European Review for Medical and Pharmacological Sciences 2019; 23: 4044-4051

Ketoprofen and tramadol pharmacokinetics in patients with chronic pancreatitis

M. SIEPSIAK-POŁOM[1], E. SZAŁEK[2], J. PORAŻKA[2], A. KARBOWNIK[2], T. GRABOWSKI[3], M. MZIRAY[4], K. ADRYCH[1], E. GRZEŚKOWIAK[2]

[1]Department of Gastroenterology and Hepatology, Medical University of Gdańsk, Gdańsk, Poland
[2]Department of Clinical Pharmacy and Biopharmacy, Medical University of Poznań, Poznań, Poland
[3]Polpharma Biologics SA, Gdańsk, Poland
[4]Department of Public Nursing and Health Promotion, Medical University of Gdańsk, Gdańsk, Poland

Abstract. – OBJECTIVE: Chronic pancreatitis (CP) is a disease leading to irreversible pancreas dysfunction. One of the main symptoms is pain. Many patients require pharmacological therapy which should be started with paracetamol or, in selected groups of patients, ketoprofen. If the effect of ketoprofen is irrelevant, patients receive tramadol. The aim of this study is the evaluation of ketoprofen and tramadol pharmacokinetics (PK) in CP patients.

PATIENTS AND METHODS: 36 patients were divided into two groups: I - receiving ketoprofen (*n*=18; mean [SD] age, 48.61 [13.32] years; weight, 73.28 [20.48] kg), II - receiving tramadol (*n*=18; mean [SD] age, 46.78 [10.28] years; weight, 74.22 [14.04] kg, and BMI (Body Mass Index), 24.61 [4.51] kg/m^2). The plasma concentrations of ketoprofen and tramadol with its active metabolite M1 (0-desmethyltramadol) were measured with the validated high-performance liquid chromatography method.

RESULTS: The main PK parameters for ketoprofen were as follows: C_{max} (maximum plasma concentration), 3.41 [2.32] mg/L; $AUC_{0\text{-}inf}$ (area under the plasma concentration-time curve from time zero to infinity), 10.45 [5.57] mg·h/L; tmax (time to first occurrence of C_{max}), 1.94 [1.25] h; Cl (clearance), 0.199 [0.165] L/kg·h, and V_d/kg (volume of distribution per kilogram of body weight), 0.71 [0.58] L/kg. The main PK parameters for TRM and M1 were as follows: C_{max}, 226.4 [80.5] and 55.6 [23] ng/mL; $AUC_{0\text{-}inf}$, 1903.3 [874.8] and 790.4 [512.4] ng·h/mL; t_{max}, 1.78 [0.73] and 2.67 [1.19] h, respectively.

CONCLUSIONS: Chronic pancreatitis led to a decrease in the total amount of absorbed ketoprofen. Consequently, the analgesic effect of the drug may be weaker. Cmax of tramadol for most CP patients was within the therapeutic range associated with its analgesic activity. M1/TRM ratios for Cmax and AUC were unchanged.

Key Words
Chronic pancreatitis, Ketoprofen, Tramadol, Pharmacokinetics.

Introduction

Chronic pancreatitis (CP) is a serious disorder leading to irreversible changes in the pancreatic gland. The annual incidence of CP according to epidemiological studies is 2-14 per 100,000 around the world. However, there is variability depending on the country and study design[1]. Diagnosing CP is very difficult, especially in an early phase due to the lack of pathognomonic signs and symptoms. However, in more advanced stages of disease exocrine and endocrine insufficiency occurs[2]. The most frequent problem reported by patients with CP is epigastric pain, which may vary according to the intensity, frequency and length of occurrence[3]. Pain treatment is based on general recommendations such as diet abiding, alcohol and smoking cessation[4,5]. In case of insufficient effect, analgesic therapy is inserted starting with paracetamol. In selected group of patients ketoprofen is used in monotherapy or in combination with other drugs for the treatment of mild to moderate pain. It is classified as a first stage drug in analgesic ladder according to the World Health Organization (WHO). Ketoprofen belongs to nonsteroidal anti-inflammatory drugs (NSAIDs), that means that besides being analgesic, it also reveals anti-inflammatory and antipyretic effect. It is easily absorbed from the gastrointestinal tract with the onset of action until 30 minutes and peak plasma concentration approximately 1 hour and 22 minutes. Above 99% of the drug is bound with plasma proteins, mainly albumins[6]. The volume of tissue distribution is 0.1-0.2 L/kg. Ketoprofen is intensively metabolized in the liver by microsomal enzymes into glucuronic metabolites. Clearance of the drug after oral administration is 1.16 mL/min/kg; elimination half-life - 2 hours. Max-

