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Comparison of the pharmacokinetics of paracetamol from two generic products in patients after total gastric resection

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Abstract:
Gastrectomy leads to pathophysiological changes within the alimentary tract, which may affect drug absorption and pharmacokinetic parameters (PK). The need to apply orally administered analgesics in this group of patients is often related with alternative application of currently available generic products. Thus, from the clinical point of view it is necessary to evaluate the PK of these drugs to confirm their equivalence. The aim of the study was therefore an analysis of the pharmacokinetics of paracetamol from two generic products in patients after total gastric resection. The research was carried out on two groups of patients after gastrectomy with Roux-en-Y reconstruction (n = 30; mean [SD] age, 63.0 [11.5] years; weight, 67.6 [13.7] kg; and height, 166.4 [9.1] cm). The patients received paracetamol in a single orally administered dose of 1,000 mg. Blood samples were collected within 6 h of drug administration. The concentration of paracetamol and paracetamol glucuronide in the blood plasma was marked by means of a validated high-pressure liquid chromatography with ultraviolet detection (HPLC-UV). The main PK for paracetamol in group 1 (n = 17) and 2 (n = 13) were as follows: C_{max}, 9.46 (3.66) and 12.79 (5.32) μg/ml, respectively (p = 0.0517); $AUMC_{0\text{-}t}$, 77.64 (30.37) and 51.01 (15.76) μg h^2/ml (p = 0.0046); $AUC_{0\text{-}inf}$, 41.61 (23.52) and 30.28 (9.74) μg h/ml (p = 0.0862); t_{max}, 1.68 (0.63) and 0.50 (0.25) h (p < 0001). The obtained C_{max} and AUC values in patients after gastrectomy were reduced in comparison with healthy subjects. Total gastrectomy therefore affected the pharmacokinetics of paracetamol administered in tablets. In our patients, we also observed significant differences between the PK of paracetamol and two generic preparations. These two drugs can thus be used interchangeably, but with caution.

Key words:
paracetamol, tablets, gastrectomy, pharmacokinetics

Introduction

The latest data shows that every year 1.4 million new cases of gastroesophageal cancer and gastric cancer are diagnosed and 1.1 million patients die of the disease [4]. In spite of progress in prophylaxis and treatment, the average five-year survival rate is 20% in most regions of the world. Low survival rates are usually accounted for by the advanced stage of disease progression at diagnosis [8].

Gastrectomy causes anatomic and functional changes in the gastrointestinal system, which may affect the process of absorption of orally administered drugs and change their pharmacokinetics [12, 13]. Oral drug administration is the most frequent method of drug application to a patient. Drugs may be absorbed from different sections of the alimentary tract, but it is the mechanical and motor function of the stomach that is responsible for fragmentation and liberation of the active substance from the solid form of the drug. Thus, gastrectomy may significantly affect the therapeutic substance absorption process [6].

Paracetamol (acetaminophen, N-acetyl-*p*-aminophenol) is widely used in monotherapy and combined therapy in order to treat pain of moderate intensity, especially in the post-operative period. Apart from its analgesic effect, paracetamol also exhibits an antipyretic effect related to the inhibition of endogenous pyrogens in the thermoregulatory center in the hypothalamus. After dissolution in the alimentary tract, paracetamol is absorbed through passive diffusion. The rate of absorption of the drug depends on its contact surface with the mucosa of the alimentary tract and regional perfusion, but it is independent of the degree of drug ionization and the pH of the gastric contents. The absorption of paracetamol also depends on gastric emptying time. Ueno et al. proved that after gastrectomy, the rate of absorption in patients of paracetamol administered in a solution depended on the surgery type, which dictated gastric emptying time. If the gastric emptying time was extended, the ability to absorb paracetamol was impaired [22]. The drug is not absorbed in the stomach, but rather rapidly and completely absorbed in the small intestine [15].

The aim of the research was an analysis of the pharmacokinetics of paracetamol from two generic products (pills) in patients after total gastrectomy. We performed a National Library of Medicine's bibliographic database (MEDLINE®) search and found no evidence in the literature regarding the effects of total gastrectomy with the Roux-en-Y procedure on the pharmacokinetics of paracetamol from tablets.

