Department of Pharmacy[1], Faculty of Medicine; Institute of Pharmacy[2]; Department of Anaesthesiology[3], Faculty of Medicine, Friedrich-Schiller-Universität Jena, Germany

## Stability of fentanyl/ropivacain preparations for epidural application

M. HARTMANN[1], H. KNOTH[1], W. KÖHLER[2], W. MEISSNER[3]

*Received June 26, 2002, accepted September 16, 2002*

*Dr. Michael Hartmann, Apotheke des Universitätsklinikums Jena, Erlanger Allee 101, D-07747 Jena, Germany, Michael.Hartmann@med.uni-jena.de*

*Pharmazie 58: 434–435 (2003)*

In addition to patient-controlled analgesia (PCA) by means of intravenous opioids, epidural analgesia also makes a major contribution to the quality of analgesia [1] and to limiting the risk of adverse effects [2] in the clinical management of postoperative pain. For this purpose, local anaesthetics as well as their combinations with opioids (notably, morphine, fentanyl, sufentanil) have been used. Among many options, mixed infusions of fentanyl with bupivacain or ropivacain are particularly well established and are used routinely [3]. These combinations are usually prepared in small batches, as needed, since information on their chemical stability is limited, particularly for ropivacain [4]. There is somewhat more information concerning fentanyl/bupivacain mixed infusions [5, 6], and this agent is known to be adsorbed by vinyl plastics employed in intravenous bags and tubing [7, 8]. However, the possible effect of adsorption to PVC (polyvinyl chloride) and EVA (ethylene-vinyl-acetate copolymer) intravenous bags on fentanyl/ropivacain is unknown. Therefore, this study evaluated the stability of fentanyl/ropivacain infusions in different kinds of packaging material without and with protection from light.

Samples of contents of all bags (PVC, EVA) and bottles (glass) were removed daily up to day 5 and then in two-day intervals up to day 51, pH was measured, and concentrations of fentanyl and ropivacain were assayed by HPLC. No water loss was found over the maintained period. Moreover, samples from EVA bag and glass bottles did not exhibit any changes in pH (mean ± SD pH = 4.95 ± 0.41 vs. 5.08 ± 0.45), or evidence of decomposition in the chromatograms.

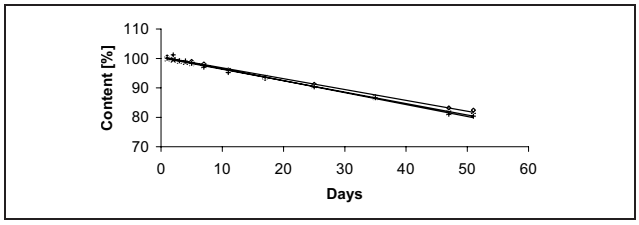


Fig.: Variations of the fentanyl content in PVC bags

In contrast, with PVC bags, concentrations of fentanyl fell by approximately 20% by day 51, independent of the type of storage, evidently due to adsorption to the container as reported previously [7, 8] (Fig.). However, the concentration of ropivacaine remained constant (by linear regression: EVA-bag $a = -0.023$, $R^2 = 0.011$; Glass bottle $a = 0.004$, $R^2 = 0.03$; PVC bag $a = 0.008$, $R^2 = 0.02$), but pH fell from 5.08 ± 0.45 to 4.55 ± 0.30.

These findings indicate that a ropivacain/fentanyl solution (0.15%; 0.0003%) was stable at room temperature in EVA bags and glass containers, unprotected from light, for 51 days (Table). However, use of PVC containers for fentanyl preparations yielded evidence of poor stability due to evident loss of soluble fentanyl by adsorption to the plastic container. EVA bags were not associated with such adsorptive losses of fentanyl, and are to be preferred. Moreover, EVA bags are preferable for ecological reasons.

## Experimental

For the preparation of samples, commercially available preparations were used. For packaging, EVA (Impromediform Corp.), PVC bags (Viaflex®, Baxter Corp.), and standard, commercially available, glass infusion bottles were used. Each of these contained 250 ml of a solution prepared from 0.785 mg fentanyl citrate (Fentanyl®, Curamed Corp., 0.5 mg/10 ml amp., Lot-Nr. 5460301. corresponding to 0.0003%); 370 mg ropivacain HCl (Naropin®, AstraZeneca Corp., 10 mg/ml, 20 ml amp., Lot-Nr. CJ924A1. corresponding to 0.15%); and 0.9% sodium chloride injection (E154® 1000 ml, Serumwerke, Bernburg, Lot-Nr. 1241). The test solutions were prepared by adding the drug solutions and the sodium chloride injection to an empty container.

