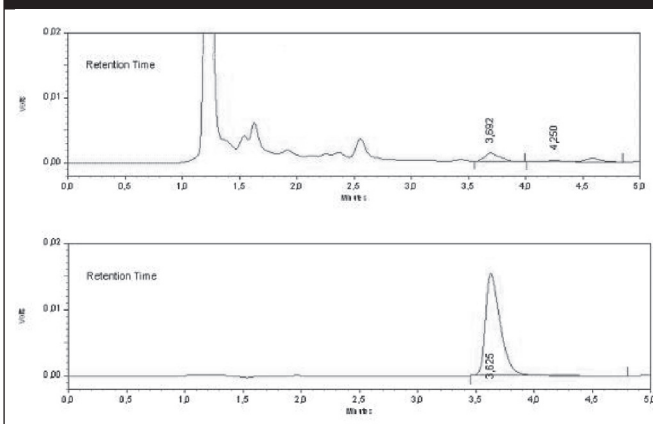
Both HPLC methods were validated. The results for linearity, trueness, precision and robustness are shown in Table 3.

As part of the determination of the specificity and selectivity, the solution exposed to oxidation and heat contained the most degradation products. Figures 1 and 2 show the chromatograms of this degraded solution for both the methods. The HPLC method for bupivacaine hydrochloride was specific and selective. The chromatogram of the HPLC method for sufentanil showed impurities of the sufentanil peak, probably because of degradation products. Although the specificity and selectivity of the method used were assumed to be sufficient. This conclusion was drawn because of the extreme conditions to which the degraded solution was exposed and the fact that none of the chromatograms of the solutions stored under normal conditions (see also Figure 2) showed these impurities.

Acceptability of the filling method

The concentrations of bupivacaine hydrochloride and sufentanil citrate in the samples, which were taken during

Figure 1: Chromatograms of the HPLC method for bupivacaine hydrochloride after the solution was exposed to oxidation and heat for four hours (above) and after the solution was stored at room temperature for 28 days (below)



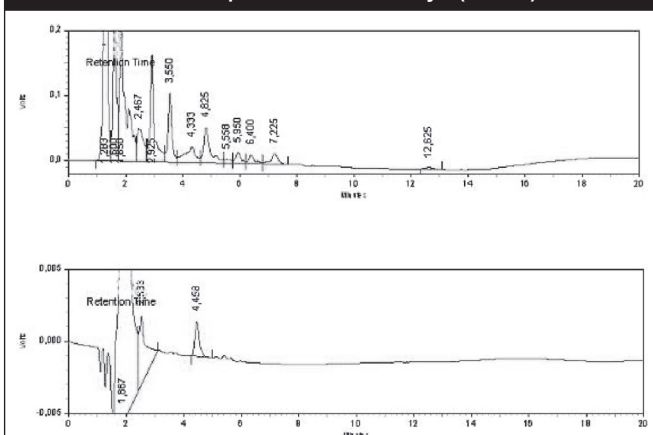
The peak at retention time 3.6 minutes is the peak of bupivacaine hydrochloride

the filling process, are shown in Table 1. The concentration of bupivacaine hydrochloride was stable during the filling process. On the other hand, the concentration of sufentanil citrate declined from 100.1% immediately after preparing the solution to 94.8% after being in the tube set for two hours.

Shelf-life

On day 28, the concentration of bupivacaine hydrochloride was 97.9 ± 0.5% in the samples stored in the refrigerator (mean ± standard deviation; n = 6) and 97.4 ± 0.4% in the samples stored at room temperature. The concentration of sufentanil

Figure 2: Chromatograms of the HPLC method for sufentanil citrate after the solution was exposed to oxidation and heat for four hours (above) and after the solution was stored at room temperature for 28 days (below)



The peak at retention time 4.3-4.4 minutes is the peak of sufentanil citrate

citrate was $99.2 \pm 0.7\%$ in the samples stored in the refrigerator and $95.6 \pm 2.1\%$ in the samples stored at room temperature. The mean concentrations are shown in Figure 3.

DISCUSSION

The preparation and filling method, using a Baxa Repeater pump, described in this study, is simple and suitable for filling 50 mL syringes with a solution containing bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 $\mu\text{g/mL}$.

During the filling process, the mean concentration of sufentanil citrate in the solution declined below 95% after being in the tube set for two hours. This is probably caused by adsorption of sufentanil citrate on to PVC in the tube set [3]. Since the filling process is not interrupted in a normal situation in the pharmacy of this hospital, the contact time of the solution and the tube set, and therefore loss by adsorption, is limited.