Materials and Methods

The research was conducted at the 1st Department of Oncological 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 of the Poznań University of Medical Sciences. The subjects of the research were patients who underwent total gastrectomy for gastric cancer between December 2009 and November 2010. 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 exposure, partial gastrectomy (Billroth I and II reconstruction), serious functional cardiac, hepatic and renal disorders and age under 18 years. The background of all 30 patients enrolled in the study is shown in Table 1. Two Polish generic drugs were subjected to analysis: Paracetamol®, Biofarm (tablets) and Paracetamol®, Polfa Łódź (tablets). Both preparations contained identical doses of paracetamol (500 mg). The excipients of Paracetamol®, Biofarm included povidone, magnesium stearate, pregelatinized starch, stearic acid, and crospovidone. Paracetamol , Polfa Łódź included povidone, magnesium stearate, potato starch, and sorbitol.

Administration and blood sampling

The patients in group I (n = 17) received paracetamol as Paracetamol®, Biofarm at a single dose of 1000 mg (two tablets, 2 × 500 mg). The patients in group II (n = 13) received paracetamol as Paracetamol®, Polfa Łódź at a dose of 1,000 mg (two tablets, 2 × 500 mg). The patients swallowed the 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, venous blood (2 ml) was collected 0, 0.25, 0.5, 0.75, 1, 2, 3, 4 and 6 h after receiving the daily dose. Further collection of samples was limited by the necessity to continue the patients' anal-

gesic treatment. The samples were collected 6–7 days after the gastrectomy. The blood samples were transferred into heparinized tubes and centrifuged at 4,000 rpm for 8 min at 4°C. Next, the plasma was transferred to propylene tubes and stored at –20°C until analysis. The paracetamol and its metabolite concentrations in plasma were measured within two months by high-performance liquid chromatography.

Assays

Paracetamol and its metabolites were detected by means of high-pressure liquid chromatography with ultraviolet detection (HPLC-UV) modified using the Brunner and Bai method [2]. The chromatography separation parameters were: an Agilent Hypersil column, BOS-C18 5 μm, 4.6 × 150 mm (Agilent); mobile phase, Na_2SO_4 (0.05M)/acetonitrile (93:7; pH 2.2); mobile phase speed, 1.5 ml/ min; detector wavelength, 254 nm; internal standard, theophylline. Samples were eluted isocratically throughout the 10 min run. The limit of quantification was estimated at 0.1 μg/ml. Inter- and intra-day coefficients of variation were less than 10%. The calibration for paracetamol was linear in the range 0.25–250 μg/ml (r = 0.997) and in the range 0.25–400 μg/ml (r = 0.999) for metabolites.

Pharmacokinetics

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: area under the plasma concentration-time curve from time zero to infinity (AUC_{0-}), area under the plasma concentration-time curve from zero to the time of last measurable concentration ($AUC_{0\text{-last}}$), maximum observed plasma concentration (C_{max}), time to the first occurrence of C_{max} (t_{max}), elimination phase plasma half-life ($t_{1/2\beta}$), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), area under the first moment curve (AUMC) and mean residence time (MRT). The pharmacokinetic parameters for the metabolites were AUC_{0-} , $AUC_{0\text{-last}}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, Vz/F and AUMC.

Statistical methods

Differences between the means were analyzed by means of a two sample *t*-test in the T-TEST procedure of the Windows SAS package, version 9.1 (SAS Institute Inc. 2002–2003, Cary, NC 27513-2414 USA). Pooled or Satterthwaite approximation standard errors were used following the results of equality of the variance test. For the ratio of geometric means, 90% confidence limits were constructed.

Results

Thirty subjects (15 men, 15 women; 44–97 years of age) were enrolled in and completed the research (first subject visit: December 9, 2009; last subject visit: November 14, 2010). In the analyzed groups, the mean ages of the subjects were similar, as were mean subject weights and BMI (Tab. 1). The patients were characterized by normal hepatic function, except for one patient whose alanine transaminase (Alat) was 54 U/l, which probably led to the reduced C_{max} value of the paracetamol metabolite (2.46 μg/ml). In 10 patients in both groups the calculated creatinine clearance value was under the limit (80 ml/min), whereas in 6 patients it exceeded the recommended value. The reduced value of the parameter may have resulted from advanced age (15 patients aged over 65 years). Nineteen patients showed hypoalbuminemia, which was likely caused by the neoplastic disease and disordered absorption after the surgery.

