Low-dose Morphine solution for spinal anaestesia – 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

Morphine HCl trihydrate	132 mg
Hydrochloric acid 25%	q.s.
0,9% Sodium chloride injection solution	ad 1328 g

- Dissolve morphine in a subset to 0,9% sodium chloride
- Adjust pH to pH 2.8 - 3.3 with hydrochloric acid
- Complete with residual 0,9% sodium chloride on final weight
- Filter with sterile filter 0,2µm in 5ml injection vials to 2.2ml
- Seale with rubber stopper and crimp seal cap
- Autoclave at 121°C, 2 bar, 20min

Picture 1: Formulation for a batch of 600 pieces

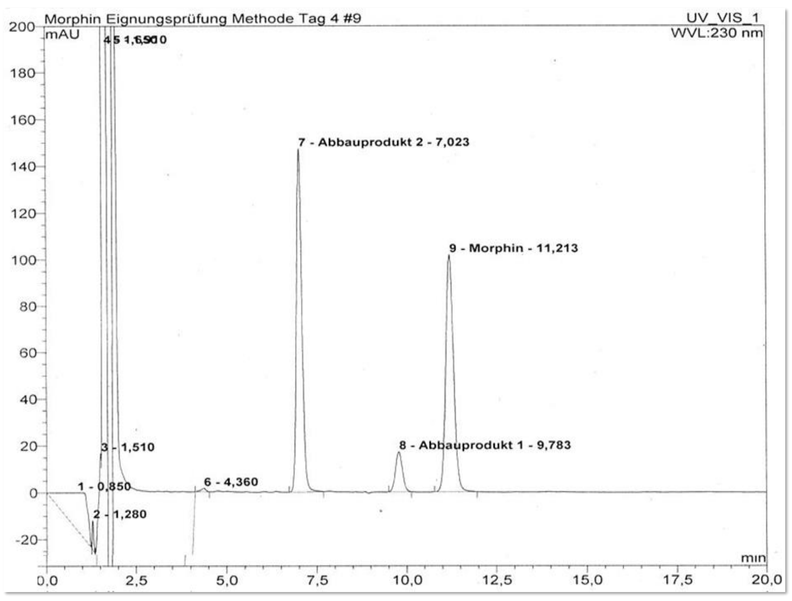
Stability testing

Method

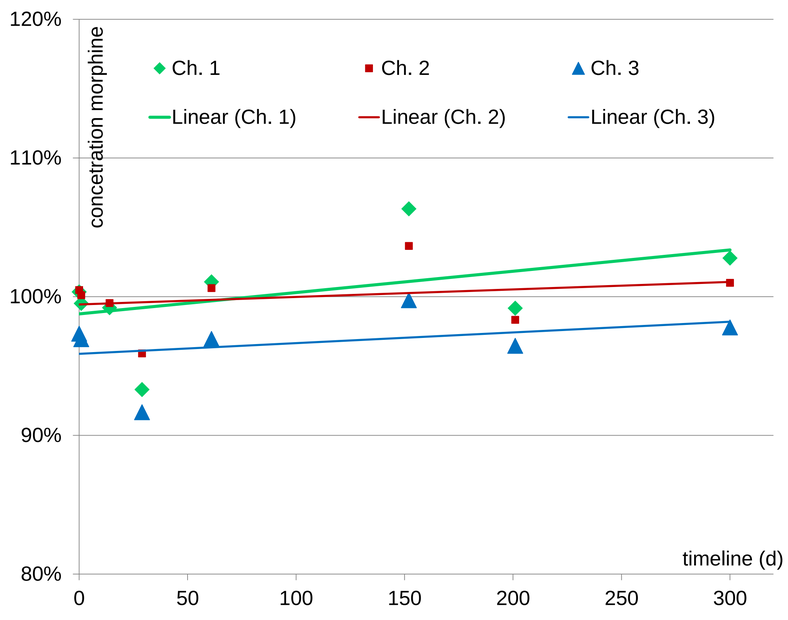
A published HPLC method was modified and tested with a freshly compounded morphine solution and different chemically degraded solutions (picture 2). The method showed to be stability-indicating.

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



Picture 2: Chromatogram of a forced oxidized morphine solution (day 4)



Picture 3: stability of morphine HCl 100 µg/ml injection solutions

Picture 4: Ready to use product: morphine-HCl 200 µg injection 2ml

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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