Februar 2019/sz

Forschungsprojekte nationaler Tragweite
Vorlage für das Einreichen eines Projekts

Ausschreibung Nr. 10

Titel des Projekts	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).		**30.04.2019**
Projektverant-wortlicher	Name, Vorname Funktion Institut Adresse Telefon E-mail	**Meier, Julian** Apotheker Spital-Pharmazie Spitalstrasse 26, Universitätsspital Basel, 4031 Basel, 061 556 59 60 julian.meier@usb.ch **Rehm, Sophia** PhD Student Klinische Chemie Petersgraben 4, Universitätsspital Basel, 4031 Basel 061 265 42 31 sophia.rehm@usb.ch	
Weitere Teilnehmer	Namen, Vornamen Funktionen Institute E-mail	**Khanna, Nina**, Prof. Dr. med., Leitende Ärztin Klinik Infektiologie und Spitalhygiene, nina.khanna@usb.ch **Bornand, Delia**, Leiterin klinische Pharmazie, Spital-Pharmazie, delia.bornand@usb.ch **Meier, Christoph**, Prof. Dr. sc. Nat, Chefapotheker, Spital-Pharmazie, christoph.meier@usb.ch **Rentsch, Katharina**, Prof. Dr. sc. Nat, Leiterin Labormedizin, katharina.rentsch@usb.ch	
Literatur **Analyse von Literaturdaten**	[1] Voumard, R., Gardiol, C., André, P., Arensdorff, L., Cochet, C., Boillat-Blanco, N., … de Vallière, S. (2018). Efficacy and safety of continuous infusions with elastomeric pumps for outpatient parenteral antimicrobial therapy (OPAT): an observational study. *Journal of Antimicrobial Chemotherapy*, *73*(9), 2540–2545. https://doi.org/10.1093/jac/dky224 [2] McDougall, D. A., & McWhinney, B. C. (2014). Stability of buffered benzylpenicillin solutions for outpatient parenteral antimicrobial therapy. *Journal of Pharmacy Practice and Research*, *44*(1), 26. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/j.2055-2335.2014.tb00012.x [3] Vella-Brincat, J. W. a, Begg, E. J., Gallagher, K., Kirkpatrick, C. M. J., Zhang, M., Frampton, C., & Chambers, S. T. (2004). Stability of benzylpenicillin during continuous home intravenous therapy. *The Journal of Antimicrobial Chemotherapy*, *53*(4), 675–7. https://doi.org/10.1093/jac/dkh146 [4] Voumard, R., Van Neyghem, N., Cochet, C., Gardiol, C., Decosterd, L., Buclin, T., & de Valliere, S. (2017). Antibiotic stability related to temperature variations in elastomeric pumps used for outpatient parenteral antimicrobial therapy (OPAT). *Journal of Antimicrobial Chemotherapy*, *72*(5), 1462–1465. https://doi.org/10.1093/jac/dkw582 [5] Carroll, J. (2005). Stability of flucloxacillin in elastomeric infusion devices. *Journal of Pharmacy Practice and Research*, *35*(2), 90. https://onlinelibrary.wiley.com/doi/abs/10.1002/j.2055-2335.2005.tb00313.x		

[6] Chapman, A. L. N. (2013). Outpatient parenteral antimicrobial therapy in a changing nhs: Challenges and opportunities. *Clinical Medicine, Journal of the Royal College of Physicians of London*, *13*(1), 35–36. https://doi.org/10.7861/clinmedicine.13-1-35
[7] Chapman, A. L. N., Dixon, S., Andrews, D., Lillie, P. J., Bazaz, R., & Patchett, J. D. (2009). Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): A UK perspective. *Journal of Antimicrobial Chemotherapy*, *64*(6), 1316–1324. https://doi.org/10.1093/jac/dkp343

Zielsetzungen des Projekts

Hypothese
Begründung
Erwartete Ergebnisse
Auswirkung für die Praxis

Setting - Background - General thoughts on β-lactam antibiotics in OPAT

Outpatient Parenteral Antimicrobial Therapy (OPAT) refers to the administration of a parenteral antimicrobial in an outpatient setting with the explicit aim of facilitating early discharge or avoiding admission. Infectious diseases most commonly treated in the OPAT program include urogenital infections, cellulitis, bone and joint infections, and infective endocarditis. Patient welfare, reduction of risk of health care associated infection and cost-effective use of hospital resources are the main drivers for OPAT. The safe practice of OPAT depends on a team approach with careful patient selection and antimicrobial management with programmed and adaptable clinical monitoring and assessment of outcome.