As required, all the subjects had total gastrectomy. The tumor was located in the proximal (19% group 1 and 8% group 2), in the middle (56% group 1 and 69% group 2) or in the distal (25% group 1 and 23% group 2) part of the stomach. The histological type was classified by Lauren's classification [10]. In the first group, 25% of the tumors were diffuse, 31% intestinal, and 44% mixed. In the second group, 15% of the tumors were diffuse, 31% intestinal, 46% mixed and 8% not classified. During the course of the research there were no serious or unexpected adverse events.

There were measurable paracetamol and metabolite concentrations within 15 min after dosing and they remained quantifiable at all of the following time points for all the subjects. Peak paracetamol concentrations

Tab. 1. Patient characteristics

Parameter	Group 1 (S ± SD)	Group 2 (S ± SD)
n	17	13
Males/females	11/6	4/9
Age [years]	63.6 ± 10.8	62.2 ± 12.7
Body mass [kg]	69.6 ± 13.2	64.8 ± 14.4
BMI [kg/m^2]	24.4 ± 3.4	24.3 ± 5.6
CL_{CR} [ml/min]	108.9 ± 31.2	100.8 ± 34.0
Albumins [g/dl]	3.3 ± 0.6	3.5 ± 0.8
Aspat [U/l]	20.9 ± 7.1	18.7 ± 6.5
Alat [U/l]	20.4 ± 11.9	16.7 ± 9.7
Tumor location		
Cardia	3	1
Body	9	9
Pylorus	4	3
Lauren's histological type		
Diffuse	4	2
Intestinal	5	4
Mixed	7	6
Unclassified	–	1
Stage		
G	3 (n = 13); 2 (n = 3)	3 (n = 11); 2 (n = 1); 1 (n = 1)
T	3 (n = 4); 2 (n = 10); 1 (n = 2)	4 (n = 2); 3 (n = 4); 2 (n = 6); 1 (n = 1)
N	3 (n = 1); 2 (n = 8); 1 (n = 5); 0 (n = 2)	3 (n = 4); 2 (n = 4); 1 (n = 2); 0 (n = 3)
M	n = 0	n = 1
HER-2	n = 3	n = 1
Lymph node metastasis	n = 14	n = 10

S – arithmetic mean, SD – standard deviation, CL_{CR} – creatinine clearance estimated by the Cockroft-Gault formula, G – graduation, T – primary tumor, N – regional lymph nodes, M – distant metastasis, HER 2 – human epidermal growth factor receptor 2 [18]

in groups 1 and 2 were achieved approximately 1.7 and 0.5 h after dosing (mean time to the first occurrence of C_{max} [t_{max}]), respectively. Figures 1 and 2 show mean plasma concentration-time profiles for paracetamol and metabolite, respectively, in the two subject groups during the six-hour period after the administration of paracetamol. Tables 2 and 3 show the pharmacokinetics of paracetamol and its glucuronide. All the data are expressed as the mean ± standard deviation (SD)

Discussion

Changes in the pharmacokinetic parameters of drugs in patients after gastrectomy result from different pathophysiological disorders, which occur after the surgeries from the physicochemical properties of the therapeutic substance in question and the form of the drug. There are few studies on the pharmacokinetics of drugs in patients after gastrectomy. In a case study

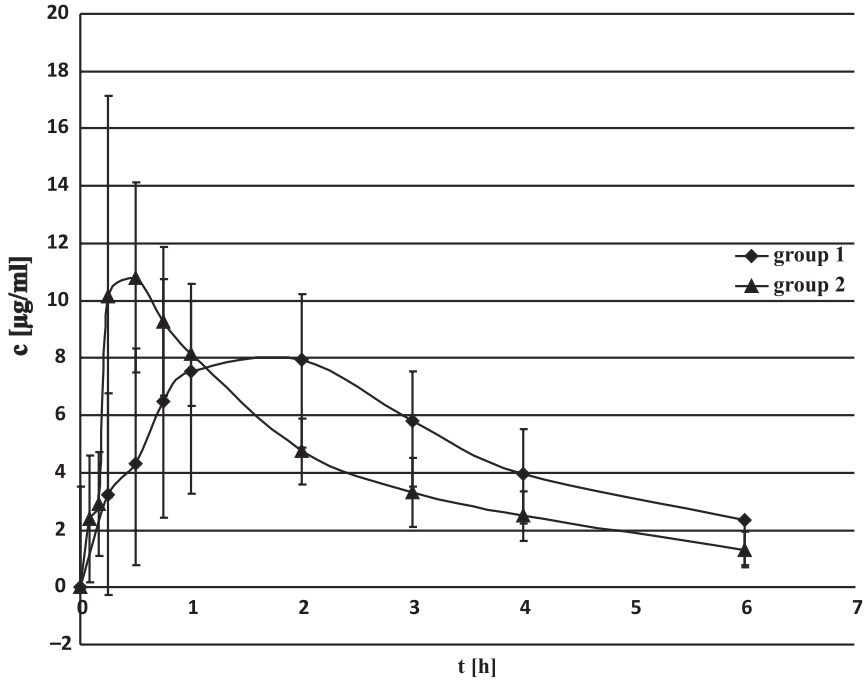

Fig. 1. Mean paracetamol plasma concentration *vs.* time following oral administration of a single 1,000 mg dose of paracetamol in groups 1 and 2

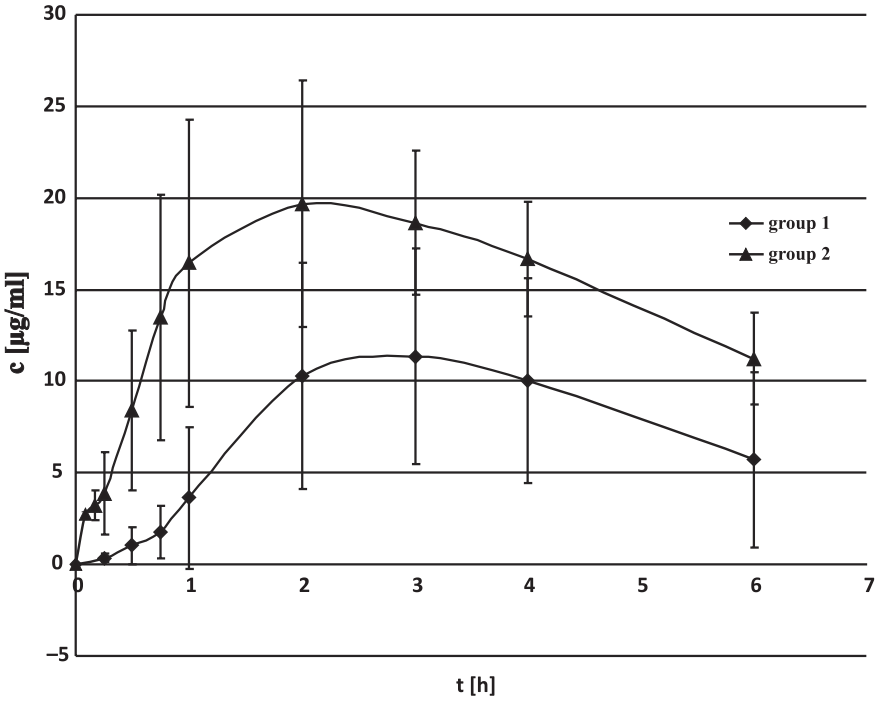

Fig. 2. Mean metabolite plasma concentration *vs.* time following oral administration of a single 1,000 mg dose of paracetamol in groups 1 and 2

on a patient treated with cyclosporine A in capsules after gastrectomy and kidney transplantation, Tewari et al. reported a very low concentration of the immunosuppressive (below the therapeutic range) [20]. Pavlovsky et al. [14] also reported reduced imatinib concentrations after resection in a patient suffering from chronic myeloid leukemia who underwent sleeve gastrectomy. Another antineoplastic drug whose pharmacokinetics after gastrectomy was examined is S-1, a drug widely used in monotherapy or in

Tab. 2. Pharmacokinetic parameters for paracetamol in plasma

Parameter	Group 1 (n = 17) [S ± SD]	Group 2 (n = 13) [S ± SD]	Group 1 *vs.* group 2 p-value
C_{max} [μg/ml]	9.46 ± 3.66	12.79 ± 5.32	0.0517
$AUC_{0\text{-}last}$ [μg h/ml]	30.01 ± 11.23	25.65 ± 7.26	0.2340
$AUC_{0\text{-}inf}$ [μg h/ml]	41.61 ± 23.52	30.28 ± 9.74	0.0862
$AUMC_{0\text{-}last}$ [μg h^2/ml]	77.64 ± 30.37	51.01 ± 15.76	0.0046
t_{max} [h]	1.68 ± 0.63	0.50 ± 0.25	< 0.0001
$t_{1/2\beta}$ [h]	2.61 ± 1.61	2.27 ± 0.60	0.4233
MRT [h]	4.52 ± 2.25	3.06 ± 0.70	0.0207
CL/F [l/h]	31.31 ± 18.33	36.17 ± 10.87	0.4044
V_d/F [l]	103.21 ± 71.25	114.02 ± 32.58	0.5848

Tab. 3. Pharmacokinetic parameters for the metabolite in plasma

Parameter	Group 1 (n = 17) [S ± SD]	Group 2 (n = 13) [S ± SD]	Group 1 *vs.* group 2 p-value
C_{max} [μg/ml]	13.63 ± 6.52	20.81 ± 5.84	0.0047
$AUC_{0\text{-}last}$ [μg h/ml]	45.49 ± 22.70	91.30 ± 22.05	< 0.0001
$AUC_{0\text{-}inf}$ [μg h/ml]	93.34 ± 104.23	180.08 ± 85.01	0.0229
$AUMC_{0\text{-}last}$ [μg h^2/ml]	151.91 ± 82.77	276.71 ± 56.06	< 0.0001
t_{max} [h]	2.88 ± 0.70	2.62 ± 0.92	0.3846
$t_{1/2\beta}$ [h]	3.75 ± 3.65	5.27 ± 4.94	0.3513

combination with other drugs in advanced gastric cancer. However, Tsuruoka et al. [21] did not observe a significant influence of stomach resection on the PK parameters of S-1 in patients before and after total and partial gastrectomy. The reduced t_{max} in patients after total gastrectomy was accounted for by the atrophy of the retentive function of the stomach [9, 21].

This study analyzed the pharmacokinetic parameters of paracetamol after single administration to patients after total gastrectomy. The drug was applied to patients in a monotherapy or in combination with opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of postoperative pain. Ueno et al. [22] also investigated the pharmacokinetics of acetaminophen after oral administration to patients undergoing stomach resection. The drug was administered as a solution. The researchers analyzed the concentration of paracetamol after partial and total gastrectomy and compared with the control group. The t_{max} was reduced by 75% and the C_{max} and AUC increased by 69% and 36%, respectively, in patients after total resection (n = 5) when compared with healthy volunteers. These changes were probably caused by reduced gastric emptying time [22].

In the study, the patients from group 1 exhibited much lower maximum paracetamol concentrations than healthy individuals (C_{max} = 9.5 (± 3.7) *vs.* 17.0 (± 3.3) [17] *vs.* 17.7 (± 4.0) [16] *vs.* 23.9 (± 9.2) μg/ml [5]). The mean C_{max} value obtained from the patients was in the lower limit of the therapeutic range (5–20 μg/ml). The minimum concentration obtained from apatient in group 1 was 1.99 μg/ml. The reduced maximum concentrations in the patients from group 1 suggested reduced absorption of the drug after total gastrectomy. In comparison with healthy volunteers, the patients from group 2 also exhibited reduced C_{max} (12.8 ± 5.3 μg/ml), but to a lesser degree. The differ-

ence between the C_{max} values in the compared groups was at the limit of statistical significance (p = 0.0517).