Corresponding Author: Magdalena Siepsiak-Połom, MD; e-mail: mag.siepsiak@gmail.com

imum of 80% of ketoprofen dosage is excreted as ketoprofen glucuronide in urine whereas 10% with faeces[6]. In some disease entities analgesic effect of ketoprofen might be insufficient. In such cases, drugs from the second step of WHO analgesic ladder, weak opioids, should be considered. Tramadol (TRM) is thought to be a popular opioid which reliefs pain by binding with μ receptors[7]. Moreover, it activates a descending system of pain inhibition leading to decrease of the reuptake of noradrenaline and it increases the release of serotonin. Similarly to ketoprofen, it is well absorbed from the gastrointestinal tract. After oral supply, the onset of action is 1 hour with the maximum plasma concentration (C_{max}) after 2 hours. Tramadol binds with plasma proteins in 20%. The volume of tissue distribution is estimated to be 2.6-2.9 L/kg[8]. Tramadol is metabolized in the liver with the participation of cytochrome P450. One of the drug's main metabolites is O-desmethyltramadol (M1) which has a higher affinity to μ receptors and secondarily better analgesic effect. Clearance of the drug after oral administration is 8.5 mL/min/kg; elimination half-life - 6 hours[8]. Tramadol and its metabolites are almost utterly excreted with urine. Ketoprofen and tramadol are supplied orally in patients with CP to alleviate pain[9]. However, it should be mentioned that pathophysiological changes in the gastrointestinal tract may occur in the course of CP, leading to disturbance of pharmacokinetics of administered orally drugs; especially their absorption. The fundamental factors which may influence on the pharmacokinetics of drugs in patients with CP are as follows: changes in intraluminal pH in the gastrointestinal tract, bacterial overgrowth leading to diarrhea, abnormal exocrine pancreatic activity, and motility disorders[10]. In a previous work concerning CP patients, the authors revealed an increase in paracetamol glucuronidation, which may indicate abnormal metabolism of drugs received orally in this selected group. Medline and PubMed databases were searched through with the use of the following keywords: tramadol, ketoprofen, pharmacokinetics and chronic pancreatitis. The authors did not find any publications concerning the pharmacokinetics of tramadol and ketoprofen in CP patients. The aim of this study was the evaluation of pharmacokinetics of tramadol and ketoprofen after single oral administration in patients suffering from CP.

Patients and Methods

Patients

The research was conducted at the Department of Gastroenterology and Hepatology, Medical University of Gdańsk and the Department of Clinical Pharmacy and Biopharmacy, Medical University of Poznań, Poland. The study protocol was approved by the Bioethics Committee from the Medical University of Gdańsk (NKBBN/221/2015 and NKBBN/552/2015-2016). The subjects of the research were patients admitted to the hospital between February 2016 and September 2018. Inclusion criteria were a diagnosis of CP, age above 18 years, no history of allergy to ketoprofen or tramadol, informed consent of participating in the research, pain greater than 4 (tramadol subgroup) according to Visual Analogue Scale (VAS). Patients unresponsive or intolerant to tramadol were allocated into a second subgroup, which received ketoprofen. The study was first explained to the patients, and those who agreed to the drug administration and blood collection were enrolled as subjects. The patients' characteristic is shown in Table I. Key exclusion criteria included previous ketoprofen or tramadol exposure, acute pancreatitis, serious cardiac (NYHA IV – New York Heart Association stage IV), hepatic (liver cirrhosis, INR – International Normalized Ratio >1.5) or renal (G4 or G5 according to KDIGO - Kidney Disease Improving Global Outcome 2012 classification) disorders, peptic ulcer disease, ingestion of drugs which may cause interactions with ketoprofen (e.g., corticosteroids, anticoagulants, selective serotonin reuptake inhibitors, antiplatelet drugs) and tramadol (e.g., selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, inhibitors and inducers of CYP3A4 and CYP2D6).

Drug Administration and Blood Sampling

36 adult patients suffering from CP (age, 47.7 ± 11.76, years) entered the study after being fully informed of its purpose and giving written consent. None of the subjects had taken ketoprofen or tramadol for 48 h at the time of the investigation. The patients were divided into two groups: I (n=18) receiving a single oral dose of 100 mg of Ketonal® Sandoz GmbH (two capsules, 2×50 mg), II (n=18) receiving once 100 mg of Tramal® Stada (two capsules, 2×50 mg) orally. On the day of a study, all subjects were fasting for 2 hours before and after administration of the drugs and pills were swal-

Table I. Characteristic of CP patients on ketoprofen (I) and tramadol (II).

Parameter	M±SD	
	I	II
Males/females [n]	17/1	15/3
Non-alcoholic/alcoholic [n]	10/8	9/9
Age [years]	48.61±13.32	46.78±10.28
Height [m]	1.78±0.07	1.74±0.05
Weight [kg]	73.28±20.48	74.22±14.04
BMI [kg/m^2]	22.94±6.17	24.61±4.51
Glycaemia [mg/dL]	144.63±103.68	141.92±123.64
CL_{cr} [mg/dL]	0.78±0.29	0.83±0.36
Amylase [U/L]	240.28±278.55	338.88±719.74
Lipase [U/L]	341.59±359.35	708.18±1679.42
AspAT [U/L]	55.4±69.19	41.65±64.68
AlAT [U/L]	57.12±55.54	32.94±27.98

M, arithmetic mean; SD, standard deviation; CLCR, creatinine clearance estimated by the Cockroft-Gault formula; BMI, body mass index; ASPAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

lowed with about 200 mL of water. To determine the concentrations of ketoprofen, venous blood (2 mL) was collected at 0, 0.17, 0.33, 0.5, 1, 2, 4, 6 and 8 hours after dosing. To evaluate the concentration of tramadol and M1, 2 mL of venous blood samples were drawn 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12 hours after dosing. Blood samples were transferred into heparinized tubes and centrifuged at 2880×g for 10 min at 4°C. Afterward, plasma was transferred to propylene tubes and stored at 20°C until analysis. Ketoprofen, tramadol and its metabolite M1 concentrations in gathered plasma were measured within two months.

Reagents

Ketoprofen and fenoprofen calcium dehydrate were purchased from LGC (Łomianki, Poland); acetonitrile, methanol, tert-butyl methyl ether, orthophosphoric acid from Merck (Warszawa, Poland), potassium dihydrogen phosphate from POCH (Gliwice, Poland). Ketonal® Sandoz GmbH in capsules (batch: FN4713, expiration date: 04.2020) was purchased from Sandoz Polska Sp. z o.o., Warszawa, Poland. Tramadol, 0-desmethyltramadol, venlafaxine, trimethylamine were purchased from LGC Standards (Łomianki, Poland), diethyl ether, heptane, acetonitrile, methanol, ethyl acetate, disodium hydrogen phosphate, sodium hydroxide from Merck (Warszawa, Poland), standardized plasma was purchased from Regional Blood Donation Center in Poznań (Poland). Tramal® Stada in capsules (batch: 316H04, expiration date: 04.2021) was purchased from STADA Poland Sp. z o. o., Piaseczno, Poland. Water used in the mobile phase was deionized, distilled and filtered through a Millipore system (Billerica, MA, USA) before use.

Drug Assay

The measurement of ketoprofen concentrations in the blood plasma was made by means of the high-performance liquid chromatography method with ultraviolet detection (HPLC-UV), which was a modification of the method developed by Roda et al[11]. The separation was achieved by isocratic elution of the mobile phase, at a flow rate of 1.0 mL/min through. The chromatography separation parameters were: Symmetry® column C18 3.5 µm, 4.6×50 mm (Warszawa, Poland, Waters®), mobile phase 0.01 M KH_2PO_4 pH 3.5 (adjusted with orthophosphoric acid) - acetonitrile (60:40, v/v), fenoprofen was used as internal standard (IS). The column temperature was maintained at 30°C, the UV detection wavelength was set at 254 nm, the injection volume was 20 µL. The total analysis time for each run was 15 minutes.