In December 2013, the university hospitals of Basel and Lausanne established the first OPAT-teams in Switzerland. Since then, these services have rapidly expanded and so far, each center has already treated more than 500 patients.
The Hospital-Pharmacy (SPH) of the University Hospital Basel (USB) played a crucial role introducing elastomeric antibiotic pumps to patients requiring 24-hour continuous antibiotic delivery.
Over the past four years, several systematic literature reviews and two lab-based stability studies were conducted at the Hospital-Pharmacy (SPH) of the USB in order to provide the OPAT program with instructions for safe use of continuous parenteral antibiotic treatment (unpublished).
The use of β-lactam antibiotics (BA) in OPAT needs special consideration. In order to sustainably achieve drug concentration levels above the minimal inhibitory concentration (MIC) BA are usually administered as short infusions three to six times daily in the in-patient setting. This impedes its application in the outpatient setting. In order to circumvent these issues, the USB and many other OPAT programs worldwide rely on disposable portable elastomeric pumps for the administration of BA [1]. Elastomeric pumps release intravenous drug solutions at an almost steady rate (unpublished in-house data) and drug levels are comparable to levels achieved using continuous infusion by standard infusion devices for stationary units [1].

BA administration using elastomeric pumps has been associated with good clinical outcome (e.g. [1]). However, stability and safety of one BA is not transferable to the whole drug group, the main limitation for its use in elastomeric pumps is the chemical stability of the active pharmaceutical ingredient (API). The BA (as API) are unstable in some solutions - this can be as pronounced as almost no API being left chemically intact in solution after 24 hours at slightly elevated room temperatures. This was for example shown for benzylpenicillin [2]. Studies investigating the temperature exposure of the API's in elastomeric pumps when carried near to the body are available. Specifically voluntary subjects where used to carry elastomeric infusion devices fitted with temperature sensors during 24 h in order to mimic the continuous administration of the drugs in OPAT. These studies show that typical administration during OPAT can lead to exposure of API's to temperatures of above 30 °C [3,4].
Combining these findings with the recommendations and regulations applicable for stability of registered drugs we are currently measuring BA for our OPAT program towards fulfilment of the following conditions:

- Stability with API concentrations above 90% in the elastomeric infusion devices when stored at 4-8 °C for 7 days and after subsequent application in a "simulated infusion" at 37 °C over 24 h.
- No toxic products are formed when the API is chemically decaying. (Literature search for toxicity of degradation products.)

The literature data for BA use in continuous infusion is incomplete and often controversial. We found that some drugs highly depend on solvent properties or specific pH-buffer. For benzylpenicillin, for example, the temperature is highly relevant [3]. To improve the stability of BA in elastomeric pumps the carrying pouches of the elastomeric pumps can be fitted with cold-packs in order to cool down the drug during infusion [3,5].

Target BA drugs for OPAT studies

Benzylpenicillin is considered non-sufficient stable for OPAT programs when applied in water for injection, and shows a quick chemical decomposition. According to McDougall *et. al.* [2] it shows much better stability and thus OPAT suitability when buffered with a citrate buffer. Because of the limited evidence for benzylpenicillin use in OPAT and the strong buffer (pH) dependency of the stability **we will start our series of stability studies with a replication study of the aforementioned study concerning benzylpenicillin stability in a simulated OPAT scenario.**

Next to this replication study we aim at conducting studies on two recently approved BA drugs against multidrug-resistant gram-negative bacteria (e.g. *Pseudomonas aeruginosa*): **ceftolozane / tazobactam** ('Zerbaxa®') and **ceftazidime / avibactam** ('Zavizefta®'), which have not yet been used in OPAT programs.

In case these drugs demonstrate suitability for OPAT we would furthermore gather therapeutic drug monitoring (TDM) data for five OPAT patients per API in order to show that the API plasma levels achieved during administration via elastomeric pump are sufficient.

Beschreibung der Methode

Protokoll, Methode, Analyse der Ergebnisse, Statistik

The following table gives an overview over the planned procedure for the three different drugs (✓: already done; ❑: necessary step; **X** not applicable; !: special case (see corresponding note)).:

	Benzylpenicillin	**Ceftolozane / tazobactam**	**Ceftazidime / avibactam**
1. Development HPLC-MS-MS method.	✓	❑ (! tazobactam method already available)	❑ (! ceftazidime method already available)
2.a) Validation HPLC-MS-MS Method	✓	❑	❑
2.b) preliminary stability studies and development of stable solution.	**X** (! replication study)	❑	❑
3. Simulated infusion stability study.	❑	❑	❑
4. Guidelines for implementation, TDM.	❑	❑	❑