In each case, three bags or three bottles were stored under the following conditions:

Condition 1: 2 °C < × < 8 °C, protected from light, Condition 2: 20 °C, protected from light, Condition 3: 20 °C, light. All bags were visually examined at all intervals and water loss was monitored with weighing. Five samples each were removed; pH (starting value pH = 5.08 ± 0.45 SD) was determined potentiometrically. Chromatographic separations were carried out according to the HPLC method of the European Pharmacopoeia with a

**Table: Fentanyl concentration (%) Mean ± SD, sample 1: 2 °C < x < 8 C, protected from light; sample 2: 20 °C, protected from light; sample 3: 20 °C, light**

| Day | EVA bag | | | Glass bottle | | | PVC bag | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 |
| 1 | 101.2 ± 0.4 | 101.6 ± 0.5 | 99.9 ± 0.5 | 99.2 ± 0.3 | 100.2 ± 0.3 | 100.1 ± 0.6 | 100.5 ± 0.2 | 99.8 ± 0.3 | 100.1 ± 0.3 |
| 2 | 100.2 ± 0.5 | 100.7 ± 0.7 | 100.3 ± 0.6 | 100.6 ± 0.5 | 100.1 ± 0.5 | 99.8 ± 0.4 | 100.3 ± 0.3 | 99.4 ± 0.4 | 101.2 ± 0.5 |
| 3 | 101.4 ± 0.7 | 99.3 ± 0.6 | 99.4 ± 0.7 | 101.4 ± 0.6 | 99.2 ± 0.3 | 101.1 ± 0.5 | 99.2 ± 0.7 | 99.0 ± 0.4 | 99.2 ± 0.6 |
| 4 | 99.2 ± 0.3 | 100.5 ± 0.6 | 100.5 ± 0.2 | 99.6 ± 0.7 | 100.6 ± 0.8 | 100.2 ± 0.6 | 99.1 ± 0.7 | 98.6 ± 0.3 | 99.1 ± 0.4 |
| 5 | 100.6 ± 0.4 | 99.1 ± 0.3 | 101.2 ± 0.3 | 101.2 ± 0.4 | 101.4 ± 0.8 | 99.8 ± 0.4 | 99.0 ± 0.5 | 98.2 ± 0.5 | 98.3 ± 0.2 |
| 7 | 100.3 ± 0.6 | 97.0 ± 0.4 | 100.9 ± 0.4 | 102.2 ± 0.3 | 100.1 ± 0.5 | 99.8 ± 0.8 | 98.1 ± 0.4 | 97.5 ± 0.7 | 97.0 ± 0.5 |
| 11 | 101.5 ± 0.4 | 99.9 ± 0.5 | 99.2 ± 0.8 | 100.5 ± 0.5 | 99.6 ± 0.4 | 99.2 ± 0.3 | 96.1 ± 0.4 | 95.9 ± 0.6 | 95.2 ± 0.6 |
| 17 | 99.0 ± 0.5 | 101.3 ± 0.3 | 99.7 ± 0.9 | 99.5 ± 0.8 | 98.2 ± 0.5 | 100.0 ± 0.5 | 93.2 ± 0.7 | 93.6 ± 0.4 | 93.6 ± 0.4 |
| 25 | 99.2 ± 0.3 | 100.2 ± 0.7 | 100.2 ± 0.4 | 100.3 ± 0.5 | 99.4 ± 0.6 | 101.1 ± 0.8 | 91.2 ± 0.6 | 90.6 ± 0.4 | 90.3 ± 0.6 |
| 35 | 100.2 ± 0.7 | 98.5 ± 0.9 | 100.0 ± 0.4 | 101.0 ± 0.5 | 99.9 ± 0.3 | 100.4 ± 0.6 | 87.0 ± 0.5 | 86.7 ± 0.5 | 86.6 ± 0.5 |
| 47 | 99.3 ± 0.6 | 100.5 ± 0.3 | 98.7 ± 0.6 | 99.2 ± 0.4 | 99.2 ± 0.5 | 98.2 ± 0.7 | 83.2 ± 0.3 | 81.5 ± 0.4 | 81.0 ± 0.7 |
| 51 | 99.2 ± 0.7 | 98.7 ± 0.7 | 97.8 ± 0.7 | 99.1 ± 0.7 | 98.2 ± 0.4 | 97.3 ± 0.4 | 82.4 ± 0.5 | 80.7 ± 0.3 | 80.4 ± 0.8 |

Shimadzu (Kyoto, Japan) chromatograph equipped with an Shimadzu LC 8A pump, SCL-6B control unit, SIL-6B auto injector, and an SPD-7A UV detector. Analytes were separated on a 5 μm LiChrospher 60 RP-select B (250 × 4 mm; Merck, Darmstadt) column. The liquid phase was a mixture of acetonitrile/phosphate buffer (30/70, vols; 0.05 M, pH 4.6) at a flow rate of 1 ml/min. UV detection was at 210 nm to accommodate the low UV absorption of fentanyl. Samples (50 μl) of undiluted infusion solution were injected, and each analysis was replicated 5 times. The content of the test solution was determined with a series of concentrations of Fentanyl (Sigma Chemie) as reference standard in the range of 0.5–5 μg/ml, according to the European Pharmacopoeia. The interday and intraday precision (coefficient of variation) was <10%. The stability-indicating capability of the assay was determined by subjecting a sample to extremes of heat (60 °C, 2 h) and pH (2 and 12). There were no interfering peaks in either chromatograms.

**References**


1 Jorgensen, H.; Wetterslev, J.; Moiniche, S.; Dahl, J. B.: Cochrane Database Syst Rev. 2000: CD001893.
2 Ballantyne, J. C.; Carr, D. B.; deFerranti, S.; Suarez, T.; Lau, J.; Chalmers, T. C.; Angelillo, I. F.; Mosteller., F.: Anesth Analg. **86**, 598 (1998)
3 Liu, S.; Carpenter, J. M.: Anesthesiology **82**, 1474 (1999)
4 Robustelli della Cuna, F. S.; Mella, M.; Magistrali, G.; Ricci, M.; Losurdo, A.; Goglio, A. M.: Am. J. Health Syst. Pharm. **18**, 1753 (2001)
5 Allen, L. V.; Stiles, M. L.; Wang, D. P.; Tu, Y. H.: Am. J. Hosp. Pharm. **50**, 714 (1993)
6 Sattler, A.; Jage, J.; Kraemer, I.: Pharmazie **53**, 386 (1998)
7 Dawson, P. J.; Bjorksten, A. R.; Duncan, I. P.; Barnes, R. K.; Beemer, G. H.: Br. J. Anaesth. **68**, 414 (1992)
8 Xu, Q. A.; Trissel, L. A.; Martinez, J. F.: Ann. Pharmacother. **31**, 297 (1997)



Research Institute for Industrial Pharmacy[1], School of Pharmacy, Potchefstroom University for CHE, Potchefstroom, South Africa, and Department of Basic Pharmaceutical Sciences[2], School of Pharmacy, University of Louisiana at Monroe, USA


## Variable temperature X-Ray Powder Diffractometry of spironolactone polymorphs


W. Liebenberg[1], E. C. van Tonder[1], T. G. Dekker[1], M. M. de Villiers[2]



*Received February 11, 2003, accepted February 19, 2003*



*Wilna Liebenberg, Ph.D., Research Institute for Industrial Pharmacy, School of Pharmacy, Potchefstroom University for CHE, Potchefstroom 2520, South Africa*
*iifwl@puknet.puk.ac.za*



*Pharmazie 58: 435–437 (2003)*


Spironolactone is a diuretic steroidal aldosterone agonist known to show variable and incomplete oral bioavailability because of poor water solubility and dissolution rate [1]. This might be due to variations in the crystal form because the crystal properties of spironolactone are complex; it can adopt polymorphic, non-stoichiometrically solvated or amorphous glass forms from the same solvents, and can undergo solvent mediated and other solid-state transformations [1–9]. This study reports the usefulness of variable temperature X-ray powder diffractometry (VTXRPD) as a fast method to characterize and measure the transformation between two spironolactone polymorphs, and mixtures thereof, found among raw material samples randomly obtained from pharmaceutical bulk suppliers.

Salole and Al-Sarraj [2] and El-Dalsh et al. [3] published the first extensive reports describing and characterizing spironolactone polymorphs. Their research identified four polymorphic forms – three metastable, and one stable form – and several pseudopolymorphs. Agafonov et al. [1] prepared two non-solvated forms (I and II) and four solvated crystalline forms and described the morphology, symmetry, and the crystallographic parameters of five of these forms. Their results showed that under general crystallization and preparation procedures spironolactone most probably crystallize either as the metastable form I and form II the thermodynamically stable form. Form I was formed by fast crystallization from various organic solvents. It most probably represents a desolvated form since structural evidence indicated that in this form the solvent molecules incompletely occupies the four allowed positions in the unit cell with space group $P2_12_12_1$. These two forms are also classified as monotropic polymorphs, because the two forms do not transform one into another by heating [1]. The most recent report on spironolactone polymorphism identified three true polymorphs similar to those described in the other reports but this study rules out the formation of stable pseudopolymorphs [9]. All these researchers concluded that the facility with which spironolactone crystallize in different crystal forms is due to a flexible lattice allowing the molecule to adopt subtly distorted conformations [5, 6, 8].

In this study, the physicochemical properties of five randomly obtained samples of spironolactone were determined. The median particle sizes by volume of all the samples were identical and small, $\leq 6$ μm. There were no