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Short communication

Pharmacokinetics of paracetamol in patients with chronic pancreatitis

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ABSTRACT

Background: Chronic pancreatitis (CP) is a progressive, irreversible disease causing damage of the gland. Abdominal pains are a typical symptom of pancreatitis both in the chronic and acute form. Paracetamol is one of analgesics used for treating mild or moderate pain. Functional and anatomical changes in the gastrointestinal tract caused by pancreatitis may influence on the pharmacokinetics of administered drugs.

Methods: In the present study we analysed the pharmacokinetics of paracetamol after oral and intravenous administration to patients with CP. The patients were allocated to one of the two groups of the drug under study: I *iv*, intravenous administration of paracetamol 1000 mg (n = 17; mean [SD] age, 46.18 [13.78] years; and BMI, 22.03 [2.62] kg/m^2) and II *po*, oral administration of paracetamol 1000 mg (n = 17; mean [SD] age, 48.29 [10.08] years; and BMI, 22.50 [2.92] kg/m^2. The plasma concentrations of paracetamol and its metabolite (glucuronide) were measured with the validated high-pressure liquid chromatography (HPLC) method with ultraviolet (UV) detection.

Results: The main pharmacokinetic parameters for paracetamol after *iv* and *po* administration to patients with CP were as follows: C_{max}, 19.00 [4.50] and C_{max}, 9.26 [3.35] μg/ml; AUC0-t, 42.37 [13.92] and 36.68 [11.7] μg × h/mL, respectively. After *iv* and *po* administration the AUC ratio between the metabolite (glucuronide) and paracetamol was enhanced.

Conclusions: The research findings revealed that patients with chronic pancreatitis had lower concentrations of paracetamol. Therefore, it may be necessary to apply additional analgesic therapy. Moreover, we observed enhanced glucuronidation in our patients.

Introduction

Chronic pancreatitis (CP) is a progressive disease leading to irreversible dysfunction of a gland. Aetiological factors of CP can be divided according to TIGAR-O classification into toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis or obstructive [1].

There are few available studies concerning pharmacokinetics of drugs in patients with CP [2]. Drug absorption in CP may be altered due to fat malabsorption, decrease of intraluminal pH, bacterial overgrowth in the small intestine and decreased pancreatic secretion. About 35% of patients with CP suffer from steatorrhea due to abnormal digestion and it may reduce gastric emptying time. Abnormal bacterial overgrowth in the small intestine may cause the degradation of bile salts, which are necessary for the absorption of lipophilic drugs. It may damage the intestinal villi and cause atrophic lesions in the mucosa as well as diarrhoea. The growth of bacteria is additionally aided by reduced production of pancreatic juice, which enzymes have bactericidal activity. In consequence of prolonged diarrhoeas patients suffer from malnutrition, which affects drug distribution [3].

CP is first asymptomatic but in an advanced stage it is characterised by abdominal pains. The causes of pain in CP may result from an increased pressure in the pancreatic duct, damaged pancreatic nerves, pancreatic ischaemia, local complications of CP, such as narrowed duodenum, large pancreatic pseudocysts and biliary obstruction. In order to control pain in CP abinding general recommendations such as diet and smoking cessation is needed. If

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it does not achieve expected effect the next step would be a substitutive enzymatic therapy, administration of antioxidants and analgesics. Paracetamol (N-acetyl-paminophenol) is one of the analgesics recommended for the treatment of mild or moderate pain in CP [4]. About 40–67% of the paracetamol dose is bound to glucuronic acid with the participation of UDP-glucuronosyl transferases (UGT), whereas 20–46% of the dose is converted to sulfate conjugate. Only 3–4% of the dose is oxidised to the indirect toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). The process is catalysed by cytochrome P-450 (CYP2E1). At therapeutic doses, the metabolite NAPQI is detoxified by binding to the sulfhydryl group of glutathione (GSH). When the reserves of endogenic GSH are exhausted, NAPQI binds to hepatic cells, causing their damage [5]. 70% of CP has alcohol-related aetiology, so it is necessary to administer paracetamol carefully to this group of patients. However, several studies on alcoholic patients proved that the drug can be safely administered at a single dose of 1 g and daily dose of 4 g/24 h [6]. Paracetamol may increase the risk of acute pancreatitis in patients with diagnosed paracetamol poisoning [7], and in combination with codeine, especially in patients with prior cholecystectomy [8].

The aim of the research was to analyse the pharmacokinetics of paracetamol and its metabolite after intravenous (*iv*) and oral (*po*) administration to patients with CP.

Material and methods

Subjects

The study protocol was approved by the local Bioethics Committee. The subjects of the research were patients admitted to the hospital between November 2014 and July 2015, who previously gave informed consent of participating in the study. Patients were included in the study if they had CP; their age was >18 years; they had no history of allergy to paracetamol and pain greater than 4 (Visual Analogue Scale – VAS); after agreement to taking part in a research. The research was explained to the patients, and those who consented to the drug administration and blood collection were enrolled as subjects. The patients' characteristic is shown in Table 1. The main criteria for exclusion included: previous paracetamol exposure, acute pancreatitis, serious functional cardiac, hepatic, renal disorders and age under 18 years.

