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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.

at a dose of 37.5 mg/325 mg. The drugs were administered in the morning with 200 ml of water and the patients did not have any meals for 60 min before and after the administration of the drug. To determine the concentrations of tramadol and paracetamol, blood samples for the group on CT were collected before drug administration and after it at the following times: 15′, 30′, 45′, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h. Blood samples for the group on ET were collected before drug administration and after it at the following times: 5′, 10′, 15′, 30′, 45′, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h. Further collection of samples was limited by the necessity to continue the patients' analgesic treatment. The samples were collected in 7–10 days following the gastrectomy. The blood samples were transferred into heparinised tubes and they were centrifuged at 2820 × *g* for 10 min at 4 °C. Next the plasma was transferred to propylene tubes and stored at −20 °C until analysis. The tramadol and paracetamol concentrations in the plasma were measured within two months by HPLC.

Assays

The measurement of tramadol concentrations in the blood plasma was made by means of the HPLC method with UV (ultraviolet) detection, which was a modification of the method developed by Gan et al. [7]. Separation was achieved by isocratic elution of the mobile phase, Na_2SO_4 pH 3.0 (adjusted with orthophospforic acid)–acetonitrile (87:13, v/v), at a flow rate of 1.5 ml/min through Hypersil column BOS-C18 5 μm, 4.6 mm × 150 mm (150 mm × 4.6 mm, 5.0 μm particle size) (Agilent). Paracetamol was detected by means of HPLC modified by the Brunner et al. method [2]. The chromatography separation parameters were: Agilent Hypersil column BOS-C18 5 μm, 4.6 mm × 150 mm (Agilent), mobile phase Na_2SO_4–acetonitrile (93:7, v/v), mobile phase speed 1.5 ml/min, internal standard fenacetyne. The column temperature was maintained at 25 °C, the UV detection wavelength was set at 202 nm and 254 nm, the injection volume was 60 μl and 50 μl for tramadol and paracetamol, respectively. The total analysis time for each run was 18 min and 10 min for tramadol and paracetamol, respectively. The lower limit of quantification (LLOQ) and limit of detection (LOD) were 6.84 ng/ml, 0.25 μg/ml and 2.26 ng/ml, 0.1 μg/ml for tramadol and paracetamol, respectively. The inter- and intra-day coefficients of variation were less than 10%. The calibration was linear within 10–500 ng/ml ($r = 0.999$) and 0.25–250 μg/ml ($r = 0.997$) for tramadol and paracetamol, respectively.

Pharmacokinetics analysis

The pharmacokinetic parameters were estimated by means of non-compartmental methods, with validated software (WinNonlin® Professional Version 5.3; Pharsight® Corp., USA). The following pharmacokinetic parameters were calculated for paracetamol and tramadol: absorption rate constant (k_a), $AUC_{0-0.25\ h}$ – area under the plasma concentration–time curve from zero to 0.25 h, $AUC_{0-0.5\ h}$ – area under the plasma concentration–time curve from zero to 0.5 h; $AUC_{0-0.75\ h}$ – area under the plasma concentration–time curve from zero to 0.75 h; $AUC_{0-1\ h}$ – area under the plasma concentration–time curve from zero to 1 h; $AUC_{0-1.5\ h}$ – area under the plasma concentration-time curve from zero to 1.5 h; area under the plasma concentration–time curve from time zero to infinity (AUC_{0-inf}), 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}), the time to maximum plasma concentration (t_{max}), half-life in elimination phase ($t_{1/2kel}$).

Statistical analysis

The effect of the type of formulation was tested by one-way analysis of variance in PROC GLM of the SAS package (SAS Institute Inc. 2002–2003. The SAS System for Windows version 9.1. Cary, NC 27513-2414, USA). 90% of confidence intervals for the ratio of geometric means were constructed, except for t_{max} for which the confidence intervals were based on the difference in medians.