Another parameter that changed in patients after gastrectomy was the time necessary to reach the maximum concentration. In the patients from group 1, t_{max} was 1.7 (± 0.6) h, whereas in group 2 it was 0.5 (± 0.3) h. These values were identical to the healthy volunteers (0.5 (± 0.1) [17] *vs.* 0.5 [16] *vs.* 0.8 (± 0.4) h) [5]. The difference in the parameter values in both of the compared groups was statistically significant (p < 0.0001). In 4 patients from group 2 the maximum concentration of paracetamol was observed in as soon as 15 min. Furthermore, reduced $AUC_{0\text{-}inf}$ values were observed in the patients in both groups: group 1 was 41.6 (± 23.5) and group 2 was 30.3 (± 9.7) mg h/l (p = 0.0862). The healthy volunteers had $AUC_{0\text{-}inf}$ values of 77.8 (± 13.7) [17] *vs.* 44.0 (± 3.7) mg h/l [16].

For patients in groups 1 and 2, the elimination half-lives ($t_{1/2\beta}$) were similar to each other (2.6 (± 1.6) *vs*. 2.3 (± 0.6) h) and to the healthy volunteers (2.7 (± 0.2) h) [16]. The obtained PK differences were not related to the form of the drug because both preparations were tablets. However, Paracetamol , Polfa Łódź contained an additional excipient, sorbitol, which may have caused the differences. Chen et al. [3] proved in their studies that ranitidine C_{max} and $AUC_{0\text{-}inf}$ were decreased by approximately 50% and 45%, respectively, in the presence of sorbitol *vs.* sucrose. Sorbitol also reduced metoprolol C_{max} by 23% in the same study [3]. In our study, we observed similarly reduced $AUC_{0–inf}$ values for paracetamol from the preparation containing sorbitol.

This study also explored the pharmacokinetic parameters of the main metabolite of paracetamol (i.e., the glucuronide adduct). Once again, distinct differences were observed between the analyzed generic formulations. In both groups a distinct increase was observed in C_{max}, t_{max} and $AUC_{0\text{-}inf}$. A larger increase in the studied values was found for the patients from group 2. The mean C_{max} of the glucuronide in patients from group 1 was 13.6 (± 6.5), whereas it was 21.5 (± 5.8) from group 2 (p = 0.0047). For comparison, the mean C_{max} measured in healthy volunteers was 10 (± 2.4) µg/ml [17]. The mean t_{max} of the glucuronide was 2.9 (± 0.7) h in patients from group 1 and 2.4 (± 0.9) h in group 2 (p = 0.3846), whereas in the healthy volunteers it was 2.0 h [17]. The $AUC_{0\text{-}inf}$ values also showed a similar tendency: for group 1 was 93.3 (± 104.2) and for group 2 was 180.1 (± 88.5) (p = 0.0229), while for healthy volunteers was 66 ± 15 µg h/ml [17].

Metabolism was slower in the patients who received the drug from Polfa Łódź. The change was not caused by a hepatic disorder because normal values of hepatic enzymes were found in the patients from this group. There were no significant differences in the t_{max} of the metabolite, but there was a large and significant difference in the C_{max} value. This fact resulted from the difference in the elimination rate of the metabolite, which was significantly lower in group 2. This difference in the elimination rate was suspected of being the main impact on pharmacokinetic profiles of the metabolite in both groups.

According to the Biopharmaceutics Classification System (BCS) criteria, paracetamol is a BCS Class III compound (high solubility and low permeability), although its properties come similar to a BCS Class I. Because of its uncomplicated PK and wide therapeutic index, a biowaiver (a drug product approval without *in vivo* pharmacokinetic bioequivalence study) for immediate release paracetamol solid oral drug products was accepted [1, 7]. However, the interchangeable application of some generic products by patients does not always guarantee their bioequivalence [11, 19]. Proving the comparability of interchangeably applied drugs to patients is particularly important from the clinical point of view. It is known that tests for bioequivalence of most drugs are made on healthy volunteers and, for class I substances according in BCS comparative studies, are only made *in vitro*. Therefore, a comparison of the pharmacokinetics of frequently prescribed generic drugs in patients could explain a wide range of doubts connected with their quality. Patients after gastrectomy are a special group as they receive an oral therapy within the first days after the surgery despite the possible disruption of their absorption ability.

Conclusion

Total gastrectomy affects the pharmacokinetics of paracetamol administered as tablets. Significant differences were observed in some pharmacokinetic parameters of paracetamol from two generic preparations. Therefore, they should only be used interchangeably with caution.

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