Abstract

Closing gaps in the Y-site compatibility data of different antibiotics and analgetics with Ringer's acetate

Ringer's acetate is a balanced crystalloid solution that is used for volume replacement at the Kantonsspital Baden (KSB). Compared to NaCl 0.9% or dextrose 5%, it carries a lower risk of inducing metabolic or dilutional acidosis while effectively maintaining blood pH and potassium levels within physiological range. The frequent use of Ringer's acetate poses particular challenges to hospital pharmacists, as stability and compatibility data is not available for many intravenous drug products that are regularly co-infused with Ringer's acetate. This represents a significant risk to medication safety. In practice, the lack of data often necessitates the interruption and flushing of Ringer's acetate infusion, or the placement of an additional venous access. The Ringer's acetate compatibility list of the KSB hospital pharmacy is frequently consulted. The aim of this thesis was to address experimentally missing data on antibiotics and analgesics of the KSB compatibility list. This included the assessment of chemical stability of selected drug products in the Ringer's acetate solution using reversed-phase high performance liquid chromatography (RP-HPLC), as well as the occurrence of potential precipitates by examination of sub-visible particles in accordance with the European Pharmacopoeia (EP). The selected drug substances encompassed piperacillin and tazobactam (Sandoz), benzylpenicillin (Penicillin "Grünenthal"®), meropenem (Meronem®) and ketorolac (Tora-dol®). Morphine was initially tested but ultimately excluded due to poor separation on the HPLC column. A multianalyte RP-HPLC-UV/VIS method was developed and validated in terms of linearity, accuracy, precision and stability. For piperacillin, tazobactam, and meropenem, the developed multianalyte method was successful. Ketorolac and benzylpenicillin followed a single-point calibration due to stability issues. To simulate co-infusion of drug product solution and Ringer's acetate via a three-way stopcock (henceforth referred to as Y-site), average and high therapeutic doses of each drug product were prepared according to the manufacturer's leaflet, mixed in equal parts with Ringer's acetate, and left at room temperature for 2.5 hours (24 hours for low-dose Tora-dol®). The concentrations of all drug substances remained above the limit of 95% relative to the time zero concentration, in accordance with the European Medicines Agency (EMA) guideline. The counting of sub-visible particles by light obscuration showed that all test solutions met the acceptance criteria of the EP. For solutions of maximum volume of 100 ml, the EP limits the number of particles greater than or equal to 10 µm in diameter to 6000, and that of particles greater than or equal to 25 µm to 600. Based on this data, the Y-site compatibility of Piperacillin/Tazobactam Sandoz®, Penicillin "Grünenthal"®, and Tora-dol® with Ringer's acetate was confirmed and integrated into the existing compatibility list of the KSB. Conversely, as Meronem® deviated by more than 10% from the nominal concentration, a conclusive statement

could not be made despite meeting the specifications of the EMA and EP. Thus, until reliable data is available, Y-site co-infusion of Meronem® and Ringer's acetate should be avoided. The result of this work will support doctors and nurses in establishing safe infusion regimes and thus, contribute to improved medication safety at the KSB. Furthermore, the presented analytical methods may serve other hospital pharmacies as a foundation for future compatibility studies.