Results

All the data was expressed as the mean ± standard deviation (SD). The two groups of patients under analysis did not differ significantly in body mass and age (Table 1). All the patients had relatively normal liver functions with the exception of one patient in group ET, whose AspAT (aspartate aminotransferase) and AlAT (alanine aminotransferase) values were much higher than the average values at 106 and 83 U/l, respectively. Six patients from both groups were found to have lower creatinine clearance than normal values. The lower values were attributed to older age rather than the symptoms of any diseases. Eighteen patients had hypoalbuminaemia, which can be both a symptom of gastric cancer and a normal postoperative response. Aside from gastric carcinoma, the patients in both groups suffered from other diseases: hypertension ($n = 9$), heart disease ($n = 2$), hypothyroidism ($n = 2$), dementia ($n = 1$), depression ($n = 1$) and diabetes mellitus ($n = 1$).

As required by protocol all the subjects had total gastrectomy. The tumor was located in the proximal (50% of group ET and 25% of group CT), in the middle (29% of group ET and 75% of group CT) and in the distal (21% of group ET) part of the stomach. The histological type was classified according to Lauren's classification [12]. In the first group 14% of tumors were diffuse, 50% – intestinal, and 36% – mixed type. In the other group 8% of tumors were diffuse, 33% – intestinal, 50% – mixed type and 8% – GIST. During the course of the research there were no serious or unexpected adverse events.

There was wide intersubject variability in the pharmacokinetic parameters, as evidenced by the coefficients of variation (CV%) (Table 2). The mean paracetamol C_{max} was similar for both the effervescent and conventional formulations (9.67 ± 3.54 and 6.75 ± 1.79 mg/l, respectively; Table 2). However, the mean C_{max} of the effervescent formulation tended to be higher. The comparison of the C_{max} for the effervescent formulation and that of the conventional tablet gave a ratio of 1.16 (90% CI 1.06, 1.27). There were no significant differences between the groups under analysis ($p = 0.7684$).

The mean paracetamol AUC_{0-t} was similar for both the effervescent and conventional formulations (25.43 ± 11.30 and 24.83 ± 6.83 mg × h/l, respectively; Table 2). The comparison of the AUC_{0-t} for the effervescent formulation and that of the conventional tablet gave a ratio of 0.99 (90% CI 0.88, 1.10). There were no significant differences between the groups under analysis ($p = 0.8753$).

The median paracetamol t_{max} was not similar for the two formulation groups. The comparison of the difference for the effervescent and conventional formulation gave an estimated decrease in t_{max} of 0.5 h (90% CI −0.63, −0.37). The mean paracetamol $t_{1/2kel}$ varied between 2.58 h (ET formulation) and 3.12 h (CT formulation). For other pharmacokinetic parameters there were no significant differences found between the formulations (Table 2).

The mean tramadol C_{max} for the effervescent formulation (152.53 ± 57.81 ng/ml) was lower than that of the conventional tablet (249.22 ± 133.42 ng/ml) (Table 3). The comparison of the C_{max} for the effervescent formulation and that of the conventional tablet gave a ratio of 0.86 (90% CI 0.72, 1.02). There were significant differences between the groups under analysis ($p = 0.0353$).

The systemic exposure of tramadol after the effervescent formulation in terms of AUC_{0-t} was slightly lower than that of the

Table 2
Paracetamol pharmacokinetic parameters from effervescent and conventional tramadol/paracetamol fixed-dose combination tablet in patients after total gastric resection.