The concentrations of tramadol and M1 were determined using HPLC with fluorescence detection (FLD). Separation was achieved by isocratic elution of the mobile phase, sodium phosphate dibasic 0.1 M pH 3.3 (adjusted with 85% orthophosphoric acid) - acetonitrile (7:3, v/v), at a flow rate of 1.0 mL/min through an YMC® (Kyoto, Japan), ODS-A C18 column (250 mm×4.6 mm, 5.0 µm particle size). The column temperature was

maintained at 30°C. The FLD wavelength was set at λ_{ex}=275 nm/λ_{em}=300 nm and the injection volume was 50 µL. Venlafaxine was used as IS. The total analysis time for each run was 9 min.

Pharmacokinetics Analysis

The pharmacokinetic parameters were estimated with the non-compartmental method, using software Phoenix® WinNonlin® 8.1 (Certara L.P.). The noncompartmental approach was used for calculations (NCA). AUC_{0-t} - area under the plasma concentration-time curve from zero to the time of the last measurable concentration was calculated using linear trapezoidal rule described by equation: C_n and C_{n+1} represents concentration points and related time span; AUC_{0-inf} - area under the plasma concentration-time curve from zero to infinity was calculated using linear trapezoidal rule described by equation: C_{last} is the last measurable concentration; k_{el} - elimination rate constant was determined from the slope of log-transformed raw data by a linear equation, curve fitting was performed using the method of least squares; $t_{1/2kel}$ – elimination half-life was calculated using equation: Cl - clearance was calculated using equation: D represents dose value; V_d - volume of distribution was calculated using equation: C_{max} - maximum plasma concentration was observed value; t_{max} - time necessary to reach C_{max} was observed value; MRT_{0-t} - mean residence time based on data between zero and the time for the last observed concentration was calculated from equation: $AUMC_{0-t}$ - area under the first moment curve from zero to the time of the last measurable concentration was calculated using linear trapezoidal rule with equation.

Results

36 patients (32 men, 4 women; 23-66 years of age) were enrolled in and completed the research. In both analyzed groups, the mean ages of the subjects were similar, as were mean subject weight and BMI (Table I). The patients were characterized by normal hepatic function, except for 9 patients (25%) whose alanine transaminase (ALAT) was above recommended concentrations (< 55 U/L) and 10 patients (27.8%) whose aspartate aminotransferase (ASPAT) was above the limit (5- 34 U/L). 2 patients (5.6%) had the calculated creatinine clearance (Cl_{CR}) value under the limit (80 mL/min), whereas in 4 patients (11.1%) it exceeded the recommended value. The values of amylase in 14 patients (38.9%) were above recommended concentrations (20-160 U/L). The concentrations of lipase were above the limit (8-78 U/L) in 21 patients (58.3%). Both analytical methods were validated according to the guidelines of the European Medicines Agency (EMA) concerning bioanalytical method validation[12]. Ketoprofen concentrations in the blood plasma were measured by means of HPLC-UV method. The lower limit of quantification (LLOQ) for ketoprofen was 0.1 µg/mL. Intra- and inter-day precision and accuracy of the low-quality control (lQC=0.3 µg/mL), medium QC (mQC=5 µg/mL), and high QC (hQC=8 µg/mL) were well within the acceptable limit of 15% coefficient of variation (CV%). The calibration for ketoprofen was linear and ranged from 0.1 to 10.0 µg/mL (r=0.998). The concentrations of tramadol and M1 were measured using HPLC-FLD method. The LLOQ for tramadol and M1 were 5 ng/mL and 3 ng/mL, respectively. Intra- and inter-day precision and accuracy of the LLOQ, lQC (15 ng/mL and 9 ng/mL), mQC (350 ng/mL and 50 ng/mL), and hQC (600 ng/mL and 100 ng/mL) for tramadol and M1 were well within the acceptable limit of 15% coefficient of variation (CV%). The calibration was linear and ranged from 5 to 700 ng/mL (r=0.998) for tramadol and from 3 to 120 ng/mL (r=999) for M1. The main aim of our pharmacokinetic study was to characterize the plasma concentration-time course of ketoprofen, tramadol and its active metabolite after a single oral dose in patients with CP. Figure 1 shows mean plasma concentration-time profile for ketoprofen in subjects during the eight-hour period after single oral administration. Figure 2 shows mean plasma concentration-time profile for tramadol and its metabolite M1 in patients with CP during the twelve-hour period after single oral administration. Table II presents the results of the noncompartmental analysis of the plasma concentration-time data from the work and shows pharmacokinetic values of ketoprofen, tramadol and its metabolite. All the data were expressed as the mean ± standard deviation (SD). There was wide intersubject variability in the pharmacokinetic parameters, as evidenced by the coefficients of variation (CV%) (Table II). Additionally, M1/TRM ratios for C_{max} and AUC_{0-t} were calculated. They were as follows: 0.25± 0.29 and 0.31 ± 0.35, respectively. An impact of other administered drugs on ketoprofen and tramadol PK parameters was excluded in analyzed patients.

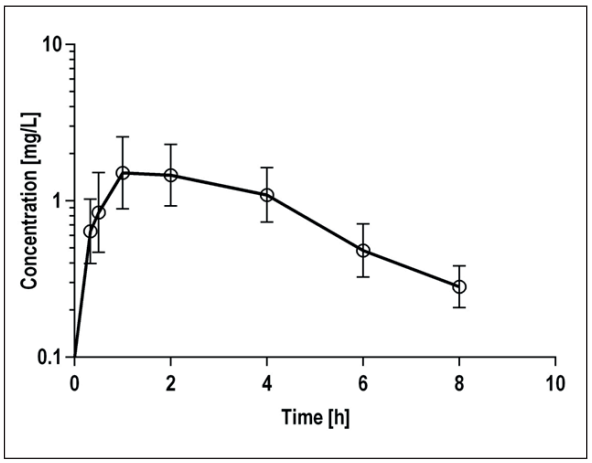

Figure 1. Ketoprofen plasma concentration-time profile following single oral administration of 100 mg of drug in patients with chronic pancreatitis (geometric means with 95%CI).

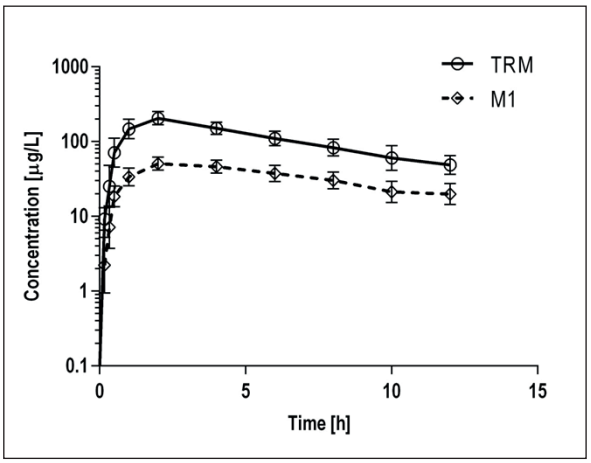

Figure 2. Tramadol and its metabolite M1 plasma concentration-time profiles following single oral administration of 100 mg of tramadol in patients with chronic pancreatitis (geometric means with 95%CI).

Table II. Pharmacokinetic parameters for ketoprofen, tramadol (TRM) and its metabolite M1 in patients with CP.

Pharmacokinetics parameters	I (n =18) M±SD (CV%)	II (n = 18) M±SD (CV%)	
		TRM	M1
C_{max}	3.41±2.32 mg/L (68%)	226.4±80.5 µg/L (36%)	55.6±23.0 µg/L (41%)
t_{max}	1.94±1.25 h (64%)	1.78±0.73 h (41%)	2.67±1.19 h (45%)
AUC_{0-t}	9.50±5.37 mg·h/L (57%)	1452.7±565.8 µg·h/L (39%)	454.6±200.2 µg·h/L (44%)
AUC_{0-inf}	10.45±5.57 mg·h/L (53%)	1903.3±874.8 µg·h/L (46%)	790.4±512.4 µg·h/L (65%)
V_d/kg	0.71±0.58 L/kg (82%)	6.06±2.05 L/kg (34%)	—
V_d	53.58±54.26 L (101%)	444.7±181.7 L (41%)	—
Cl/kg	0.199±0.165 L/kg·h (85%)	0.89±0.39 L/kg·h (44%)	—
Cl	14.64±13.02 L/h (89%)	65.04±32.28 L/h (44%)	—
MRT_{0-t}	2.91±0.87 h (30%)	4.89±0.42 h (9%)	5.44±0.46 h (8%)
$AUMC_{0-t}$	27.7±15.4 mg·h2/L (56%)	7175.4±3025.3 µg·h2/L (42%)	2517.9±1229.0 µg·h2/L (49%)

M, arithmetic mean; SD, standard deviation; CV%, coefficient of variation; Cmax, maximum observed plasma concentration; t_{max}, time to first occurrence of C_{max}; AUC_{0-t}, area under the plasma concentration-time curve from zero to the time of last measurable concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time zero to infinity, V_d, volume of distribution; V_d/kg, volume of distribution per kilogram of body weight; Cl, clearance; Cl/kg, clearance per kilogram of body weight; MRT_{0-t}, mean residence time from zero to the time of last measurable concentration; $AUMC_{0-t}$, area under the first moment curve from zero to the time of last measurable concentration.

Discussion

As abdominal pain is one of the main disorders reported by patients suffering from CP, the analgesic treatment seems to be a core issue. Pathogenesis of pain generation in CP is complicated and multifactorial, composed of pancreatic but also extra-pancreatic factors[13,14]. Pharmacological therapy starts with the insertion of paracetamol according to the WHO analgesic ladder. In case of insufficiency of such treatment, tramadol is frequently applied. In a strictly selected group of patients (unresponsive or intolerant to analgesics from other groups) ketoprofen may be a reasonable therapeutic option. According to the UEG (United European Gastroenterology) guidelines published in 2017, neither pancreatic enzyme supplementation nor antioxidants are recommended for pain treatment in patients with CP. Simultaneously alcohol and smoking cessation are highly advised[15]. Despite recommendations, many patients suffering from CP are actively abusing alcohol. Alcohol abuse is the most frequent (more than 80%) etiological factor of CP[16]. As a consequence of chronic consumption of alcohol increased microsomal enzymes activity occurs, even without detectable ethanol concentration in blood. In CP patients, metabolism of concomitantly ingested drugs may be significantly escalated, which leads to a reduction of drug concentration in plasma and secondarily to decrease of pharmacological effect. Jin et al[17] reveal that alcohol consumption results in the induction of CYP2E1, as well as CYP3A4 activity. Of note, ethanol may cause induction of cerebral CYP2D6, leading to action disturbances of drugs which are metabolized by this isoenzyme[18]. There is no precise data in the literature concerning the influence of ethanol on glucuronidation, which is the second phase of drug metabolism. Glucuronidation is also a metabolic pathway for ketoprofen. Antonilli et al[19] revealed that ethanol increases the synthesis of morphine-3-glucuronide (M3G) without any impact on morphine-6-glucuronide (M6G) synthesis in a study on animals receiving morphine.

In the present work, the pharmacokinetics of ketoprofen and tramadol in patients with CP has been evaluated. Ketoprofen $AUC_{0\text{-}inf.}$ for CP patients (10.45±5.57 mg·h/L) was lower in comparison to the healthy population from the study by Ishizaki et al[20] (21.91±1.57 mg·h/L). Therefore, the weaker analgesic effect may be expected in CP patients. It is also worth to notice that C_{max} of ketoprofen in the analyzed group (3.40±2.32 mg/L) is lower than in healthy volunteers (10.5 mg/L)[11], what might arise from the disease of the pancreas. Patients with CP often suffer from diarrhea, which may lead to faster elimination of ingested drugs (increase of clearance) and as a consequence reduction of Cmax. Siepsiak et al[21] in a previous study concerning analgesic intake in patients with CP have already proved lower drug exposition for paracetamol[21]. Significantly higher V_d/kg of ketoprofen in CP patients in comparison to healthy volunteers from the study by Ishizaki et al[20] (0.71±0.58 *vs.* 0.100±0.007 L/kg) can result from hypoalbuminemia, which also correlates with alcohol intake. Ketoprofen similarly to other NSAIDs is strongly bound with plasma albumins (99%). PK alterations of ketoprofen, such as reduction of C_{max} and faster Cl, observed in CP subjects suggest ketoprofen dose modification should be speculated. However, hypoalbuminemia and increase of the unbound fraction of the drug should also be taken into consideration. In the second arm of this research tramadol and its metabolite M1 pharmacokinetics in CP patients have been estimated. So far 11 different metabolites of TRM have been identified, but only M1 is pharmacologically active. M1 acts twice to forth stronger than the parent compound. C_{max} of tramadol in 14 participants (77.8%) of the study (226.4±80.5 µg/L) was within the therapeutic range (100-300 µg/L) associated with its analgesic activity[22]. In 4 patients (22.2%) C_{max} slightly exceeded 300 µg/L (338.1, 321.5, 312.8, 353.2). Additionally, indirect evaluation of CYP2D6 activity by calculation of M1/TRM ratios for C_{max} and $AUC_{0\text{-}t}$ has been performed. Average M1/TRM ratios for C_{max} or $AUC_{0\text{-}t}$ in the analyzed group were as follows 0.25±0.29 and 0.31±0.35, respectively, and were comparable with other populations (M1/TRM $AUC_{0\text{-}t}$ ratio= 0.27)[23]. Therefore, a conclusion can be made, that the metabolism of tramadol in CP patients was not changed. Tramadol V_d (L) in CP patients (445±182) was higher in comparison to healthy male population (374±82) as well as to healthy female population (384±63)[24], probably because of possible hypoalbuminemia. The main limitation of this work is the lack of measurements of ketoprofen glucuronide concentrations in patients' plasma. It could be valuable according to the previous authors' research concerning paracetamol pharmacokinetics, in which the authors revealed intensification of the glucuronidation process[21]. Authors attempted to evaluate concentrations of the metabolite; however, adapted analytical method did not allow to execute measurements with adequate accuracy and

precision. Consideration of the usage of a more sensitive method (e.g., HPLC with mass-spectrometric detection) should be taken into account as a continuation of this study, as it could enable measurement of very low ketoprofen glucuronide concentrations in patients' plasma. Another limitation of this research is the lack of evaluation of pain intensity after receiving analyzed analgesics that could enable assessment of the pharmacodynamic effect of administered drugs. It was not possible due to the fact that patients who were the subjects of this study demanded meanwhile additional analgesic therapy what excluded rational evaluation of pain intensity.

Conclusions

Analgesic effect of ketoprofen after oral ingestion may be much weaker, whereas tramadol seems to be a drug, which could be supplied orally to CP patients without any dosage modifications.

Funding Acknowledgements

The study was financed with the academic grant of the Gdańsk University of Medical Sciences (grant No. 01-0357/08/121).

