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Agnieszka Karbownik
Poznań University of Medical Sciences

Miłosz Miedziaszczyk
Poznań University of Medical Sciences

Tomasz Grabowski
Polpharma Biologics SA

Joanna Stanisławiak-Rudowicz
Univeristy Hospital of Lord's Transfiguration

Radosław Jaźwiec
Institute of Biochemistry and Biophysics PAS

See next page for additional authors

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In vivo assessment of potential for UGT-inhibition-based drug-drug interaction between sorafenib and tapentadol

Abstract

Sorafenib (SR) is one of the most potent UGT (1A1, 1A9) inhibitors (in in vitro tests). The inhibition of UGT1A1 may cause hyperbilirubinaemia, whereas the inhibition of UGT1A9 and 1A1 may result in drug-drug interactions (DDIs). Tapentadol (TAP) is a synthetic μ-opioid agonist and is used to treat moderate to severe acute pain. Tapentadol is highly glucuronidated by the UGT1A9 and UGT2B7 isoenzymes. The aim of the study was to assess the DDI between SR and TAP.

Wistar rats were divided into three groups, with eight animals in each. The rats were orally treated with SR (100 mg/kg) or TAP (4.64 mg/kg) or in combination with 100 mg/kg SOR and 4.64 TAP mg/kg. The concentrations of SR and sorafenib N-oxide, TAP and tapentadol glucuronide were respectively measured by means of high-performance liquid chromatography (HPLC) with ultraviolet detection and by means of ultra-performance liquid chromatography-tandem mass spectrometry.

The co-administration of TAP with SR caused TAP maximum plasma concentration (Cmax) to increase 5.3-fold whereas its area under the plasma concentration-time curve (AUC0-∞) increased 1.5-fold. The tapentadol glucuronide Cmax increased 5.3-fold and whereas its AUC0-∞ increased 2.0-fold. The tapentadol glucuronide/TAP AUC0–∞ ratio increased 1.4-fold ($p = 0.0118$). TAP also increased SR Cmax 1.9-fold, whereas its AUC0-∞ increased 1.3-fold. The sorafenib N-oxide Cmax increased 1.9-fold whereas its AUC0-∞ increased 1.3-fold. The sorafenib N-oxide/SR AUC0–t ratio increased 1.4-fold ($p = 0.0127$).

The results show that the co-administration of sorafenib and tapentadol increases the exposure to both drugs and changes their metabolism. In consequence, the pharmacological effect may be intensified, but the toxicity may increases, too.

Keywords

Sorafenib, Sorafenib N-oxide, Tapentadol, Tapentadol glucuronide, Pharmacokinetics, Drug-drug interaction

Disciplines

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Authors

Agnieszka Karbownik, Miłosz Miedziaszczyk, Tomasz Grabowski, Joanna Stanisławiak-Rudowicz, Radosław Jaźwiec, Anna Wolc, Edmund Grześkowiak, and Edyta Szałek

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Original article

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Agnieszka Karbownik[a,*,1], Miłosz Miedziaszczyk[a], Tomasz Grabowski[b], Joanna Stanisławiak-Rudowicz[c], Radosław Jaźwiec[d], Anna Wolc[e,f], Edmund Grześkowiak[a], Edyta Szałek[a,1]

[a] Department of Clinical Pharmacy and Biopharmacy, Poznań University of Medical Sciences, 14 Św. Marii Magdaleny Str., 61-861, Poznań, Poland
[b] Polpharma Biologics SA, Trzy Lipy 3 Str., 80-172, Gdańsk, Poland
[c] Univeristy Hospital of Lord's Transfiguration, 84/86 Szamarzewskiego Str., 60-101, Poznań, Poland
[d] Institute of Biochemistry and Biophysics PAS, Laboratory of Mas Spectromery, Polish Academy of Sciences, 5A Pawińskiego Str, 02-106, Warsaw, Poland
[e] Department of Animal Science, Iowa State University, 239E Kildee Hall, Ames, IA, 50011, USA
[f] Hy-Line International, 2583 240th Street, Dallas Center, IA, 50063, USA

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ABSTRACT

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The co-administration of TAP with SR caused TAP maximum plasma concentration (C_{max}) to increase 5.3-fold whereas its area under the plasma concentration-time curve ($AUC_{0-\infty}$) increased 1.5-fold. The tapentadol glucuronide C_{max} increased 5.3-fold and whereas its $AUC_{0-\infty}$ increased 2.0-fold. The tapentadol glucuronide/TAP $AUC_{0-\infty}$ ratio increased 1.4-fold ($p = 0.0118$). TAP also increased SR C_{max} 1.9-fold, whereas its $AUC_{0-\infty}$ increased 1.3-fold. The sorafenib N-oxide C_{max} increased 1.9-fold whereas its $AUC_{0-\infty}$ increased 1.3-fold. The sorafenib N-oxide/SR AUC_{0-t} ratio increased 1.4-fold ($p = 0.0127$).

The results show that the co-administration of sorafenib and tapentadol increases the exposure to both drugs and changes their metabolism. In consequence, the pharmacological effect may be intensified, but the toxicity may increases, too.

1. Introduction

Sorafenib is an oral anticancer drug. It inhibits the proliferation and angiogenesis of cancer cells by targeting numerous serine-threonine and tyrosine kinases (RAF, RAF1, BRAF), vascular endothelial growth factor receptor (VEGFR) 1, 2, 3, platelet-derived growth factor receptor (PDGFR), mast/stem cell growth factor receptor (KIT), Fms-like tyrosine kinase receptor (FLT3), fibroblast growth factor receptor 1 (FGFR1) and rearranged during transfection (RET) in many oncogenic signaling pathways. Blocking these kinases and their further signaling molecules strongly inhibits the proliferation, differentiation, migration, and invasion of cancer cells. It also disables angiogenesis and induces cancer cell apoptosis by inhibiting eIF4E phosphorylation [1–3]. After oral administration sorafenib is characterised by low bioavailability due to its poor water solubility and high lipophilicity (logP = 3.8) [4]. Sorafenib is metabolised partly into its active metabolite, i.e. sorafenib N-oxide by cytochrome P450 3A4 (CYP3A4) and into sorafenib glucuronide by uridine diphosphate-glucuronosyltransferase family 1

* Corresponding author.
E-mail address: agnieszkakarbownik@o2.pl (A. Karbownik).
[1] These authors contributed equally to this work.