Pharmacokinetic parameters[a]	Effervescent tablet ($n = 14$)	Conventional tablet ($n = 12$)	G mean ratio[b] (90% CI)	p-Value
			Effervescent *vs.* conventional	
k_a (1/h)	4.47 ± 3.75	3.85 ± 3.28	1.11 (0.75, 1.64)	0.6604
$AUC_{0-0.25\ h}$ (mg × h/l)	1.74 ± 0.87	0.46 ± 0.27	1.81 (1.50, 2.18)	0.0002
$AUC_{0-0.5\ h}$ (mg × h/l)	3.73 ± 1.82	1.65 ± 0.69	1.41 (1.22, 1.63)	0.0015
$AUC_{0-0.75\ h}$ (mg × h/l)	5.48 ± 2.60	3.15 ± 1.02	1.29 (1.14, 1.47)	0.0057
$AUC_{0-1\ h}$ (mg × h/l)	7.00 ± 3.21	4.63 ± 1.34	1.18 (1.05, 1.32)	0.0265
AUC_{0-t} (mg × h/l)	25.43 ± 11.30	24.83 ± 6.83	0.99 (0.88, 1.10)	0.8753
$AUC_{0-\infty}$ (mg × h/l)	27.89 ± 11.92	29.78 ± 10.76	0.96 (0.85, 1.08)	0.6826
$C_{0.25\ h}$ (mg/l)	8.55 ± 4.24	3.67 ± 2.19	1.47 (1.24, 1.76)	0.0019
$C_{0.5\ h}$ (mg/l)	7.40 ± 3.81	6.00 ± 1.84	1.07 (0.95, 1.21)	0.2527
$C_{0.75\ h}$ (mg/l)	6.58 ± 2.84	5.99 ± 1.83	1.03 (0.92, 1.15)	0.5467
$C_{1\ h}$ (mg/l)	5.55 ± 2.63	5.82 ± 1.76	0.96 (0.85, 1.07)	0.7684
C_{max} (mg/l)	9.67 ± 3.54	6.75 ± 1.79	1.16 (1.06, 1.27)	0.7684
t_{max} (h)	0.25	0.75	−0.5 (−0.63, −0.37)	0.0010
$t_{1/2kel}$ (h)	2.58 ± 0.67	3.12 ± 0.95	0.93 (0.86, 1.00)	0.1033
MRT (h)	2.92 ± 0.52	3.32 ± 0.43	0.94 (0.90, 0.99)	0.0450
$AUMC_{0-t}$ (mg × h^2/l)	73.73 ± 35.77	85.56 ± 34.88	0.92 (0.81, 1.05)	0.4036

CI: confidence interval, k_a: absorption rate constant, $AUC_{0-0.25\ h}$: area under the plasma concentration–time curve from zero to 0.25 h, $AUC_{0-0.5\ h}$: area under the plasma concentration–time curve from zero to 0.5 h, $AUC_{0-0.75\ h}$: area under the plasma concentration–time curve from zero to 0.75 h, $AUC_{0-1\ h}$: area under the plasma concentration–time curve from zero to 1 h, 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 reach maximum concentration, $t_{1/2kel}$: elimination half-life time, MRT: mean residence time, $AUMC_{0-t}$: area under the first moment curve.
[a] Arithmetic means ± standard deviations (CV%) are presented, except for t_{max}, where medians (ranges) are presented.
[b] Ratio of geometric means (Gmeans) between groups (%), except for t_{max}, where median differences are presented.

conventional tablet (793.48 ± 315.06 and 947.29 ± 554.00 ng × h/ml, respectively; Table 3). The comparison of the AUC_{0-t} for the effervescent formulation and that of the conventional tablet gave a ratio of 1.00 (90% CI 0.82, 1.22). There were no significant differences between the groups under analysis ($p = 0.3841$).

After the effervescent formulation, t_{max} for tramadol was 0.25–1.5 h, as compared with 0.5–1.0 h after the conventional tablet. The comparison of the difference for the effervescent and conventional formulation gave an estimated decrease in t_{max} of 0.13 h (90% CI −0.09, 0.34). The mean tramadol $t_{1/2kel}$ varied between 5.15 h (ET formulation) and 4.42 h (CT formulation). There were no significant differences found between the formulations (Table 3).

The plasma concentration–time profiles for tramadol and paracetamol are shown in Figs. 1 and 2, respectively.

Discussion

This study analyses the pharmacokinetic parameters of tramadol/paracetamol after single administration of the effervescent or conventional formulation to patients after total gastrectomy.