References

1) Machicado JD, Rebours V, Yadav D. Epidemiology of chronic pancreatitis. Pancreapedia: exocrine pancreas knowledge base, DOI: 10.3998/panc.2016.13
2) Laterza L, Scaldafferi F, Bruno G, Agnes A, Boškoski I, Ianiro G, Gerardi V, Ojetti V, Alfieri S, Gasbarrini A. Pancreatic function assessment. Eur Rev Med Pharmacol Sci 2013; 17: 65-71.
3) Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, Garg PK, van Goor H, Halloran C, Isaji S, Neoptolemos JE, Olesen SS, Palermo T, Pasricha PJ, Sheel A, Shimosegawa T, Szigethy E, Whitcomb DC, Yadav D. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017; 17: 720-731.
4) Strum WB. Abstinence in alcoholic chronic pancreatitis. Effect on pain and outcome. J Clin Gastroenterol 1995; 20: 37-41.
5) Coté GA, Yadav D, Slivka A, Hawes RH, Anderson MA, Burton FR, Brand RE, Banks PA, Lewis MD, Disario JA, Gardner TB, Gelrud A, Amann ST, Baillie J, Money ME, O'Connell M, Whitcomb DC, Sherman S. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2011; 9: 266-273.
6) Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. Clin Pharmacokinet 1990; 19: 197-217.
7) Niemann T, Madsen LG, Larsen S, Thorsgaard N. Opioid treatment of painful chronic pancreatitis. Int J Pancreatol 2000; 27: 235-240.
8) Klotz U. Tramadol- the impact of its pharmacokinetic and pharmacodynamic properties on the clinical management of pain. Arzneimittelforschung 2003; 53: 681-687.
9) Mayerle J, Hoffmeister A, Werner J, Witt H, Lerch MM, Mössner J. Chronic pancreatitis - definition, etiology, investigation and treatment. Dtsch Arztebl Int 2013; 110: 387-393.
10) Olesen AE, Brokjaer A, Fisher IW, Larsen IM. Pharmacological challenges in chronic pancreatitis. World J Gastroenterol 2013; 19: 7302-7307.
11) Roda A, Sabatini L, Mirasoli M, Baraldini M, Roda E. Bioavailability of a new ketoprofen formulation for once-daily oral administration. Int J Pharm 2002; 241: 165-172.
12) Committee for Medicinal Products for Human Use. Guideline on bioanalytical method validation. European Medicines Agency 2011.
13) Löhr JM, Haas SL, Lindgren F, Enochsson L, Hedström A, Swahn F, Segersvärd R, Arnelo U. Conservative treatment of chronic pancreatitis. Dig Dis 2013; 31: 43-50.
14) Coluzzi F, Fornasari D, Pergolizzi J, Romualdi P. From acute to chronic pain: tapentadol in the progressive stages of this disease entity. Eur Rev Med Pharmacol Sci 2017; 21: 1672-1683.
15) Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, Haas S, Akisik F, Kartalis N, Iglesias-Garcia J, Keller J, Boermeester M, Werner J, Dumonceau JM, Fockens P, Drewes A, Ceyhan G, Lindkvist B, Drenth J, Ewald N, Hardt P, de Madaria E, Witt H, Scheider A, Manfredi R, Brondum FJ, Rudolf S, Bollen T, Bruno M. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J 2017; 5: 153-199.
16) Jupp J, Fine D, Johnson CD. The epidemiology and socioeconomic impact of chronic pancreatitis. Best Pract Res Clin Gastroenterol 2010; 24: 219-231.
17) Jin M, Arya P, Patel K, Singh B, Silverstein PS, Bhat HK, Kumar A, Kumar S. Effect of alcohol on drug efflux protein and drug metabolic enzymes in U937 macrophages. Alcohol Clin Exp Res 2011; 35: 132-139.
18) Miller RT, Miksys S, Hoffmann E, Tyndale RF. Ethanol self-administration and nicotine treatment increase brain levels of CYP2D in African green monkeys. Br J Pharmacol 2014; 171: 3077-3088.
19) Antonilli L, Petecchia E, Caprioli D, Badiani A, Nencini P. Effect of repeated administrations of heroin, naltrexone, methadone, and alcohol on morphine glucuronidation in the rat. Psychopharmacology (Berl) 2005; 182: 58-64.
20) Ishizaki T, Sasaki T, Suganuma T, Horai Y, Chiba K, Watanabe M, Asuke W, Hoshi H. Pharmacokinetics of ketoprofen following single oral, intramuscular and rectal doses and after repeated oral administration. Eur J Clin Pharmacol 1980; 18: 407-414.

21) Siepsiak M, Szałek E, Karbownik A, Grabowski T, Mziray M, Adrych K, Grześkowiak E. Pharmacokinetics of paracetamol in patients with chronic pancreatitis. Pharmacol Rep 2016; 68: 733-736.
22) Michaud K, Augsburger M, Romain N, Giroud C, Mangin P. Fatal overdose of tramadol and alprazolam. Forensic Sci Int 1999; 105: 185-189.
23) Quetglas EG, Azanza JR, Cardenas E, Sádaba B, Campanero MA. Stereoselective pharmacokinetic analysis of tramadol and its main phase I metabolites in healthy subjects after intravenous and oral administration of racemic tramadol. Biopharm Drug Dispos 2007; 28: 19-33.
24) Ardakani YH, Rouini MR. Pharmacokinetics of tramadol and its three main metabolites in healthy male and female volunteers. Biopharm Drug Dispos 2007; 28: 527-534.