	1. First part: - Development of a HPLC-MS-MS method for the API's in plasma and in watery solutions **2. Second part:** a) - Validation of HPLC-MS-MS method in plasma and watery solutions using commercial reference standard for the single API's. (Milestone 1) b) - Measuring stability of API's dissolved in pure H_2O, in 0.9 % NaCl and in glucose 5% at 37 °C for 24 h. - If needed, further development of solutions by additional buffering, using different pH ranges and testing the effect of cooling on drug stability. - Milestone 2. (Selection of candidate solutions and assessment of the necessity of a cooling system.) **3. Third part:** - Conducting adapted stability study depending on the outcome of the first and second parts. - Milestone 3. (Can we achieve stability after 7 days at 4-8 °C plus 24 hours at 37 °C using one of the tested solutions?) **4. Fourth part:** - Write manufacturing protocol for in-house and external manufacturing of the elastomeric pumps containing the measured API solvent mixture. - Write supporting manuals if needed (e.g. for cooling during application). - Monitor API plasma levels for five patients included in OPAT and treated with the subject API. **Additional research question**: During the stability study, we will use a qualitative full scan HPLC-MS-MS method to observe the appearance of degradation products. If we observe any relevant degradation products, we will use the obtained MS spectra to try to determine the chemical structure of the products in order to assess toxicity.
Ort (e) der Studie **Institute, die am Forschungsprojekt teilnehmen**	Departments «Spital-Pharmazie», «Labormedizin», «Medizinische Poliklinik (OPAT Unit)» and «Infektiologie und Spitalhygiene» at University Hospital Basel (USB).
Outcomes **Erwartete Hauptergebnisse**	We hope to prove that benzylpenicillin can be safely used in OPAT when combined with a citrate buffer. Further, we are confident that we can show the suitability of ceftolozane / tazobactam and ceftazidime / avibactam for OPAT when using defined buffers and solvents. By gathering TDM data, we are going to present clinicians with an idea of what drug plasma levels to expect in OPAT for our API's of interest.
Nationale Tragweite **Aspekte hervorheben, die einen nationalen Impact rechtfertigen (z.B. Bedeutung der Ergebnisse, multizentrisch, interdisziplinär)**	The economic pressure on the healthcare system in Switzerland is increasing. To reduce the financial burden, over the last years more effort has been put on early discharge from the hospitals and on outpatient treatments. Intravenous antimicrobial therapy often prolongs hospital stay unnecessarily [6]. OPAT has shown cost reductions in several countries (e.g. United Kingdom [7]). OPAT at USB and CHUV, Lausanne are the most progressed programs in Switzerland, which provide BA using elastomeric pumps to patients since 2015. Other hospital such as the university hospitals of Bern and Zurich and cantonal hospitals (e.g. Kantonsspital Baden and Winterthur) have established or are planning to establish OPAT in their ambulatory infectious disease units as well. The OPAT programs in Switzerland mostly rely on drug stability data from foreign countries, or on their own small non-validated stability studies. Correct treatment with antibiotics will become even more important in the future to fight resistances. Therefore, all OPAT programs are going to profit

<table>
<tr><td></td><td>by being able to broaden their BA portfolio or at least by being able to base their daily actions on improved evidence. The results are not just going to be significant for many centers, and relevant in this interdisciplinary setting, but will also directly improve quality of treatment on an individual patient level.</td></tr>
<tr><td>Planung
Vorgesehener Zeitplan
Etappen (milestones)</td><td>Preparations for benzylpenicillin (May-June 2019):
Tests using the established validated analytical method. Influence of freeze thawing cycles, preparation for stability study. Literature refresher.
Benzylpenicillin (June-July 2019):
Testing of the elastomeric pumps used at the USB, including the added citrate buffer. Replication study of Doughall 2014.
Ceftolozane / tazobactam (August - September 2019):
Conduction of ceftolozane / tazobactam study according to general study plan.
Ceftazidime / avibactam (October - November 2019):
Conduction of ceftazidime / avibactam study according to general study plan.
Publication of stability data (December 2019 - January 2020)
Publication of TDM data (2020)</td></tr>
<tr><td>Finanzierung
Notwendiger Betrag
Verwendung
Andere Finanzierungsquellen</td><td>Budget
<table>
<tr><th></th><th>Benzyl-penicillin</th><th>Ceftolozane / tazobactam</th><th>Ceftazidime / avibactam</th></tr>
<tr><td>hplc columns (separating and preparational column)</td><td>1800</td><td>1600</td><td>1600</td></tr>
<tr><td>drug reference standard</td><td>-</td><td>ceftolozane: 7500</td><td>avibactam: 1500</td></tr>
<tr><td>consumables (plasticware, solvents)</td><td>2000</td><td>2000</td><td>2000</td></tr>
<tr><td>elastomeric pumps</td><td>500</td><td>500</td><td>500</td></tr>
<tr><td>drug products</td><td>200</td><td>2000</td><td>3000</td></tr>
<tr><td>TDM (sampling and analysis)</td><td>3000</td><td>3000</td><td>3000</td></tr>
<tr><td>publication costs</td><td colspan="3">Open access publication (estimated 1000)</td></tr>
<tr><td>pharmacist salary LAB</td><td colspan="3">Doctoral student for four month (spread over study period)
(including 14 % social security deduction employers share).
19015 CHF</td></tr>
<tr><td>pharmacist salary SPH</td><td colspan="3">Two months (spread over study period)
(including 14 % social security deduction employers share).
19000 CHF</td></tr>
<tr><td>total costs [CHF]</td><td colspan="3">74715 CHF
Additional costs are covered by the USB.</td></tr>
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Unternehmen als Forschungspartner: