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Original research article

The pharmacokinetics of the effervescent *vs.* conventional tramadol/paracetamol fixed-dose combination tablet in patients after total gastric resection

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ABSTRACT

Background: Tramadol/paracetamol is a fixed-dose combination prescribed for the relief of moderate to severe pain. The combination acts synergistically and guarantees the rapid onset of paracetamol and the prolonged analgesic effect of tramadol with good tolerability. These drugs are often used in various formulations in the treatment of patients with postoperative pain, *e.g.* after stomach resection. Gastrectomy leads to pathophysiological changes within the alimentary tract, which may affect the process of drug absorption. The aim of the research was an analysis of the pharmacokinetics of tramadol/paracetamol from effervescent and conventional tablets in patients after total gastrectomy.
Methods: The research was carried out on patients after gastrectomy with Roux-en-Y reconstruction. The patients received two tramadol/paracetamol fixed-dose combination tablets in a single orally administered dose of 75/650 mg (2 × 37.5/325 mg). The patients were subjected to one of the two study drug group with: I. effervescent tablet (ET) (n = 14; mean [SD] age, 63.4 [10.1] years; weight, 75.5 [15.3] kg; and BMI, 26.0 [4.6] kg/m^2) and II. conventional tablet (CT) (n = 12; mean [SD] age, 66.8 [7.7] years; weight, 79.8 [17.8] kg; and BMI, 27.4 [5.3] kg/m^2). Blood samples were collected within 10 h after the drug administration. The plasma concentrations of tramadol and paracetamol were measured with validated HPLC (high-performance liquid chromatography) method with UV detection.
Results: The comparison of the paracetamol and tramadol C_{max} ratio for the ET group with that of the CT group gave ratios of 1.16 [90% confidence interval (CI) 1.06, 1.27] and 0.86 (90% CI 0.72, 1.02), respectively. The comparison of the paracetamol and tramadol AUC_{0-t} ratio for the ET group with that of the CT group showed ratios of 0.99 (90% CI 0.88, 1.10) and 1.00 (90% CI 0.82, 1.22), respectively. The comparison of the difference for the effervescent and conventional formulation gave an estimated decrease in t_{max} of 0.5 h for paracetamol and 0.13 h for tramadol.
Conclusions: In view of the changes in the pharmacokinetics of paracetamol and tramadol in the patients after gastric resection for both formulations compared the conventional tablet seems to be more appropriate due to the comparable rate of absorption of both substances, higher concentrations of tramadol and comparable exposure to paracetamol.

Introduction

Paracetamol (acetaminophen) is a non-opiate analgesic and antipyretic drug reserved for patients experiencing mild to moderate pain [21] and tramadol is a centrally-acting, synthetic, weak opiate, structurally similar to codeine and morphine. Tramadol has

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numerous indications, including trauma, renal or biliary colic, labor, chronic pain of malignant or non-malignant origin [9,29]. Opioid/paracetamol 37.5 mg/325 mg is a fixed-dose combination often prescribed for the relief of moderate to severe pain. Many studies revealed its good effectiveness in the treatment of adult patients with postoperative pain after minor surgery, musculoskeletal pain, painful diabetic peripheral neuropathy or migraine pain, ankle sprain pain or subacute lower back pain [3]. Tramadol/paracetamol 37.5/325 mg provided similar efficacy to that of codeine/paracetamol 30/300 mg in patients with chronic back pain and similar analgesia to hydrocodone/paracetamol 10/650 mg in patients with postoperative dental pain [15,16]. The combination acts synergistically and guarantees the rapid onset of paracetamol and the prolonged analgesic effect of tramadol good tolerability [6,23,24].

According to the current BCS criteria (Biopharmaceutics Classification System), acetaminophen is a BCS Class III (high solubility and low permeability) and tramadol is a BCS Class I (high solubility and high permeability) compound [8,11]. Paracetamol is rapidly and almost completely absorbed from the small intestine with t_{max} 30–90 min for tablets or capsules and 15 min for effervescent [4]. t_{max} for oral tablets with tramadol is approximately 2 h [3]. The mean absolute bioavailability of tramadol is approximately 70% [9]. After the administration of fixed-dose tramadol/paracetamol, both tramadol and paracetamol are absorbed rapidly. The administration of oral tramadol/paracetamol with food does not affect the peak plasma concentration.

This combination of two analgesic substances is an interesting therapeutic option also in patients after gastrectomy. The pathophysiological changes that take place in the alimentary tract after the surgery have physiological and anatomical nature [17,18] and they may implicate changes in the pharmacokinetics of orally administered drugs, which will finally affect their strength and duration of action [10,20,28,30,31,34].