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member A9 (UGT1A9) [5]. Sorafenib glucuronide is degraded by β-glucuronidase into sorafenib, which undergoes enterohepatic circulation again [6]. Miners et al. [7] proved that sorafenib is a potent inhibitor of human liver microsomes UGT1A1 and UGT1A9. According to the authors, regorafenib and sorafenib are the strongest inhibitors of the human UGT enzyme which have been identified so far [8]. The inhibition of UGT1A1 by regorafenib and sorafenib causes hyperbilirubinaemia in patients treated with these drugs. Sorafenib is the only effective first-line drug approved for the treatment of advanced hepatocellular carcinoma (HCC) [9] and other solid tumors [10]. HCC is one of the most common cancers and the fourth most common cause of cancer-related deaths worldwide. The incidence of HCC shows that it is increasing more rapidly than any other cancer in the United States. The number of HCC cases has doubled in the last decade due to higher incidence of obesity and diabetes type 2 [11]. In addition, advanced cancer is diagnosed in about 80 % of patients with HCC [12]. There is an urgent it apply more aggressive therapy. As Karen Kaiser [12] concluded, frequent assessment of pain should be an integral element of care for patients with advanced HCC. Nathaniel Christian-Miller noted that 9 out of 10 HCC patients interviewed also complained about pain ≥8 in a 0–10 scale. HCC patients may suffer from abdominal pain, related with bone metastases pain or, in some cases, pain caused by local-regional therapy [13]. Opioid drugs are used to treat moderate to severe pain. Tapentadol is one of the latest opioids. Since 2008 this drug has been used to treat patients aged over 18 years, who suffer from moderate to severe pain. Since 2011 it has been applied to adult patients with moderate to severe chronic pain and neuropathic pain in painful diabetic neuropathy [14]. Like tramadol, tapentadol has a dual mechanism of action. It is a μ-opioid receptor (MOR) agonist and a noradrenaline reuptake inhibitor (NRI). In addition, this drug exhibits minimal adverse effects such as nausea, gastrointestinal adverse reactions, and drug resistance [15]. The drug is characterised by low bioavailability (32 %) and low protein binding (20 %) [16]. Tapentadol undergoes phase II metabolism, mainly by conjugation with glucuronic acid (55 %) and sulphonate (15 %) into inactive metabolites. The conjugation takes place through enzymes (UGT) 1A9 and 2B7. Apart from that, tapentadol is less affected by phase I oxidative reactions due to the participation of CYP2C9, CYP2C19 and CYP2D6 isoenzymes [16,17].

In view of the need to properly treat pain in cancer patients, which often involves polytherapy, and in view of the metabolic pathways of sorafenib and tapentadol, the aim of this study was to assess the effect of sorafenib on the glucuronidation pathway of tapentadol and the effect of tapentadol on the pharmacokinetics of sorafenib and its active metabolite.

2. Materials and methods

2.1. Reagents

Sorafenib (CAS number 284461-73-0), sorafenib N-oxide, tapentadol hydrochloride, tapentadol glucuronide were purchased from LGC Standards (Łomianki, Poland). Lapatinib (CAS number 231277-92-9), tapentadol-D3 hydrochloride solution, methanol, acetonitrile, ethyl acetate, glacial acetic acid, ammonium acetate, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (Poznań, Poland). Sorafenib tosylate (Nexavar®, batch number BXHT61) was purchased from Bayer Polska Sp. z o.o. (Warsaw, Poland). Tapentadol (Palexia® retard, batch number 829H02) was purchased from Grünenthal Sp. z o.o. (Piaseczno, Poland). Ultrapure water used throughout the study was prepared using a Millipore water purification system (Direct Q3, Millipore, USA) supplied with 0.22 μm filter.

2.2. Animals

The experimental protocol for this study was reviewed and approved by the Local Ethics Committee for Animal Experimentation in Poznan (No. 37/2018). All procedures were performed in accordance with the European Union regulations concerning the handling and use of laboratory animals. The study was based on the required minimum number of animals and observation time in order to obtain consistent data. Adult male Wistar rats (weight 475 − 530 g) were used in the study. Male animals were chosen for the study to avoid the effects of hormone fluctuations and the reproductive cycle. This assumption may also apply to the reproducibility of results within one sex. Minor changes in the conditions of the experiment, experimenter and living conditions may affect the results, even if males and females are considered independently. Therefore, being guided by animal welfare and following the 3R principle, we chose male animals for the experiment. All the animals were kept in cages under standard laboratory conditions; a well-ventilated place, a regular 12 h day/night cycle, a controlled room temperature (25 ± 2 °C), and a relative humidity of 50 ± 10 % and given ad libitum access to food and water. The rats were divided into three groups. One group received sorafenib and tapentadol (I_{SR+TAP}), another group received sorafenib (II_{SR}), whereas the last group received tapentadol (III_{TAP}). Sorafenib (100 mg/kg body weight (BW) [18]) was dissolved in 1 mL 10 % DMSO and administered directly into the animals' stomachs using a gastric probe. In order to make sure that the animals received the entire dose of the drug, 1 mL of 10 % DMSO was then administered to rinse the probe. 100 μL of blood was collected from each rat by cutting off a piece of his tail. The blood samples were collected into heparinized test tubes at the following time points: 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 30, 48, 72, 96 h. Tapentadol was administered at a dose of 4.64 mg/kg BW [19] to the I_{SR+TAP} and III_{TAP} groups. Blood samples for tapentadol analysis were collected before (0') and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 24 h, after the drug administration. All the blood samples were centrifuged at 2,880 × g for 10 min at 4 °C. The groups of rats did not differ significantly in terms of body mass.

2.3. HPLC-UV assay

The concentrations of sorafenib, sorafenib N-oxide in rat plasma were assayed using the high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection [20]. Lapatinib was used as the internal standard (IS). Separation was achieved by gradient elution of the mobile phase, comprising ammonium acetate 0.1 M pH 3.4 (adjusted with glacial acetic acid) – eluent A and acetonitrile – eluent B, at a flow rate of 1.0 mL/min through an reversed phase C8 column (Symmetry® C8, 250 mm × 4.6 mm, 5.0 μm particle size) (Waters Corporation®, Milford, MA, USA). Flow rate of 1.0 mL/min with a run time of 22 min was used for separation. Linear gradient started at 60 % eluent A and 40 % eluent B to 29 % eluent A and 71 % eluent B. The column temperature was maintained at 25 °C, the UV detection wavelength was set at 265 nm and the injection volume was 20 μL.

2.4. UPLC-MS/MS assay

Tapentadol and its metabolite were quantitated ultra-performance liquid chromatography tandem by means of mass spectrometry. Samples were analyzed on Waters Xevo TQ-S with a standard ESI ion source coupled to Waters Acquity I-class UPLC. The separation was done using 2.5 min gradient method. Phase A was 0.1 % formic acid in MQ, phase B was 0.1 % formic acid in ACN. The gradient started at 20 % B and increased linearly to 80 %B in 1.5 min, on 1.9 min it returned to starting condition for column equilibration. The flow rate was 600 μL/min. Chromatography was run on Waters Acquity BEH C18, 1.7 μm, 2.1 mm x 50 mm analytical column thermostatted at 70 °C. The internal standard solution was 20 ng/mL TapD3 in methanol. 1 μL of each sample was injected on the instrument. The retention time of Tap and TapD3 was 0.73 min and TapG was 0.77 min. MS was working in

positive polarity mode, the capillary voltage was 3 kV, desolvation temperature 550 °C, desolvation gas flow 900 l/h. Tapentadol was analyzed using two transmissions 222.19 > 107.1 (Collision energy 25) and 222.19 > 121.1 (CE 20); TapD3 225.16 > 107.1 (CE 25) and 225.16 > 121.1 (CE 20); TapG 398.22 > 107.1 (CE 40) and 398.22 > 222.18 (CE 20).

2.5. Pharmacokinetic evaluation

Noncompartmental pharmacokinetic analysis was performed by the Phoenix WinNonlin software version 8.1 (Certara, Princeton, NJ) for tapentadol, tapentadol glucuronide, sorafenib, and sorafenib-N-oxide. The following parameters were calculated: elimination rate constant (k_{el}), absorption rate constant (k_a), the elimination half-life ($t_{0.5}$), the maximum plasma concentration (C_{max}), the time to reach the C_{max} (t_{max}), the total area under the concentration-time curve ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$), the area under the first moment curve ($AUMC_{0\text{-}t}$ and $AUMC_{0\text{-}\infty}$), the apparent plasma drug clearance (Cl/F), the apparent volume of distribution (V_d/F) and mean residence time ($MRT_{0\text{-}t}$, $MRT_{0\text{-}\infty}$).

2.6. Statistical analysis

Normality of the distribution was tested for all of the parameters using the Shapiro-Wilk test. Based on heterogeneity of variance test pooled (heterogeneity of variance test p-value > 0.05) or Satterthwaite (heterogeneity of the variance test p-value < 0.05) t-tests were used to verify the significance of differences between the I_{SR+TAP} and II_{SR} or I_{SR+TAP} and III_{TAP}. Differences between the I_{SR+TAP} and II_{SR} or I_{SR+TAP} and III_{TAP} in the characteristics which showed significant deviation from normality were tested with the Kruskal-Wallis test. The analysis was performed using capability, *t*-test and npar1way procedures of SAS (SAS Institute Inc. 2002 − 2012. The SAS System for Windows version 9.4. Cary, NC, USA).

3. Results

3.1. Method validation

The calibration curve for tapentadol was linear within the range of 0.1–100.0 ng/mL (r = 0.999), and for tapentadol glucuronide within the range of 10–4800.0 ng/mL (r = 0.998). The high precision (coefficient of variation, CV < 10 %) and accuracy (%bias ≤ 10.0 %) for tapentadol and tapentadol glucuronide of the applied methodology was obtained.

The calibration curve for sorafenib was linear within the range of 0.025–5.0 μg/mL (r = 0.999) and for sorafenib N-oxide within the range of 0.025 − 0.40 μg/mL (r = 0.999). The lower limit of quantification for sorafenib and sorafenib N-oxide was 0.025 μg/mL. The high precision (coefficient of variation, CV < 10 %) and accuracy (% bias ≤ 8.8 %) of the applied methodology was confirmed for both analytes.

All the data were expressed as the mean value ± standard deviation (SD).

3.2. The influence of sorafenib on the pharmacokinetics of tapentadol and tapentadol glucuronide

The arithmetic means of plasma concentrations for tapentadol and tapentadol glucuronide after oral administration to the groups are shown in Fig. 1a and b. The main pharmacokinetic parameters from noncompartmental methods are summarized in Table 1. One rat from the III_{TAP} group was excluded from the statistical analysis due to the high AUC_{res} value (80 %). Sorafenib significantly increased tapentadol C_{max} by 428.1 % (p = 0.0012). When sorafenib and tapentadol were administered, the $AUC_{0\text{-}t}$ and the $AUC_{0\text{-}\infty}$ increased by 64.0 % (p = 0.0067) and 48.9 % (0.0099), respectively. The ratios for C_{max}, $AUC_{0\text{–}t}$, $AUC_{0\text{–}\infty}$ (I_{SR+TAP} group/II_{TAP} group) of tapentadol were increased 5.3, 1.6, 1.5-fold, respectively. In the I_{SR+TAP} group the tapentadol t_{max} was about four times shorter (0.47 h) than in the III_{TAP} group (1.96 h) (p = 0.1235). Statistically significant differences were revealed for Cl/F (p = 0.0047), V_d/F (p = 0.0210), $MRT_{0\text{–}t}$ (p = < 0.0001), and $MRT_{0\text{–}\infty}$ (p = 0.0008). There were no significant differences among the groups for the following pharmacokinetic parameters of tapentadol: k_{el} (p = 0.4288), $t_{0.5}$ (p = 0.2421), k_a (p = 0.8608), $AUMC_{0\text{-}t}$ (p = 0.2824), $AUMC_{0\text{-}\infty}$ (p = 0.2014). Sorafenib elevated tapentadol glucuronide C_{max} by 428.7 % (p = 0.0012). The exposition to tapentadol glucuronide was significantly higher in the presence of sorafenib, what was reflected by increased values of $AUC_{0\text{-}t}$ (p = 0.0001), $AUC_{0\text{-}\infty}$ (p = 0.0001). The ratios C_{max}, $AUC_{0\text{–}t}$, $AUC_{0\text{–}\infty}$ (I_{SR+TAP} group/II_{TAP} group) of tapentadol glucuronide were increased 5.3, 2.0, 2.0-fold, respectively. The ratios C_{max}, $AUC_{0\text{–}t}$, $AUC_{0\text{–}\infty}$ of tapentadol glucuronide/tapentadol were increased by 23.4, 24.9, 40.1 % in comparison to III_{TAP} group, respectively. In the I_{SR+TAP} group the tapentadol glucuronide t_{max} was about eight times shorter (p = 0.0038) than in the III_{TAP} group. Statistically significant differences were revealed for k_{el} (p = 0.0199), $t_{0.5}$ (p = 0.0263), $MRT_{0\text{-}t}$ (p = < 0.0001), $MRT_{0\text{-}\infty}$ (p = < 0.0001). There were no significant differences among the groups for the following pharmacokinetic parameters of tapentadol glucuronide: $AUMC_{0\text{-}t}$ (p = 0.8525), $AUMC_{0\text{-}\infty}$ (p = 0.9275).

3.3. The influence of tapentadol on the pharmacokinetics of sorafenib and sorafenib N-oxide

The mean concentration–time profiles for sorafenib and sorafenib N-oxide when administered alone (group II_{SR}) and in combination with a single dose of tapentadol (group I_{SR+TAP}) are shown in Fig. 2a and b. The main pharmacokinetic parameters from noncompartmental methods are summarized in Table 2. Tapentadol significantly increased sorafenib C_{max} by 91.0 % (p = 0.0040). When sorafenib and tapentadol were administered, the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of sorafenib increased by 39.2 % (p = 0.0058) and 33.8 % (p = 0.0114), respectively. The ratios C_{max}, $AUC_{0\text{–}t}$, $AUC_{0\text{–}\infty}$ (I_{SR+TAP} group/II_{SR} group) of sorafenib were increased 1.91, 1.4, 1.3-fold, respectively. Statistically significant differences were revealed for t_{max} (p = 0.0222), k_a (p = 0.0286), Cl/F (p = 0.0157), V_d/F (p = 0.0460), $MRT_{0\text{–}t}$ (p = < 0.0010), and $MRT_{0\text{–}\infty}$ (p = 0.0016). There were no significant differences between groups with respect to the following parameters: k_{el} (p = 0.1144), $t_{0.5}$ (p = 0.1152), $AUMC_{0\text{-}t}$ (p = 0.3623), $AUMC_{0\text{-}\infty}$ (p = 0.8812). The C_{max} of sorafenib N-oxide was increased by 90.9 % (p = 0.0002) in the I_{SR+TAP} group. The exposition to sorafenib N-oxide was significantly higher in the I_{SR+TAP} group. The $AUC_{0\text{-}t}$ increased by 105.1 % (p = 0.0002), whereas the $AUC_{0\text{-}\infty}$ increased by 26.9 % (p = 0.0385). Statistically significant differences were revealed for k_{el} (p = 0.0286), $t_{0.5}$ (p = 0.0157), $AUMC_{0\text{-}t}$ (p = 0.0003), $MRT_{0\text{–}t}$ (p = 0.0379), and $MRT_{0\text{–}\infty}$ (p = 0.0209). The ratios C_{max}, $AUC_{0\text{–}t}$, $AUC_{0\text{–}\infty}$ (I_{SR+TAP} group/II_{SR} group) of sorafenib N-oxide were increased 1.9, 2.1, 1.3-fold, respectively. There were no significant differences among the analyzed groups for the following pharmacokinetic parameters of sorafenib N-oxide: t_{max} (p = 1) and $AUMC_{0\text{-}\infty}$ (p = 0.2067). The ratios C_{max}, $AUC_{0\text{–}t}$, of sorafenib N-oxide/sorafenib were increased 1.1, 1.4-fold, respectively in comparison to II_{SR} group.

4. Discussion

The liver function is often reduced (Child-Pugh Class B or C) in patients with advanced HCC. In consequence, the drug metabolism in which CYP and UGT participate is impaired [21] and albumin production is reduced. Both processes may increase the free fraction of the drug and intensify adverse reactions during therapy. The GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma [HCC] and Of its treatment with sorafeNib) test did not reveal differences in the incidence of adverse drug reactions between patients

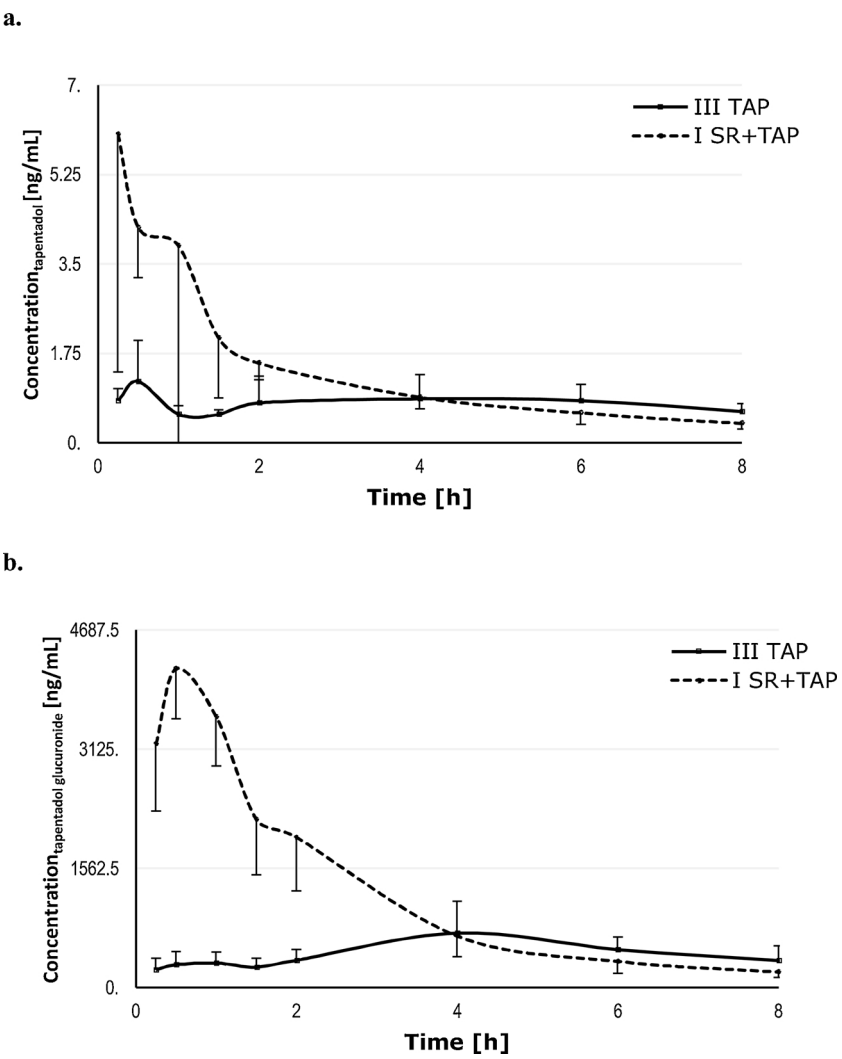

Fig. 1. Plasma concentration-time profiles of tapentadol (**a**), tapentadol glucuronide (**b**) in rats receiving tapentadol (III_{TAP}) and sorafenib + tapentadol (I_{SR+TAP}).

with Child-Pugh class A hepatic function and those with Child-Pugh class B. However, according to some reports, the incidence of severe adverse reactions, which resulted in discontinuation of the treatment, was higher in patients with Child-Pugh liver function class B than in those with Child-Pugh class A [22]. According to the study by Labeur [23], patients with Child-Pugh class B hepatic function will benefit less from sorafenib treatment due to the higher risk of adverse reactions related to cirrhosis. Furthermore, according to data in publications, CYP and UGT enzymes play an important role in carcinogenesis and tumor response to cancer treatment [21]. Ye proved that sorefenib metabolism was significantly altered in the hepatic tumor tissue of HCC patients due to a significant decrease in the expression of CYP3A4 and UGT1A9 [21]. Ge et al. proved that the high UGT1A9 expression was associated with better prognosis for HCC patients treated with sorafenib after surgery [24]. Multi-medication is an additional aspect of HCC therapy. It involves the risk of interaction and a different response to treatment. For example, the patients who developed HCC during long-term metformin therapy are resistant to sorafenib treatment, whereas those treated with insulin exhibit a better response and their survival is longer [25].

UGTs play a major role in the detoxification of xenobiotics, including narcotic drugs, and in the metabolism of endogenous compounds (bilirubin, steroid hormones, bile and fatty acids). They help to protect the body from dangerous chemicals and regulate the activity of several endogenous mediators involved in cell growth and differentiation [26]. Many drugs, including anti-cancer drugs, are UGT substrates. Human UGT1A1 (bilirubin coupling enzyme) plays an important role in the hepatic glucuronidation of SN-38, the active metabolite of irinotecan. In addition, the effect of UGT1A modulators administered concurrently with sorafenib is poorly known [26].

Phase I of a clinical trial on sorafenib with irinotecan, a substrate of UGT1A1 and UGT1A9, revealed increased exposure to irinotecan and SN-38 at the highest dose of sorafenib (400 mg twice daily). This study showed that sorafenib had an in vitro inhibition constant (Ki) of 2.7 μmol/L in human liver microsomes. This suggests that increased exposure to SN-38 was caused by sorafenib-induced inhibition of glucuronidation mediated by UGT1A1 and/or UGT1A9 [27]. According to studies conducted on human hepatocytes, sorafenib is a UGT1A1 inhibitor, but it is not metabolised by this isoenzyme [28–31]. To date, the activity of sorafenib in rats has not been determined due to the fact that it is a new drug and many studies on its activity are still in progress and many hypotheses require further research.

According to the data published in the Australian Public Assessment Report for Tapentadol [32], after repeated oral administration of tapentadol to mice, rats, dogs and humans its metabolism was similar in all of them. Tapentadol glucuronide was the main metabolite in the plasma/serum (79–84 % of total plasma/serum exposure (AUC)), followed by tapentadol catechol-glucuronide (4–10 %) and N-demethyltapentadol glucuronide (4–9 %). Tapentadol sulphate was also found in the dog plasma (3%) and human plasma (4%), but not in rats. Tapentadol metabolism has been investigated in in vitro studies on liver

Table 1
Plasma pharmacokinetic parameters of tapentadol and its metabolite glucuronide after oral administration of single dose of tapentadol (4.64 mg/kg BW) to the III_{TAP} group and sorafenib + tapentadol (100 mg/kg BW + 4.64 mg/kg BW) to the I_{SR+TAP} group.

Pharmacokinetic parameters[a]	III_{TAP} (n = 7)	I_{SR+TAP} (n = 8)	G_{mean} ratio[b] (90% CI) I_{SR+TAP} *vs.* III_{TAP}
Tapentadol			
C_{max} (ng/mL)	1.46 ± 0.86 (59.0)	7.71 ± 5.46 (70.7)	4.95 (2.93; 8.36)
AUC_{0-t} (ng × h/mL)	7.15 ± 2.14 (30.0)	11.73 ± 3.18 (27.1)	1.65 (1.31; 2.07)
$AUC_{0-\infty}$ (ng × h/mL)	8.97 ± 2.14 (23.8)	13.36 ± 3.28 (24.6)	1.49 (1.21; 1.84)
t_{max} (h)	1.96 ± 2.23 (113.5)	0.47 ± 0.25 (52.9)	0.40 (0.16; 1.00)
k_a (h^{-1})	3.62 ± 3.77 (104.1)	4.08 ± 3.64 (89.4)	1.69 (0.29; 9.86)
k_{el} (h^{-1})	0.19 ± 0.08 (40.7)	0.22 ± 0.06 (25.0)	1.19 (0.89; 1.59)
$t_{0.5}$ (h)	4.02 ± 1.38 (34.3)	3.30 ± 0.88 (26.8)	0.84 (0.63; 1.13)
Cl/F (L/h x kg)	264.08 ± 62.11 (23.5)	177.60 ± 34.14 (19.2)	0.68 (0.55; 0.84)
V_d/F (L)	1552.25 ± 653.30 (42.1)	867.13 ± 327.06 (37.7)	0.57 (0.37; 0.88)
$AUMC_{0-t}$ (ng × h^2/mL)	33.10 ± 9.82 (29.7)	28.27 ± 6.76 (23.9)	0.86 (0.68; 1.10)
$AUMC_{0-\infty}$ (ng × h^2/mL)	63.13 ± 22.72 (36.0)	50.59 ± 12.66 (25.0)	0.82 (0.62; 1.08)
MRT_{0-t} (h)	4.63 ± 0.54 (11.6)	2.45 ± 0.44 (18.1)	0.52 (0.45; 0.61)
$MRT_{0-\infty}$ (h)	7.01 ± 1.71 (24.4)	3.88 ± 1.04 (26.8)	0.55 (0.44; 0.69)
tapentadol glucuronide			
C_{max} (ng/mL)	775.54 ± 400.75 (51.7)	4100.09 ± 731.92 (17.9)	5.68 (4.23; 7.64)
AUC_{0-t} (ng × h/mL)	5487.32 ± 1592.62 (29.0)	11173.50 ± 2325.65 (20.8)	2.09 (1.60; 2.72)
$AUC_{0-\infty}$ (ng × h/mL)	5500.09 ± 1591.36 (28.9)	11205.75 ± 2330.98 (20.8)	2.09 (1.60; 2.71)
t_{max} (h)	4.36 ± 1.97 (45.3)	0.53 ± 0.31 (58.7)	0.13 (0.07; 0.25)
k_{el} (h^{-1})	0.29 ± 0.05 (17.3)	0.23 ± 0.03 (14.9)	0.80 (0.69; 0.93)
$t_{0.5}$ (h)	2.47 ± 0.45 (18.0)	3.08 ± 0.48 (15.7)	1.25 (1.07; 1.45)
$AUMC_{0-t}$ (ng × h^2/mL)	34086.97 ± 13089.64 (38.4)	32949.81 ± 10111.77 (30.7)	0.99 (0.70; 1.40)
$AUMC_{0-\infty}$ (ng × h^2/mL)	34442.59 ± 13054.97 (37.9)	33880.82 ± 10385.92 (30.7)	1.00 (0.71; 1.42)
MRT_{0-t} (h)	6.13 ± 0.96 (15.6)	2.91 ± 0.51 (17.5)	0.47 (0.40; 0.55)
$MRT_{0-\infty}$ (h)	6.19 ± 0.95 (15.3)	2.99 ± 0.54 (18.1)	0.48 (0.41; 0.56)
tapentadol glucuronide/tapentadol			
C_{max}	626.09 ± 249.50 (39.9)	772.32 ± 436.43 (56.5)	1.15 (0.60; 2.21)
AUC_{0-t}	787.13 ± 231.33 (29.4)	983.67 ± 243.49 (24.8)	1.27 (0.98; 1.63)
$AUC_{0-\infty}$	611.72 ± 123.25 (20.1)	857.16 ± 189.27 (22.1)	1.40 (1.15; 1.71)

