Universitätsspital Basel

Interdisciplinary GSASA-project team

DE: Forschungsprojekt nationaler Tragweite 2019: Zwischenbericht 2020
EN: GSASA-research-project 2019: interim report 2020

Project title: “Drug stability testing of continuous infusion of β-lactam antibiotics in elastomeric pumps and determination of drug plasma levels in patients for improved outpatient parenteral antimicrobial therapy (OPAT).”

This *interim report* is provided due to delayed project progress. For better readability, we summarize the project parts, but also refer to the original application form for completeness. Briefly summarized: the project involves measuring of simulated-infusion stability for three marketed drugs and the corresponding pharmaceutical ingredients (API), namely Penicillin Grünenthal® (benzylpenicillin), Zerbaxa® (ceftolozane / tazobactam) and Zavicefta® (ceftazidime / avibactam). Further, we are trying to establish the OPAT usage of these API combinations, if considered safe in the stability study. At last, we plan to gather plasma level data for five patients for each of the drug combinations in the OPAT setting.

We now describe the current progress in the different parts (according to the application form) of the study in more details:

Part 1 **Development of HPLC-MS-MS methods for the API’s in plasma and in watery solutions.**	May-July 2019 A quantitative method for benzylpenicillin was already available at the time of the project start. A qualitative method was successfully developed based on the existing method. July 2019 - ongoing For ceftolozane / tazobactam we are still optimizing the quantitative method. The currently applied method for tazobactam results in fluctuating results. We will try to gain better results by using isotopic labeled tazobactam for tazobactam quantification, instead of the isotopic labeled ceftolozane we have used so far. September-October 2019 The ceftazidime / avibactam method was developed.
Part 2 **Preliminary testing and searching for candidate solutions for simulated infusion experiment.**	Since we reproduced a published study, no optimization step was necessary for benzylpenicillin. October 2019 - ongoing For ceftolozane / tazobactam the readily available drug Zerbaxa® already contains citrate buffer, L-Arginine and NaCl. We tried additional buffering with citrate buffer, and varying the solvent (0.9 % NaCl or 5 % Glucose), but could not improve stability further. Therefore, we proceeded to

conduct the stability study (Part 3) after promising preliminary study results with the original preparation.

October 2019 - ongoing
Ceftazidime / avibactam shows clearly insufficient stability (well below the -10 % threshold) in our preliminary studies. Since the drug product Zavicefta® does not contain any buffer aside from sodium carbonate, we tried different buffer solutions to increase the stability of both APIs, but could as of yet not find satisfactory conditions. If that optimization continues to fail, our next step is to evaluate the temperature dependency of the drug stability and to find out which temperature limit would be applicable for OPAT usage. The stability study would then be performed at 37 °C and at this new temperature, in order to confirm this upper temperature limit.

Part 3
Conducting stability study for publication.

April 2020
We finished the stability study for benzylpenicillin and were able to reproduce the previous study from McDougall et al. (2014) as mentioned in the proposal.

April 2020 - ongoing
In December 2019 Raby et al., published a study for ceftolozane / tazobactam stability at 37 °C. Therefore, we now also conduct this part as a reproduction study to some extent. Our project differs from the published data insofar, as we are taking into account 7 days at 2-8 °C on top of the subsequent 24 h at 37 °C for stability, while the Australian publication only considered the 37 °C part. At the moment, we are still struggling to confirm the findings of the publication by Raby et al., but mostly because our analytical method for tazobactam is not stable yet. After improving the method, we hope to be able to confirm these finding and add this to our publication portfolio. If we cannot confirm the published data, we will repeat the study at a lower temperature.

For ceftazidime / avibactam we did not reach part 3 of the project, yet.

Part 4
Write manufacturing protocol for OPAT usage of the suitable candidates and determine plasma levels of five patients.

Benzylpenicillin is used in OPAT on a regular basis already. Therefore, we made good progress in collecting the therapeutic drug monitoring (TDM) data (plasma levels) and could already include four of the five intended patients.

Ceftolozane / tazobactam is not yet used in OPAT in Switzerland. We found that its usage in the outpatient setting is dependent on the status of the marketed drug in the

	"Spezialitätenliste" of the swiss health department "Bundesamt für Gesundheit". As long as the drug is not listed there, financing in the outpatient setting is not covered by insurance without a discrete application by the treating physician. In consequence of these circumstances, it will probably not be possible to collect outpatient TDM data from five separate patients. As a replacement, we will try to collect TDM data for continuous infusion from in-patients. For ceftazidime / avibactam, these restrictions with the "Spezialitätenliste" don't apply. In case we manage to obtain a safe protocol for OPAT usage, we could potentially start to treat patients and to collect TDM data correspondingly.
Additional research question	April 2020 Using a qualitative LC-MS method, we compared fresh and stored benzylpenicillin solutions, detecting several break down products. Some of these compounds could be identified using their MS spectra and comparing them against available spectra, while others have not yet been identified. The same approach will be applied to ceftolozane / tazobactam and ceftazidime / avibactam.

Summary
The project's delay is caused by delays in conduction the experiments, but also by the need to repeat the experiments due to issues concerning the analytical method for ceftolozane / tazobactam and the outcomes of the experiments with ceftazidime / avibactam.

We are close to completing the research on benzylpenicillin and are collecting the last of the five TDM samples from patients in the OPAT program. We are currently putting together all data for publication.
For ceftolozane / tazobactam further work on method development is needed, but preliminary stability data looks promising, while ceftazidim / avibactam shows insufficient stability in our tested conditions as of yet and further experiments are needed.

Basel, 14.07.2020
Responsible for the project:

Sophia Rehm

Julian Meier