Oral drug administration is the most common and most convenient way used in clinical therapy. Oral drug absorption is determined by drug properties and the physiology of the gastrointestinal tract. The important factors which influence drug absorption include drug dissolution from the dosage form, the manner in which the drug interacts with the aqueous environment and membrane, permeation through the membrane, and irreversible removal by first-pass organs by the intestine and liver [19]. There are few studies on the pharmacokinetics of drugs in patients after gastrectomy [10,20,28,30,31]. They revealed significant changes in pharmacokinetic parameters in this group of patients. Ueno et al. also researched the pharmacokinetics of acetaminophen after oral administration to patients after stomach resection. The drug was administered as a solution. t_{max} reduced by 75% and C_{max} increased by 69% and AUC by 36% were observed in their patients ($n = 5$) in comparison with the healthy volunteers. The change was probably caused by reduced gastric emptying time [32].

The aim of the research was an analysis of the pharmacokinetics of tramadol/paracetamol from two formulations in patients after total gastrectomy. We searched the bibliographic database of the National Library of Medicine (MEDLINE®) and found no evidence in the literature regarding the effects of total gastrectomy with Roux-en-Y procedure on the pharmacokinetics of tramadol/paracetamol from a fixed-dose combination tablet.

Materials and methods

Reagents

Tramadol, paracetamol, HPLC grade acetonitrile, and phenacetin were purchased from Sigma–Aldrich, and methanol, n-heksan, orthophosphoric acid, 2 M sodium hydroxide from Merck, and sodium sulphate from Fluka. Water used in the mobile phase was deionized, distilled and filtered through a Milipore system before use. Zaldiar® (batch: 00259B, expiration date: 10.2012) and Zaldiar eff® were purchased (batch: 00164B, expiration date: 10.2012) from Grünenthal Sp. z o.o., Piaseczno, Poland.

Subjects

The research was conducted at the 1st Department of Surgical Oncology and General Surgery, Wielkopolska Cancer Center, Poznań and the Department of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznań, Poland with the approval from the Bioethics Committee, University of Medical Sciences, Poznań, Poland. The subjects of the research were patients who underwent total gastrectomy for gastric cancer between January 2010 and April 2012. The patients were included in the study if they had total gastrectomy; if their age was >18 years; if they had no history of allergy to paracetamol and tramadol; if they had pain greater than 4 (NRS – Numerical Rating Scale: 0–10); if they agreed to take part in the research. The research was explained to the patients, and those who consented to the drug administration and blood collection were enrolled as subjects. The chief criteria for exclusion included previous paracetamol and/or tramadol exposure, partial gastrectomy, serious functional cardiac, hepatic and renal disorders and age under 18 years. The background of all 26 patients enrolled in the research is shown in Table 1.

Administration and blood sampling

The patients in group I ($n = 12$) received 2 conventional coated tablets (CT) tramadol/paracetamol (Zaldiar®) at a dose of 37.5 mg/325 mg. The patients in group II ($n = 14$) also received 2 effervescent tablets (ET) tramadol/paracetamol (Zaldiar eff®)

Table 1
Patients' characteristics.

Parameter	Patients on effervescent tablets (S ± SD)	Patients on conventional tablets (S ± SD)
n	14	12
Males/females	9/5	9/3
Age [years]	63.4 ± 10.1	66.8 ± 7.7
Body mass [kg]	75.5 ± 15.3	79.8 ± 17.8
BMI [kg/m^2]	26.0 ± 4.6	27.4 ± 5.3
CL_{CR} [ml/min]	121.4 ± 44.4	112.0 ± 50.4
Albumins [g/dl]	3.3 ± 0.6	3.3 ± 0.7
Aspat [U/l]	26.8 ± 20.2	27.8 ± 25.7
Alat [U/l]	15.7 ± 7.6	25.7 ± 21.0
Tumor location		
Cardia	7	3
Body	4	9
Pylorus	3	–
Lauren's histological type		
Diffuse	2	1
Intestinal	7	4
Mixed	5	6
Other		1 (GIST)
Stage		
G	3 ($n = 9$); 2 ($n = 4$); 1 ($n = 1$)	3 ($n = 10$); 2 ($n = 1$)
T	4 ($n = 3$); 3 ($n = 8$); 2 ($n = 3$)	3 ($n = 7$); 2 ($n = 4$)
N	3 ($n = 5$); 2 ($n = 1$); 1 ($n = 5$); 0 ($n = 3$)	3 ($n = 3$); 2 ($n = 5$); 1 ($n = 2$); 0 ($n = 1$)
M	$n = 0$	$n = 0$
Lymph node metastasis	$n = 11$	$n = 10$

S: arithmetic mean, SD: standard deviation, CL_{CR}: creatinine clearance estimated by the Cockroft–Gault formula, AspAT: aspartate aminotransferase, AlAT: alanine aminotransferase, G: graduation, T: primary tumor, N: Regional lymph nodes, M: distant metastasis [27], GIST: gastrointestinal stromal tumor.