[a] AUC_{0-t}. area under the plasma concentration-time curve from zero to the time of last measurable concentration; $AUC_{0-\infty}$. area under the plasma concentration-time curve from zero to infinity; C_{max}. maximum observed plasma concentration; t_{max}. time to first occurrence of C_{max}; $t_{0.5}$. half-life in elimination phase; Cl/F. clearance (Cl); V_d/F. volume of distribution per kilogram; k_a. absorption rate constant, k_{el}. elimination rate constant, $AUMC_{0-t}$. area under the first moment curve from zero to the time of last measurable concentration; $AUMC_{0-\infty}$. area under the first moment curve from zero to infinity; MRT_{0-t}. mean residence time; $MRT_{0-\infty}$. mean residence time from zero to infinity; arithmetic means ± standard deviations (SD) are shown with CV (%) in brackets; [b]ratio of geometric means (G_{mean}) between groups (%) with the upper and lower bounds of a 90 % confidence interval (CI) in the brackets.

microsomes from mice, rats, hamsters, guinea pigs, rabbits, mini-pigs, dogs, cynomolgus monkeys and humans and on human hepatocytes. When incubated under the conditions for phase II metabolism, tapentadol glucuronidation was observed, although its rate in human liver microsomes was ≥5 times lower than in the microsomes of other species.

In addition, according to the report, tapentadol is a substrate of UGT1A9 and 2B7 in humans. The studies on the animal model focused mainly on pharmacodynamic tests. Therefore, there were no data concerning the UGT inducer/inhibitor/substrate properties of tapentadol.

Human UGT1A enzymes are primarily expressed in the liver but have also been detected in the small intestine and kidney. Similarly, rat UGT1A enzymes are expressed in the liver, small intestine, and kidney, but some isoforms are observed at higher levels in the small intestine than in the liver. Thus, the small intestine is also regarded as an important site of metabolism [33]. The urinary excretion data obtained from rats differ considerably from that of humans [34]. Although the urinary excretion pattern in rats differs from that of humans, the kinetic parameters showed for rats were similar to those for humans in some aspects, suggesting that the rat might be a useful animal model for human considerations [35].

The influence of sorafenib on the pharmacokinetics of tapentadol and tapentadol glucuronide

The dose of tapentadol needs to be reduced when it is administered to patients with moderate hepatic function disorder. The drug is not recommended and should not be administered to patients with severe hepatic disorders [36]. Tapentadol does not inhibit CYP1A2, CY2A6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4 in vitro. It exhibits low CYP2D6 inhibition capacity. Tapentadol does not induce CYP1A2, CYP2C9 or CYP3A4 in fresh human hepatocytes [37]. It has low potential for pharmacokinetic drug interactions [36,37]. Smit proved that there were no statistically significant differences in the C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $t_{0.5}$ of tapentadol and its glucuronide when administered as tapentadol vs. tapentadol + paracetamol or tapentadol + acetylsalicylic acid or tapentadol + naproxen. The authors concluded that the administration of tapentadol alone or with the above mentioned drugs metabolised by glucuronidation was safe and it was well tolerated by healthy volunteers [38]. The study was significantly limited by the fact that the PK parameters of paracetamol, ASA and naproxen were not assessed. Tapentadol does not interact with omeprazole, metoclopramide or probenecid [37]. Sorafenib is one of the most potent UGT inhibitors [8]. When tapentadol and sorafenib were co-administered, the C_{max} and $AUC_{0-\infty}$ of tapentadol increased in the I_{SR+TAP} group 5.3 and 1.5-fold, respectively (Table 1). Additionally, the time necessary to reach the C_{max} was reduced to an average value of 0.47 h in the group under study vs. 1.96 h in the III_{TAP} group. Increased exposure to tepentadol involves the risk of intensified adverse reactions such as constipation and respiratory depression, whereas the shortening of the t_{max} may accelerate the time necessary to achieve the analgesic effect. This study showed the inhibitory effect of sorafenib on the tapentadol glucuronidation process. In the group under study the C_{max} and $AUC_{0-\infty}$ increased 5.3 and 2.0-fold, respectively. In addition, this was confirmed by the difference in the ratio values for the $AUC_{0-\infty}$ of tapentadol glucuronide/tapentadol ($p = 0.0118$).

The phase I clinical trial showed no significant effect of sorafenib on the PK parameters of lapatinib. However, the concentrations of lapatinib were reduced when it was administered in combination with