In other studies healthy volunteers that were given 650 mg of paracetamol had the following C_{max} values: 11.58 [1] *vs.* 10.9 mg/l [5], both showing values higher than in the group of our patients receiving conventional tablets (6.75 ± 1.79 mg/l). There were no

Table 3
Tramadol pharmacokinetic parameters from effervescent and conventional tramadol/paracetamol fixed-dose combination tablet in patients after total gastric resection.

Pharmacokinetic parameters[a]	Effervescent tablet ($n = 14$)	Conventional tablet ($n = 12$)	G mean ratio[b] (90% CI)	p-Value
			Effervescent *vs.* conventional	
k_a (1/h)	4.46 ± 4.94	3.83 ± 2.93	0.86 (0.56, 1.32)	0.7019
$AUC_{0-0.25\ h}$ (ng × h/ml)	11.07 ± 5.93	5.96 ± 4.27	1.37 (1.12, 1.68)	0.0263
$AUC_{0-0.5\ h}$ (ng × h/ml)	33.35 ± 18.55	31.51 ± 17.39	1.02 (0.85, 1.23)	0.7973
$AUC_{0-0.75\ h}$ (ng × h/ml)	66.33 ± 38.87	73.21 ± 33.21	0.95 (0.80, 1.14)	0.6400
$AUC_{0-1\ h}$ (ng × h/ml)	91.31 ± 38.24	130.81 ± 46.42	0.86 (0.74, 0.99)	0.0322
$AUC_{0-1.5\ h}$ (ng × h/ml)	186.37 ± 95.39	221.46 ± 109.76	0.96 (0.80, 1.16)	0.4212
AUC_{0-t} (ng × h/ml)	793.48 ± 315.06	947.29 ± 554.00	1.00 (0.82, 1.22)	0.3841
$AUC_{0-\infty}$ (ng × h/ml)	1119.16 ± 440.75	1371.05 ± 1169.52	1.00 (0.82, 1.23)	0.4930
$C_{0.25\ h}$ (mg/l)	88.53 ± 43.62	51.23 ± 33.79	1.33 (1.09, 1.61)	0.0427
$C_{0.5\ h}$ (mg/l)	105.27 ± 41.92	153.04 ± 65.77	0.86 (0.75, 0.99)	0.0483
$C_{0.75\ h}$ (mg/l)	120.30 ± 42.09	190.40 ± 92.13	0.86 (0.73, 1.02)	0.0296
$C_{1\ h}$ (mg/l)	137.27 ± 57.03	211.52 ± 69.06	0.82 (0.73, 0.93)	0.0122
$C_{1.5\ h}$ (mg/l)	134.95 ± 60.29	204.93 ± 71.79	0.81 (0.72, 0.94)	0.0291
C_{max} (mg/l)	152.53 ± 57.81	249.22 ± 133.42	0.86 (0.72, 1.02)	0.0353
t_{max} (h)	1.00	0.87	0.13 (−0.09, 0.34)	0.9715
$t_{1/2kel}$ (h)	5.15 ± 2.33	4.42 ± 1.82	1.06 (0.94, 1.19)	0.3938
MRT (h)	3.92 ± 0.53	3.67 ± 0.82	1.04 (0.97, 1.11)	0.3469
$AUMC_{0-t}$ (ng × h^2/ml)	3163.43 ± 1424.31	3336.61 ± 1176.88	0.97 (0.84, 1.13)	0.7559

CI: confidence interval, k_a: absorption rate constant, $AUC_{0-0.25\ h}$: area under the plasma concentration–time curve from zero to 0.25 h, $AUC_{0-0.5\ h}$: area under the plasma concentration-time curve from zero to 0.5 h, $AUC_{0-0.75\ h}$: area under the plasma concentration–time curve from zero to 0.75 h, $AUC_{0-1\ h}$: area under the plasma concentration–time curve from zero to 1 h, $AUC_{0-1.5\ h}$: area under the plasma concentration–time curve from zero to 1.5 h, 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 reach maximum concentration, $t_{1/2kel}$: elimination half-life time, MRT: mean residence time; $AUMC_{0-t}$: area under the first moment curve.
[a] Arithmetic means ± standard deviations (CV%) are presented, except for t_{max}, where medians (ranges) are presented.
[b] Ratio of geometric means (Gmeans) between groups (%), except for t_{max}, where median differences are presented.

