Abstract

Implementation of Prolonged Infusion Times for Meropenem and Piperacillin/Tazobactam: Stability Testing and Organizational Aspects

Introduction:
The aim of this thesis is the introduction of prolonged infusion times for meropenem and piperacillin (PIP)/tazobactam (TAZ) at the University Hospital Basel (USB). Prolonged infusion times were implemented at the Intensive Care Unit (ICU) and the Outpatient Parenteral Antibiotic Therapy (OPAT) program at the USB. The OPAT program is a method of delivering intravenous antibiotics in an ambulatory setting, as an alternative to inpatient care.

Materials and Methods:
Systematic literature review: A systematic literature review was conducted in 2016 to evaluate the stability of meropenem and PIP/TAZ. PubMed, Embase, databases and grey search were used. Inclusion criteria: stability of the antibiotic was examined for a minimum of 2 hours at ≥20°C. Stability was defined as ≤ 10% degradation of the active ingredient.
Stability testing PIP/TAZ: Due to the lack of literature data a stability study was conducted to investigate if a generic PIP/TAZ brand shows sufficient stability under the OPAT conditions: manufacturing pumps in advance, storing them refrigerated and administrating them at elevated temperatures (37°C). This included development of a stability testing method with High Pressure Liquid Chromatography (HPLC), validation of the method and a final in-use-stability study. The stability of three different pump compositions (Tazobac®, Piperacillin/ Tazobactam Sandoz® and Piperacillin/Tazobactam Sandoz® buffered using sodium citrate) was evaluated to examine the influence of an additional buffer on the chemical stability of the PIP/TAZ solution. A validated HPLC method was used to determine the drug concentration. Acceptance criteria were 90-110% of initial concentration.
Implementation to clinical practice: The introduction of the continuous infusion of meropenem and PIP/TAZ at the ICU with the help of a multidisciplinary team (physicians, nurses, pharmacists) was investigated. The team discussed the practical aspects with the aim to develop a standard operation procedure (SOP). A feasibility study with 18 patients was conducted. Problems for 25 patients were documented after the implementation.

Results:
Systematic literature review: meropenem and PIP/TAZ are stable for prolonged infusion times, if concentration and solvent are considered. Meropenem is not suitable for the OPAT setting, because it is unstable at temperatures above 25°C over 24 hours.
Stability testing PIP/TAZ: The original product and the generic buffered pumps fulfilled acceptance criteria for stability at the OPAT setting.
Implementation to clinical practice: continuous PIP/TAZ administration was easier than continuous administration of meropenem due to missing compatibility data. Not enough data on compatibility with commonly administered drugs exist for the concentrations used at the ICU. A SOP for PIP/TAZ and meropenem was developed and successfully implemented.

Conclusion:
Systematic literature review showed a huge difference in settings, and it was difficult to decide how the data can be translated into the hospital setting. Stability testing of PIP/TAZ supported the data found and helped to define a shelf life for the pumps manufactured at the hospital pharmacy. The SOP development in a multidisciplinary team was successful and many problems discussed could be resolved. However, the problem with a dedicated line for the continuous infusion remains. Too few compatibility data exist to overcome this problem yet.