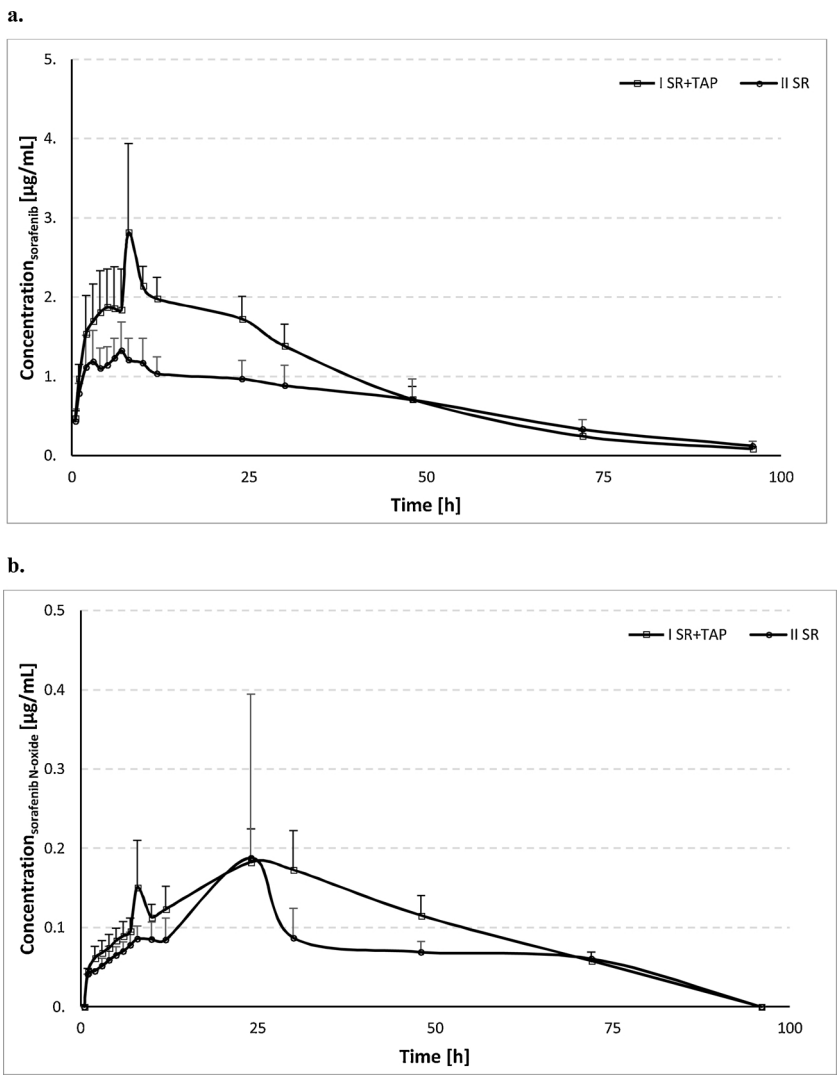

Fig. 2. Plasma concentration-time profiles of sorafenib (**a**), sorafenib N-oxide (**b**) in rats receiving sorafenib (II_{SR}) and sorafenib + tapentadol (I_{SR+TAP}).

sorafenib for 14 days. The authors additionally stress the fact that the changes in the concentration may have been caused by concomitant medications or by congenital variability [39]. During the administration of sorafenib and calcineurin inhibitors sorafenib had no effect on ciclosporin A levels despite increasing the SR doses [40]. When sorafenib and capecitabine were co-administered at doses of 750 mg/m^2 and 1000 mg/m^2, the AUC increased by 15 % and 16 %, respectively. However, capecitabine did not change the sorafenib C_{max} or $AUC_{(0–12)}$ [41].

The influence of tapentadol on the pharmacokinetics of sorafenib and sorafenib N-oxide

The administration of sorafenib and tapentadol also increased the exposure of the tested TKI. It was manifested by changes in the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, which increased 1.9, 1.4 and 1.3-fold, respectively. Apart from that, a decrease in the k_a (0.34 vs. 0.74 h-1) was observed in the group under study receiving combined treatment. It may have been caused by an increase in the C_{max}. There was a similar dependency observed for the active metabolite of sorafenib, where the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ also increased 1.9, 2.1 and 1.3-fold, respectively. Intensified exposure may increase the penetration of the drug into cancerous tissues and the response. However, it may also cause more severe adverse reactions, which may reduce patients' quality of life. Surprisingly, the research showed the influence of tapentadol on increased the values of N-oxide sorafenib/sorafenib ratios for AUC_{0-t} in the I_{SR+TAP} group ($p = 0.0127$). It may have been related with the blockade of the glucuronidation pathway for sorafenib and intensified drug metabolism in the oxidation pathway.

Sorafenib is one of the first-choice drugs for the treatment of advanced HCC. However, studies have shown that the disease progression is still high due to the development of drug resistance. Therefore, it is justified to search for new therapeutic strategies which may intensify the anticancer effect of sorafenib. Numerous studies showed that a combination therapy of sorafenib with other drugs, diet or dietary supplements increased the oncological response. Fang et al. showed that when melatonin and sorafenib were combined in the therapy of pancreatic ductal adenocarcinoma, they synergistically inhibited the growth of cancer cells and induced apoptosis [42]. According to Lu et al., the addition of sorafenib 20(S)-Ginsenoside Rg3 to the HCC therapy resulted in a synergistic effect by modulation of the PTEN/Akt signaling pathway [43]. Mao et al. conducted in vitro and in vivo studies which showed that sorafenib in combination with silibinin significantly delayed the growth of HCC cells, induced their apoptosis and intensified the inhibition of STAT3/ERK/ATK pathways [44]. A combination therapy with meloxicam and sorafenib has a stronger anticancer effect on human hepatocellular cancer SMMC-7721 cells than a monotherapy with either of these drugs [45]. There was a similar effect of another nonsteroidal anti-inflammatory drug. A combination therapy with sorafenib and celecoxib resulted in a strong synergistic cytotoxic effect on the human hepatocellular carcinoma cell lines HepG2 and Huh7. The effect was confirmed in gene expression tests. The sorafenib

Table 2
Plasma pharmacokinetic parameters of sorafenib and its metabolite N-oxide after oral administration of single dose of sorafenib (100 mg/kg BW) to the II_{SR} group and sorafenib + tapentadol (100 mg/kg BW + 4.64 mg/kg BW) to the I_{SR+TAP} group.

