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Pharmacokinetic drug-drug interaction between erlotinib and paracetamol: A potential risk for clinical practice

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ABSTRACT

Background: Erlotinib is a tyrosine kinase inhibitor available for the treatment of non-small cell lung cancer. Paracetamol is an analgesic agent, commonly used in cancer patients. Because these drugs are often co-administered, there is an increasing issue of interaction between them.
Objective: The aim of the study was to investigate the effect of paracetamol on the pharmacokinetic parameters of erlotinib, as well as the influence of erlotinib on the pharmacokinetics of paracetamol.
Methods: The rabbits were divided into three groups: the rabbits receiving erlotinib (I_{ER}), the group receiving paracetamol (II_{PR}), and the rabbits receiving erlotinib + paracetamol (III_{ER+PR}). A single dose of erlotinib was administered orally (25 mg) and was administered intravenously (35 mg/kg). Plasma concentrations of erlotinib, its metabolite (OSI420), paracetamol and its metabolites – glucuronide and sulphate were measured with the validated method.
Results: During paracetamol co-administration we observed increased erlotinib maximum concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) by 87.7% and 31.1%, respectively. In turn, erlotinib lead to decreased paracetamol $AUC_{0-\infty}$ by 35.5% and C_{max} by 18.9%. The mean values of paracetamol glucuronide/paracetamol ratios for C_{max} were 32.2% higher, whereas paracetamol sulphate/paracetamol ratios for C_{max} and $AUC_{0-\infty}$ were 37.1% and 57.1% lower in the II_{PR} group, when compared to the III_{ER+PR} group.
Conclusions: Paracetamol had significant effect on the enhanced plasma exposure of erlotinib. Additionally, erlotinib contributed to the lower concentrations of paracetamol. Decreased glucuronidation and increased sulphation of paracetamol after co-administration of erlotinib were also observed.

1. Introduction

Pain is one of the most common and aggravating symptoms associated with lung cancer (Lee et al., 2014). Patients experience acute and chronic pain at all stages of the disease. At the time of diagnosis, approximately 20% of patients with lung cancer have chest pain (Chandrasekar et al., 2016). Meta-analysis conducted by Potter and Higginson (2004) revealed that the overall pain frequency in patients with lung cancer was in the range of 6–100%. In 44–87% of patients pain symptoms were related to cancer, whereas in 5–17% of patients pain was the result of cancer treatment (Simmons et al., 2012). Because the pain has a significant negative impact on the patient's quality of life, it requires thorough assessment and effective management (Chandrasekar et al., 2016; Lekka et al., 2014).

Paracetamol is an analgesic drug, which is considered safe in therapeutic doses. However, when taken excessively, paracetamol can cause hepatotoxicity (Shahid et al., 2015). Paracetamol is extensively metabolised in the liver. The main metabolic pathways include glucuronidation (around 55%, by uridine diphosphate glucuronosyltransferases [UGTs]) and sulphation (around 30%, by sulphotransferase), while <10% undergo oxidation to toxic metabolite (*N*-acetyl-p-benzoquinone, NAPQI) (Allegaert et al., 2014) and only 2–5% of paracetamol is excreted unchanged (van Rongen et al., 2016).

Erlotinib is the epidermal growth factor receptor (EGFR) inhibitor, currently available for first-line treatment of patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) and, in combination with gemcitabine, for the treatment of EGFR mutation-positive metastatic pancreatic cancer (Goel et al., 2016). The minimal effective

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therapeutic level of erlotinib for wild type EGFR, as deduced from half maximal inhibitory concentration *in vitro*, after correction for plasma protein binding, is 183 ng/mL (Lankheet et al., 2015). Bioavailability of erlotinib following a 150 mg oral dose is about 60%, with maximum plasma concentrations (C_{max}) occurring 4 h after dosing. In plasma, ~93% of erlotinib is bound to albumin and [alpha]1-acid glycoprotein. Erlotinib has an elimination half-life ($t_{1/2kel}$) of about 36 h and an apparent volume of distribution (V_d) of 232 L (Calvert et al., 2014; Frohna et al., 2006). It is metabolised by CYP3A4/3A5 and, to a lesser extent by the CYP1A1/1A2 isoenzymes, to the active metabolite – desmethyl erlotinib (OSI420) (Peters et al., 2014; Liu et al., 2015). Moreover, erlotinib is a potent inhibitor of CYP1A1, a moderate inhibitor of CYP3A4, CYP2C8 and a strong inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1), that is responsible for glucuronidation (Peters et al., 2014; Liu et al., 2010a; Czejka et al., 2013).

Due to the fact, that many enzymes are involved in the metabolism of erlotinib, as well as the fact, that erlotinib affect activity of enzymes responsible for biotransformation of many co-administered drugs, there is high risk of clinically relevant drug interactions.

In this study, we conducted *in vivo* assessment of the pharmacokinetics of orally administered erlotinib after co-administration with paracetamol in rabbits. Another aspect of the research was the assessment of the influence of erlotinib on the pharmacokinetics of paracetamol and its glucuronidation and sulphation.