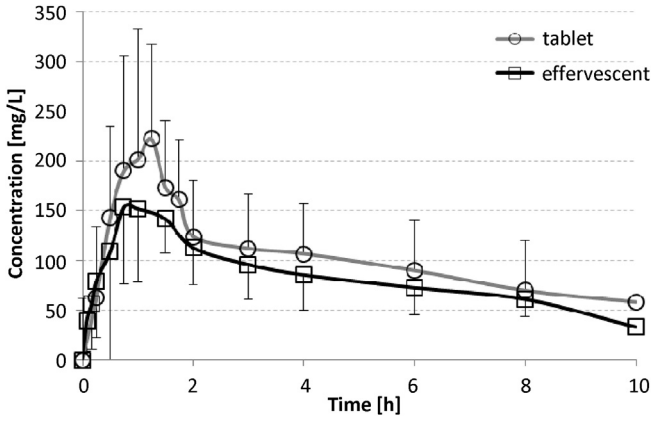

Fig. 1. Mean tramadol plasma concentration *vs.* time profiles following single oral administration of a conventional (CT) formulation or effervescent (ET) formulation of tramadol and paracetamol combination tablets.

studies found where healthy volunteers were administered 650 mg of paracetamol in the effervescent tablet formulation. Paracetamol C_{max} was higher in the group on ET than in the group on CT. Regardless of the overall lower mean C_{max} obtained as compared with the healthy volunteers, all the patients on ET and most patients on CT fell within the therapeutic range of 5–20 mg/l. Three patients on CT had individual C_{max} values lower than 5 mg/l (4.11, 4.57 and 4.28 mg/l). The values below the therapeutic range should indicate the absence of therapeutic effect. However, on the basis of the patients' ratings in the Numerical Rating Scale, which was performed before administration of the drug and at one and two hours afterwards, no pain was indicated. These NRS results may be misleading in describing the therapeutic effect of paracetamol in this case, as the patients received the second analgesic, tramadol. In comparison with the healthy volunteers the overall lower mean C_{max} obtained may be due to lowered absorption after complete gastrectomy. In the previous study the authors discovered lower mean C_{max} values for two generics of paracetamol in patients after gastrectomy as compared with healthy volunteers [28].

Another parameter that may change as a result of gastrectomy is the time to maximum paracetamol concentration. t_{max} was significantly shorter in the group on ET than in the group on CT (0.25 h *vs.* 0.75 h; $p = 0.0010$). The patients in the group receiving ET achieved t_{max} in 0.25 h, which was almost twice as fast as the healthy volunteers given effervescent tablets: 0.4 h [25] *vs.* 0.45 [22]. The patients in the group receiving CT achieved t_{max} comparable to healthy volunteers [1,5,22,25,33].

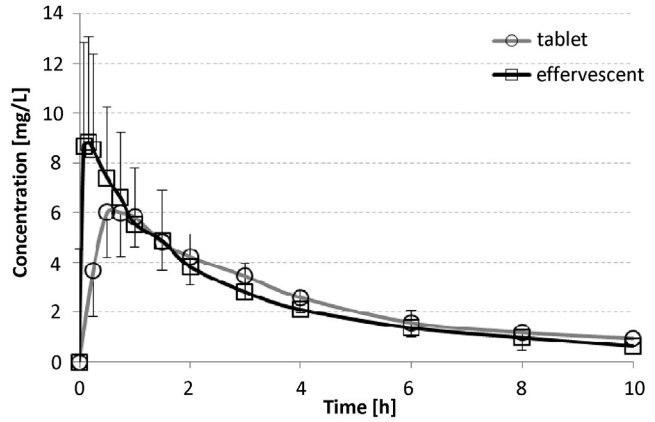

Fig. 2. Mean paracetamol plasma concentration *vs.* time profiles following single oral administration of a conventional (CT) formulation or effervescent (ET) formulation of tramadol and paracetamol combination tablets.