Pharmacokinetic parameters[a]	II_{SR} (n = 8)	I_{SR+TAP} (n = 8)	G_{mean} ratio[b] (90% CI) I_{SR+TAP} vs. III_{SR}
Sorafenib			
C_{max} (μg/mL)	1.56 ± 0.35 (22.6)	2.98 ± 0.97 (32.7)	1.87 (1.48; 2.37)
AUC_{0-t} (μg × h/mL)	62.83 ± 16.14 (25.7)	87.46 ± 14.04 (16.1)	1.42 (1.17; 1.73)
$AUC_{0-\infty}$ (μg × h/mL)	67.05 ± 16.70 (24.9)	89.64 ± 14.25 (15.9)	1.36 (1.12; 1.65)
t_{max} (h)	5.13 ± 2.17 (42.3)	7.75 ± 1.91 (24.6)	1.61 (1.14; 2.28)
k_a (h^{-1})	0.74 ± 0.31 (42.5)	0.34 ± 0.20 (60.3)	0.38 (0.21; 0.71)
k_{el} (h^{-1})	0.035 ± 0.011 (30.3)	0.044 ± 0.004 (10.2)	1.30 (1.04; 1.64)
$t_{0.5}$ (h)	21.89 ± 7.79 (35.6)	16.06 ± 1.66 (10.3)	0.77 (0.61; 0.97)
Cl/F (L/h x kg)	0.80 ± 0.22 (27.1)	0.56 ± 0.09 (15.8)	0.72 (0.59; 0.86)
V_d/F (L)	25.30 ± 11.59 (45.8)	16.18 ± 1.88 (11.6)	0.69 (0.51; 0.93)
$AUMC_{0-t}$ (μg × h^2/mL)	2109.23 ± 615.06 (29.2)	2370.18 ± 485.88 (20.5)	1.15 (0.90; 1.47)
$AUMC_{0-\infty}$ (μg × h^2/mL)	2671.99 ± 804.12 (30.1)	2620.37 ± 523.14 (20.0)	1.01 (0.78; 1.32)
MRT_{0-t} (h)	33.25 ± 2.67 (8.0)	26.96 ± 1.43 (5.3)	0.81 (0.76; 0.86)
$MRT_{0-\infty}$ (h)	39.53 ± 6.91 (17.5)	29.08 ± 1.36 (4.7)	0.74 (0.66; 0.84)
sorafenib N-oxide			
AUC_{0-t} (μg × h/mL)	4.10 ± 1.56 (38.1)	8.41 ± 1.80 (21.4)	2.17 (1.61; 2.93)
$AUC_{0-\infty}$ (μg × h/mL)	8.61 ± 2.19 (25.4)	10.93 ± 1.86 (17.0)	1.30 (1.05; 1.61)
C_{max} (μg/mL)	0.11 ± 0.02 (21.8)	0.21 ± 0.04 (19.8)	1.82 (1.53; 2.18)
t_{max} (h)	16.38 ± 8.21 (50.1)	16.75 ± 9.56 (57.1)	0.99 (0.59; 1.66)
k_{el} (1/h)	0.016 ± 0.010 (60.9)	0.026 ± 0.005 (19.7)	1.78 (1.24; 2.56)
$t_{0.5}$ (h)	53.31 ± 25.23 (47.3)	27.46 ± 6.06 (22.1)	0.56 (0.39; 0.81)
MRT_{0-t} (h)	25.80 ± 6.72 (26.1)	31.97 ± 2.48 (7.8)	1.27 (1.06; 1.52)
$MRT_{0-\infty}$ (h)	83.19 ± 34.94 (42.0)	49.82 ± 7.16 (14.4)	0.64 (0.48; 0.87)
$AUMC_{0-t}$ (μg × h^2/mL)	113.08 ± 64.21 (56.8)	270.73 ± 68.51 (25.3)	2.77 (1.74; 4.41)
$AUMC_{0-\infty}$ (μg × h^2/mL)	749.37 ± 405.53 (54.1)	544.38 ± 120.36 (22.1)	0.83 (0.54; 1.30)
sorafenib N-oxide/sorafenib			
C_{max}	0.07 ± 0.02 (26.8)	0.08 ± 0.03 (37.1)	0.97 (0.73; 1.30)
AUC_{0-t}	0.07 ± 0.02 (37.1)	0.10 ± 0.02 (16.4)	1.53 (1.14; 2.04)
$AUC_{0-\infty}$	0.14 ± 0.05 (38.1)	0.12 ± 0.01 (11.6)	0.95 (0.73; 1.24)

[a] AUC_{0-t}. area under the plasma concentration-time curve from zero to the time of last measurable concentration; $AUC_{0-\infty}$. area under the plasma concentration-time curve from zero to infinity; C_{max}. maximum observed plasma concentration; t_{max}. time to first occurrence of C_{max}; $t_{0.5}$. half-life in elimination phase; Cl/F. clearance (Cl); V_d/F. volume of distribution per kilogram; k_a. absorption rate constant, k_{el}. elimination rate constant, $AUMC_{0-t}$. area under the first moment curve from zero to the time of last measurable concentration; $AUMC_{0-\infty}$. area under the first moment curve from zero to infinity; MRT_{0-t}. mean residence time; $MRT_{0-\infty}$. mean residence time from zero to infinity; arithmetic means ± standard deviations (SD) are shown with CV (%) in brackets; [b]ratio of geometric means (G_{mean}) between groups (%) with the upper and lower bounds of a 90 % confidence interval (CI) in the brackets.

and celecoxib therapy involved the modulation of various sets of genes for each cell line. These were completely different sets than those that exhibited an altered expression after a monotherapy [46]. Lu et al. showed that the combination of sorafenib and aspirin reduced the HCC invasiveness and metastasis by increasing the regulation of the HTATIP2 gene expression, which was mediated by the inhibition of the COX-2 gene expression [47]. The co-administration of 300 μg of levothyroxine, which inhibits cytochrome P450 (CYP) 3A4 and UGT enzymes, in combination with sorafenib had no effect on the pharmacokinetics of sorafenib and its active metabolite. The authors stressed the fact that the co-administration of levothyroxine with sorafenib to patients with differentiated thyroid carcinoma was not a matter of concern [48]. A study on animals showed that an earlier exposure to verapamil (10 mg/kg) caused an increase in the sorafenib C_{max} and AUC_{0-t}, as compared with the control group [49]. When interpreting the findings of this study it is important to note its limitations. First of all, no animals with model HCC and induced pain were used in the experiment. For this reason, PK/PD analysis could not be made, either. However, the authors chose healthy animals for the model (isolated experiment) so that comorbidities would not affect inter-individual variability in animals and in consequence, the test results. In phase 0 and I clinical trials the PK parameters of drugs (with the exception of e.g. cytostatics) are also assessed on healthy volunteers. Another limitation to the experiment was the absence of UGT knockout animals and the lack of in vitro tests. However, the experiment was a preliminary study, which let us conclude that further research was necessary. Second of all, the concentrations of sorafenib glucuronide were not measured. In addition, the total sorafenib and tapentadol drug fractions were assayed. For sorafenib, the free fraction is 99.7 in humans and rats [50]. This fact can be omitted in PK analysis. Measurement of the free fraction of tapentadol would be more important because the drug binds to blood proteins in 20 % [51]. The HPLC MS would result in a lower LLOQ concentration for sorafenib and its active metabolite.

5. Conclusion

The study showed that sorafenib inhibited tapentadol glucuronidation, therefore, caution should be exercised when using this TKI and other glucuronidated drugs. If sorafenib and tapentadol are co-administered to patients in combination therapy, it may be necessary to reduce the dose of the drugs, because of higher plasma concentrations and risk of their adverse effects. This is important, because both drugs cause intensified adverse reactions. Sorafenib is most likely to cause gastrointestinal disorders, palmar-plantar erythrodysesthesia syndrome, fatigue, increased lipase and amylase activity. Tapentadol may cause constipation and drowsiness. On the other hand, obtaining such high plasma concentrations of sorafenib, as a DDI effect, gives a chance better response to anti-cancer treatment and break drug resistance mechanisms.

Institutional ethics committee approval

All applicable international, national, and/or institutional guidelines concerning the care and use of animals were followed. The experimental protocol for this study was reviewed and approved by the Local Ethics Committee for Animal Experimentation in Poznan (No. 37/2018).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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