2. Materials and methods

2.1. Reagents

Erlotinib and OSI420 were purchased from LGC Standards (Łomianki, Poland), HPLC grade acetonitrile, ammonium acetate, paracetamol, paracetamol glucuronide, paracetamol sulphate, perchloric acid, theophyllinum, acetic acid, sodium sulphate anhydrous were purchased from Sigma-Aldrich (Poznań, Poland), 85% orthophospforic acid, 2M sodium hydroxide and methanol were purchased from Merck (Darmstadt, Germany). Erlotinib formulation (Tarceva®, batch number M1000B01) was purchased from Roche Polska (Warszawa, Poland). Paracetamol (Paracetamol Kabi®, batch number 14IC34) were purchased from Fresenius Kabi Polska (Warszawa, Poland).

2.2. Animals

Adult New Zealand male rabbits, weighing 3.1–4.2 kg, were used for experiment. They were acclimatized for four weeks prior to the experiment and were maintained under standard conditions of temperature (23 ± 2 °C) and humidity (56–60%). The rabbits were provided with 150 g of commercial pelleted diet (Labofeed KB®, Kcynia, Poland) and tap water *ad libitum*. All experimental procedures were approved by the Local Ethics Committee.

2.3. Evaluation of erlotinib and OSI420, paracetamol, paracetamol glucuronide and paracetamol sulphate pharmacokinetics

The rabbits were divided into three groups: the rabbits receiving erlotinib (I_{ER}), the group receiving paracetamol (II_{PR}), and the rabbits receiving erlotinib + paracetamol (III_{ER+PR}) (Fig. 1). Erlotinib was administered *p.o.* at the single dose of 25 mg (suspended in 1 mL of normal saline) to the I_{ER} and the III_{ER+PR} groups. Blood samples (2.5 mL) for erlotinib and OSI420 assays were collected from the central auricular artery (22G catheter) before and 0.5, 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 24, 48 h following drug administration. Paracetamol was administrated intravenously (*i.v.*) *via* the marginal ear vein in the dose of 35 mg/kg of body weight (Bienert et al., 2012) to the II_{PR} and the III_{ER+PR} group. Blood samples (0.5 mL) for paracetamol analysis were collected before and 5, 15, 30, 60, 90, 120, 180, 240 and 300 min after drug administration. The blood samples were transferred into heparinised tubes and they were centrifuged at 2719 × *g* for 10 min at 4 °C. The obtained plasma samples were stored at −20 °C until the analysis.

The measurement of erlotinib, paracetamol, paracetamol glucuronide, paracetamol sulphate concentrations in the blood plasma was made by means of the HPLC (high-performance liquid chromatography) methods with UV detection (Faivre et al., 2011; Brunner and Bai, 1999).

2.4. Pharmacokinetics analysis

Pharmacokinetic parameters were estimated by non-compartmental methods using validated software (WinNonlin® Professional Version 5.3; Pharsight® Corp., USA). The following pharmacokinetic parameters were calculated for erlotinib: elimination rate constant based on last 3–4 observed sampling points (k_{el}), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from zero to the time of last measurable concentration (AUC_{0-t}), area under the first moment curve ($AUMC_{0-t}$), maximum observed plasma concentration (C_{max}), time to first occurrence of C_{max} (t_{max}), half-life in elimination phase ($t_{1/2kel}$), mean residence time from zero to the time of last measurable concentration (MRT_{0-t}). The pharmacokinetic endpoints for OSI420 were $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, t_{max}. The following pharmacokinetic parameters were calculated for paracetamol: k_{el}, $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, $t_{1/2kel}$, CL, V_d, $AUMC_{0-t}$, MRT_{0-t}. The pharmacokinetic endpoints for paracetamol glucuronide and paracetamol sulphate were $AUC_{0-\infty}$, AUC_{0-t}, C_{max}.

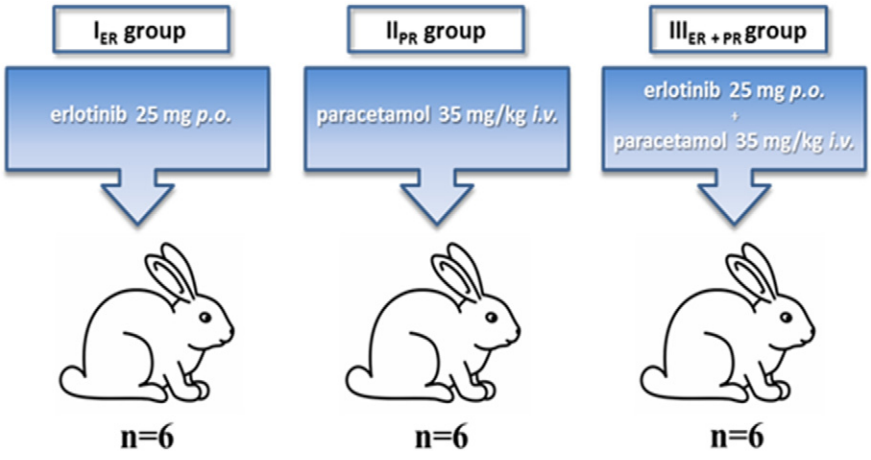

Fig. 1. The scheme demonstrating the study design.