Table 1
Patients' characteristics.

Parameter	S ± SD
Males/females	21/7
Age [years]	49.04 ± 11.87
Height [m]	1.72 ± 0.09
Weight[kg]	69.04 ± 12.58
BMI [kg/m^2]	23.31 ± 3.48
HbA1c [%] (n = 20)	161.05 ± 142.70
C_{cr} [mg/dL]	0.70 ± 0.19
Total cholesterol [mg/dL] (n = 5)	188.00 ± 99.05
TG [mg/dL] (n = 5)	113.80 ± 54.8
HDL [mg/dL] (n = 5)	40.20 ± 23.16
LDL [mg/dL] (n = 5)	131.00 ± 80.03
Amylase [U/L] (n = 23)	179.35 ± 331.15
Lipase [U/L] (n = 22)	336.85 ± 634.53
AspAT [U/L] (n = 24)	55.88 ± 98.03
AlAT [U/L] (n = 25)	45.84 ± 37.37
Diarrhoea	n = 2
Aetiology: alcohol/other	20/8

S, arithmetic mean; SD, standard deviation; CL_{CR}, creatinine clearance estimated by the Cockroft–Gault formula; ASPAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

Drug administration and blood sampling

The patients were divided into two groups. The patients in group I_{iv} (n = 17) received paracetamol by intravenous route (15-min infusion) at a single dose of 1000 mg (Paracetamol® Kabi 10 mg/ml). The patients in group II_{po} (n = 17) received oral paracetamol as Paracetamol®, Polfa Łódź at a dose 1000 mg (two tablets, 2× 500 mg). The patients swallowed pills with water (about 200 ml) and did not eat 30 min before and after the administration of the drug. To determine the concentration of paracetamol after *iv* and *po* administration, venous blood (2 ml) was collected 0, 5 min, and 0.5, 1, 2, 4, 6, 8 h and 0, 10, 20 min, and 0.5, 1, 2, 4, 6, 8 h after receiving the dose, respectively. The blood samples were transferred into heparinised tubes and they were centrifuged at 4000 rpm for 10 min at 4 °C. Next the plasma was transferred to propylene tubes and stored at −20 °C until analysis. The paracetamol and its metabolite (glucuronide) concentrations in the plasma were measured within two months.

Reagents

Paracetamol, HPLC (high-performance liquid chromatography) grade acetonitrile, perchloric acid, paracetamol glucuronide were purchased from Sigma–Aldrich (Poland), 85% orthophospforic acid, metanol from Merck (Poland), sodium sulfate anhydrous from Fluka (Poland). Water used in the mobile phase was deionized, destilled and filtered through a milipore system before use. Paracetamol Kabi® (batch: 141E28, expiration date: 04.2017) were purchased from Fresenius Kabi Polska Sp. z o.o., Warszawa, Poland. Paracetamol® in tablets (batch: 140822, expiration date: 08.2017) were purchased from Polfa, Łódź, Poland.

Drug assay

The concentrations of paracetamol and paracetamol glucuronide were assayed using HPLC method with UV detection [9]. Separation was achieved by isocratic elution of the mobile phase, natrium sulfate 0.05 M pH 2.2 (adjusted with 85% orthophospforic acid) – acetonitrile (93:7, v/v), at a flow rate of 1.5 mL/min through a ODS Hypersil® C18 column (150 mm × 4.6 mm, 5.0 μm particle size) (Thermo Electron Corporation®). The column temperature was maintained at 25 °C, the UV detection wavelength was set at 261 nm, and the injection volume was 50 μL. The total analysis time for each run was 10 min. The lower limit of quantification (LLOQ) and limit of detection (LOD) for paracetamol and paracetamol glucuronide were 0.05 μg/mL and 0.01 μg/mL. Intra- and inter-day precision and accuracy of the LLOQ, low quality control (1.0 μg/mL), medium quality control (10.0 μg/mL), and high quality control (50.0 μg/mL) were well within the acceptable limit of 10% coefficient of variation (CV %) for paracetamol and paracetamol glucuronide. The calibration for paracetamol was linear in the range 0.05–50 μg/mL (r = 0.999), for paracetamol glucuronide in the range 0.01–50 μg/mL (r = 0.997).

Pharmacokinetics analysis

PK parameters were estimated by non-compartmental methods using Phoenix™ WinNonlin® v. 6.3; Certara L.P. USA software (Certara L.P., USA) and Biokinetica 3.1 (Dominus Kinetics Sp. z o.o., Poland). The following pharmacokinetic parameters were calculated for paracetamol: absorption rate constant (k_{ab}), 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}), maximum observed plasma concentration (C_{max}), time to first occurrence of C_{max} (t_{max}), half-life in elimination phase ($t_{1/2kel}$), clearance (Cl), volume of distribution (V_d), area under the first