Commentary

This habilitation thesis is being presented as a collection of previously published scholarly works.

The first research paper describes the bioavailability of clopidogrel in patients with acute myocardial infarction after cardiac arrest. We designed a prospective clinical trial that proved significantly lower plasma levels of clopidogrel inactive metabolite in comparison to a reference group of patients undergoing elective coronary stent implantation. This pharmacokinetic analysis was accompanied by a functional thrombocyte test, which has proved significantly lower platelet inhibition in patients after cardiac arrest. This study was the first evidence of significantly impaired effect of enterally administrated clopidogrel in patients after cardiac arrest, which presents a potential risk of stent thrombosis.

The second theme is the analysis of drug losses during preparation and administration of drugs through a feeding tube. An in-vitro study investigated 5 different methods of drug crushing, dissolving and administration in combination with 6 dosage forms. We have proved that dissolution of crushed tablets or pellets directly in a mortar leads to significantly lower losses that transfer of crushed drug into a syringe, where it is dissolved. All techniques preserving intact pellets led to feeding tube clogging and cannot be recommended for clinical practice. Another study, which included analysis of active substance losses by high-performance liquid chromatography, confirmed significantly lower losses for the method dissolving a crushed tablet or pellets in a mortar. Moreover, a poorly soluble coating presents a higher proportion of losses in case of tablets with enteric coating, which overestimates the active substance losses. These findings allow to minimize losses during drug preparation and administration via a feeding tube.

The third theme – a prospective pharmacokinetic trial – studied the bioavailability of subcutaneously administered prophylactic doses of nadroparin in comparison to a reduced intravenous dose in critically ill patients requiring vasopressors. Subcutaneous doses had heterogeneous absorption and the peak anti-Xa activity did not reach sufficient levels for thromboprophylaxis in 79 % of patients. The bioavailability of subcutaneous nadroparin was negatively influenced by vasopressor dose at the administration and even strongly with peripheral perfusion assessed by the capillary refill time. On the other hand, intravenous nadroparin administration led to uniform anti-Xa activity course. Furthermore, we have

developed a pharmacokinetic model based on the acquired data to demonstrate a potential clinical application.

The above stated studies point at some pharmacokinetic pitfalls in critically ill patients and, moreover, suggest solutions of selected problems. Since the optimization of drug dosage is a complex issue, a collaboration with clinical pharmacist or pharmacologist can improve prescription and broaden the scope of intensivists.

My contribution to the previously mentioned articles is summarized below:

Součková L, Opatřilová R, Suk P, Čundrle I, Pavlík M, Zvoníček V, et al. Impaired bioavailability and antiplatelet effect of high-dose clopidogrel in patients after cardiopulmonary resuscitation (CPR). Eur J Clin Pharmacol. 2013 Mar;69(3):309–17.

data analysis 80%, study design 20%, collection of clinical data 20%, manuscript preparation 20%

Ruzsíková A, Součková L, Suk P, Opatřilová R, Kejdušová M, Šrámek V. Quantitative analysis of drug losses administered via nasogastric tube--In vitro study. Int J Pharm. 2015 Jan 15;478(1):368–71.

data analysis 80%, manuscript preparation 30%, study design 20%

Papiez A, Odehnalova K, Sramek V, Suk P. Comparison of Active Substance Losses and Total Weight Losses of Tablets Administered Via Feeding Tube. Pharmacology. 2019;103(5–6):246–9.

data analysis 80%, manuscript preparation and corrections 40%, study design 30%

Cihlar R, Sramek V, Papiez A, Penka M, Suk P. Pharmacokinetic Comparison of Subcutaneous and Intravenous Nadroparin Administration for Thromboprophylaxis in Critically Ill Patients on Vasopressors. Pharmacology. 2020;105(1–2):73–8.

pharmacokinetic model 100%, data analysis 80%, manuscript preparation and corrections 40%, study design 30%