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Microbiological stability of solutions containing local anesthetics and opioids in closed infusion systems used for epidural analgesia

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Nine solutions containing opiod analgesics and local anesthetics as typically use in epidural catheters were tested for antimicrobial stability. Administration via a pefusor syringe requires several refill processes. It was shown that repetitive refilling of the syringes did not result in any microbiological contamination.

In postoperative and posttraumatic pain therapy, analgesic and anesthetic solutions are administered through epidural catheters (epidural analgesia) (Jage and Harte 1997). Mostly, the analgesic and anesthetic solutions consist of a low-dose local anesthetic (like ropivacaine or bupivacaine) and an opioid addition (like fentanyl or sufentanil). The infusions are often administered by a perfusor pump – the solution is flowing out of the infusion bag into a perfusor syringe and is administered continuously at a certain infusion rate. Since the volume of the infusion bag is higher than that one of the syringe, the syringe has to be refilled several times without disconnection of the system. While refilling the syringes the systems remain closed, but the inside of the syringe is exposed to environmental air. The aim of this study was to investigate if repetitive refilling of the syringes resulted in any microbiological contamination .

Microbiological stability of nine solutions containing local anesthetic and opioid components was tested (Table). A tenth test run, intentionally contaminated with *Staphylococcus epidermidis*, was carried out as positive control.

For each test run, four infusion bags with 500 ml solution have been produced under aseptic conditions in the hospital pharmacy of the University Hospital Jena. Directly after the manufacturing of the infusion bags, one bag was microbiological investigated to prove the aseptic state (control sample), while the other three bags were stored for 18 days at a temperature of 2–8 °C and then used for the simulation of epidural administration.

Table: Composition of solutions investigated

Test run	Fentanyl 3 µg/ml	Sufentanil 0,5 µg/ml	Ropivavaine 1,5 mg/ml	Bupivacaine 1,5mg/ml	Sodium chloride solution (0,9%)
1	–	–	–	–	500 ml
2	–	–	75 ml	–	425 ml
3	–	–	–	150 ml	350 ml
4	30 ml	–	–	–	470 ml
5	–	5 ml	–	–	495 ml
6	30 ml	–	75 ml	–	395 ml
7	–	5 ml	75 ml	–	420 ml
8	30 ml	–	–	150 ml	320 ml
9	–	5 ml	–	150 ml	345 ml

All samples of the first nine test runs - independently of the used solutions – did not show any bacterial growth. Therefore, in view of a potential microbiological contamination, it seems to be irrelevant which of the tested local anesthetics and opioids are combined. The last test run with intentional bacterial contamination was carried out to prove the suitability of the microbiological investigation method and was unequivocally identified as contaminated. However, when being evaluated for possible contamination, all taken samples were sterile. Most probably, the used epidural filter system with its 0,2 µm size is able to restrain bacteria.

The main requirement of the microbiological stability and of bacteria-free administration is the use of sterile infusion solutions (Kost-Byerly et al. 1998; Barreto 1961, James et al. 1976). All infusion solutions used in our investigations were manufactured under aseptic conditions and proved to be sterile. Besides that one with intentional contamination at test run 10, all control samples demonstrated sterility, thus confirming an aseptic manufacturing process.

Conditions of practical use have been imitated as far as possible with the use of exactly the same components and conditions as in clinical practice. Therefore, the results and conclusions can be regarded as relevant for clinical practice.

Experimental

Fentanyl (Fentanyl-Janssen® 0.5 mg ampoules, 10 ml, charge: 8LB0700, Janssen-Cilag), Sufentanil (Sufenta® 50 µg/ml ampoules, 5 ml charge: 9AB0F00, 8LB1200, Janssen-Cilag), Ropivacaine (Naropin® 10 mg/ml ampoules with 20 ml (Charge: LA 1711, AstraZeneca) and Bupivacaine (Bucain® 0,5% bottles with 50 ml charge: 098072B, DeltaSelect). Isotonic sodium chloride solution (0,9%) was the dilution of the solutions (charge: 14BF1016, Fresenius Kabi). The composition of the solutions is shown in the Table.

The investigation system consisted of perfusor devices from B. Braun Melsungen AG (type 8713820) and a sterile infusion set commonly used for epidural analgesia to imitate the practical conditions as far as possible. The solutions flew via an Intrafix® safeset out of the infusion bag through an interim 3-way-tap (Discofix®) into a syringe (original perfusor® syringe). The perfusor device administered the solutions by constant speed via a Perfusor® line, a Perifix® EF filter 0,2 µm and an epidural catheter (Perifix® miniset, charge: 4511000) into an empty collection bag (Impromediform, EVA infusion bags) which replaced the real patient.

The experiments took place in a treatment room of the pain clinic of the University Hospital Jena to simulate real treatment conditions. For collecting the solution, a sterile 500 ml EVA infusion bag (collecting bag) was used. The epidural needle was inserted under aseptic conditions. It remained in the infusion bag to maintain the closed system. After the connection of the remaining components, a treatment of five days was simulated. The infusion rate varied between 3 and 12 ml/h. The perfusor syringes were refilled ten times. A sample of 10 ml was taken directly after the connection and then every 24 hours (i.e. after 0, 24, 48, 72 and 96 h) from every collecting bag by sterile syringes. Appropriate to Ph. Eur. 6, 2.6.1, the investigation of sterility was performed by incubating the solutions for 14 days with liquid thioglycolate for anaerobic bacteria and with caseinpepton-sojapepton for aerobic bacteria and fungi. Before use, the suitability of the nutrition mediums was checked with testing organisms.

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