At each 15-min interval from $t = 15$ min to $t = 1$ h AUC was higher in the group on ET than in the group on CT with p-values showing statistical significance in each case: $AUC_{0–0.25\ h}$ ($p = 0.0002$), $AUC_{0–0.5\ h}$ ($p = 0.0015$), $AUC_{0–0.75\ h}$ ($p = 0.0057$), $AUC_{0–1\ h}$ ($p = 0.0265$), which points to higher exposure within the first hour following administration of the drug. $AUC_{0–t}$ and AUC_{inf} for paracetamol were very similar between the two groups ($p = 0.8753$ and $p = 0.6826$, respectively). Concentrations at the same intervals within the first hour closely followed the same trend, but above $t = 15$ min the concentrations between the two groups grew closer together and statistically were not found to be significantly different: ($C_{15\ min}$, $p = 0.0019$; $C_{30\ min}$, $p = 0.2527$; $C_{45\ min}$, $p = 0.5467$; $C_{1\ h}$, $p = 0.7684$). Statistically insignificant differences were found between the effervescent and regular formulations of paracetamol/tramadol for biological half time and AUC_{inf}.

In the group of patients receiving CT there were significantly higher C_{max} for tramadol for the conventional tablet than for the effervescent tablet (249.22 *vs.* 152.53 ng/ml) and noticeably higher $AUC_{0–\infty}$ (1119.16 ng × h/ml *vs.* 1371.05 ng × h/ml), which may indicate more effective analgesia after the administration of a coated tablet. However, there were no statistically significant differences obtained for $AUC_{0–\infty}$. We could not exclude that these differences were caused by the small size of the sample and different conditions of the studies (*e.g.*, study population). For the effervescent tablet only $C_{0.25\ h}$ and $AUC_{0.25\ h}$ were higher than in the conventional tablet ($p = 0.0427$, $p = 0.0263$, respectively). However, at the other time points the concentrations of tramadol were higher for CT.

In the patients receiving ET there were lower values of C_{max} (= 152.53 ng/ml for the dose of 75 mg) than in the healthy volunteers (284.23 ng/ml for the dose of 100 mg) [26]. One patient from the CT group and two from the ET group achieved lower concentrations than 100 ng/ml (the total tramadol plasma concentrations associated with effective analgesia were suggested as 100 ng/ml by Lintz et al. [14]). In both groups of patients the tramadol t_{max} was almost identical (about 1 h), but it was noticeably shorter than in the group of healthy volunteers (1.5–2 h) [13,14,26]. Lowered t_{max} values in both groups may result from more rapid absorption of tramadol in the patients after gastrectomy and be related with shorter GER (gastric emptying rate). Besides, there were noticeably lower $AUC_{0–\infty}$ values observed in the patients from both groups under analysis (CT: 1371.05, ET: 1119.16 ng × h/ml for the dose of 75 mg), as compared with the healthy volunteers (2274.64 ng × h/ml for the dose of 100 mg) [26].

The bioequivalence between the film-coated tablet and effervescent tablet for the preparation containing tramadol/paracetamol in healthy volunteers [3] enables interchangeable application of both forms of the drug. In the patients under analysis the $AUC_{0–t}$ is also similar for both substances (80–125%), but the tramadol C_{max} is significantly higher for the film-coated tablet.

The article presents pilot studies which were carried out on a small group of patients. In order to precisely determine variations in the pharmacokinetics of paracetamol/tramadol in patients after stomach resection, studies will be continued on a larger group of patients, including those who underwent partial resection of the stomach. Studies will also be extended with the analysis of the pharmacokinetics of the drugs in patients in 6 and in 12 months after the surgery. It is unquestionable that the possibility to make a comparison between the oral and intravenous administration and to determine the absolute bioavailability (F) in patients after gastrectomy would provide significant information about changes in the process of absorption in this group of patients.

Conclusion

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.

Conflict of interest

No conflict of interest.

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