Low-dose Morphine solution for spinal anaesthesia – ready to use to improve patient safety in drug therapy

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Background
Standard operating procedure for spinal anaesthesia during elective caesarean section is the addition of a lipophilic opioid like sufentanil to hyperbaric local anaesthetic (e.g. bupivacaine). Addition of low dose morphine 0.1-0.2mg has shown to increase the duration of postoperative analgesia without increasing maternal or neonatal side-effects.

Challenge
In Germany no low-dose morphine solution is licensed. Available morphine solutions need to be diluted 100 fold to reach the desired concentration of 0.1mg/ml. This two-step diluting procedure holds not only a relevant risk of contamination, but also of accidental overdose resulting in delayed respiratory depression. Therefore, anaesthesiologists requested the hospital pharmacy to supply a 0.1mg/ml morphine solution for intrathecal administration.

Formulation development
Two different options were considered:

1. Ready to administer
   Aseptically dilution of licensed morphine solutions with normal saline under controlled conditions in syringes ready to administer
   - For intrathecal administration two-piece syringes are commonly used to avoid extraction of syringe material components into the solution
   - Two-piece syringes are considered more permeable for evaporation and contamination than three-piece syringes
   - Therefore prefilled syringes can be supplied only with a shelf life of 24 hours

2. Ready to use
   Dissolving morphine hydrochloride trihydrate in normal saline under controlled conditions in amber glass vials with final sterilisation by autoclaving
   - Little published data available for stability of low dose morphine solutions
   - Relevant stability criteria are pH value 2.8-3.3 and depletion of oxygen by degassing with nitrogen
   - Development of a new formulation (picture 1) without degassing with nitrogen

Stability testing
Method
A published HPLC method was modified and tested with a freshly compounded morphine solution and different chemically degraded solutions (picture 2). The method showed to be stability-indicating.

Stability of the morphine solution: procedures and results
- Three batches were compounded for stability testing
- Assays were performed on day 1 before and after sterilisation, on day 14, 30, 60, 150, 200 and 300
- Neither relevant loss of morphine content through sterilisation nor over time tested (picture 3)
- No degradation products could be detected over the whole testing period
- Extrapolation of data allows a batch production with a shelf life of at least one year without oxygen depletion

Discussion
- An instruction leaflet as well as standard operating procedure for safe clinical use of RTU low dose morphine solution was developed in collaboration with anaesthesiologists and hospital pharmacists
- Interdisciplinary collaboration of anaesthesiologists and hospital pharmacists enables to develop a simple and stable RTU low dose morphine formulation for easy application. Patient safety in drug therapy with a high-risk procedure was improved comprehensively.

Literature

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