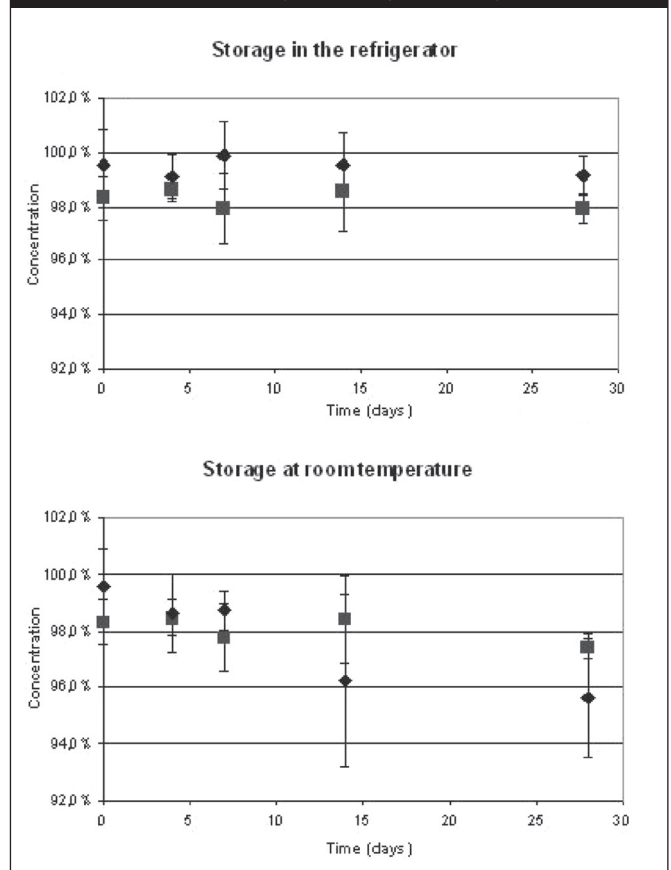
After storage for 28 days in the refrigerator or at room temperature, the mean concentration of bupivacaine hydrochloride in the syringes was still above 95%. The same result was found for the mean concentration of sufentanil citrate in syringes stored in the refrigerator. On the other hand, after storage for 28 days at room temperature, the mean concentration of sufentanil citrate in the syringes was just a little above 95%. Therefore, and also from a microbiological point of view, it is preferable to store the syringes in the refrigerator. The syringes can be kept in the refrigerator for at least 28 days. These results agree with the results of an earlier, comparable study [3].

In this study, the chemical stability of a solution of bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 $\mu\text{g/L}$ was investigated. In Sint Franciscus Gasthuis, this combination of concentrations is the only one that is routinely used and therefore standardised. It is expected that solutions with higher concentrations of one or both drugs will also be chemically stable during the described filling process and during storage in the refrigerator for 28 days. It is uncertain if solutions with lower concentrations of one or both drugs are also chemically stable. Therefore, this study should be repeated using lower concentrations if those are the ones to be used.

REFERENCES

1. Graffhorst JP van, Foudraine NA, Nooteboom F, et al. Schone schijn bedriegt. Bereiding van perfusorspuiten op de intensive care. *Pharm Weekbl.* 2001;136(20):732-7.
2. Roos PJ, Glerum JH, Meilink JW. Stability of sufentanil citrate in a portable pump reservoir, a glass container and a polyethylene container. *Pharm Weekbl Sci.* 1992;14(4):196-200.
3. Roos PJ, Glerum JH, Schroeders MJH. Effect of glucose 5% solution and bupivacaine hydrochloride on absorption of sufentanil citrate in a portable pump reservoir during

Figure 3: Concentrations (mean \pm standard deviation, n = 6) of bupivacaine HCl (■) and sufentanil citrate (♦) in syringes stored in the refrigerator (above) and at room temperature (below) immediately after filling and on days 4, 7, 14 and 28



CONCLUSION

For the preparation of 50 mL syringes filled with bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 $\mu\text{g/mL}$, the filling method using a Baxa Repeater pump can be used. In a normal situation, the loss of sufentanil citrate by adsorption on to the PVC-containing tube set during the filling process is negligible.

When stored in the refrigerator, syringes filled with bupivacaine hydrochloride 0.125% and sufentanil citrate 0.5 $\mu\text{g/mL}$ can be kept for at least 28 days.

- storage and simulated infusion by an epidural catheter. *Pharm World Sci.* 1993;15(6):269-75.
4. Van der Vaart FJ. Richtlijnen voor analytische validatie. *Pharm Weekbl.* 1992;127(46):1229-35.
5. Movig KLL, Langen MCJ, Egberts ACG. Analysis of low concentration sufentanil citrate/bupivacaine hydrochloride admixtures, using solid phase extraction followed by high-performance liquid chromatography. *J Pharm Biomed Anal.* 1999;21(4):845-50.