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# The pharmacokinetics of oral ketoprofen in patients after gastric resection

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ABSTRACT

*Background:* Total and partial gastric resection may affect the pharmacokinetics of drugs, especially orally administered a few days after surgery. Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) broadly used to treat postoperative pain, including patients after gastric resection. The aim of the research was to analyse the pharmacokinetics (PK) of orally administered ketoprofen in patients after gastrectomy.

*Methods:* The research was carried out on two groups of patients after total (TG; Roux-Y procedure) and partial (PG; Billroth II procedure) gastrectomy. The patients in group TG (n = 15; mean [SD] age 61.86 [14.15] years; and BMI 24.20 [3.73] kg/m$^2$) and group PG (n = 5; mean [SD] age 62.40 [16.80] years; and BMI 23.98 [3.45] kg/m$^2$) received ketoprofen in a single oral dose of 100 mg. The measurement of ketoprofen plasma concentrations was made by means of the HPLC (high performance liquid chromatography) method.

*Results:* The PK parameters in group TG and PG were as follows: maximum plasma concentration ($C_{max}$), 3.42 [0.99] and 4.66 [0.81] mg/l ($p = 0.0220$); area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), 9.12 [2.78] and 9.17 [2.87] mg × h/ml ($p = 0.9734$); area under the first moment curve from zero to the time of infinity ($AUMC_{0-\infty}$), 25.95 [8.52] and 26.53 [11.43] mg × h$^2$/l ($p = 0.9056$); time to reach maximum concentration ($t_{max}$), 0.47 [0.25] and 0.55 [0.27] h ($p = 0.5327$), respectively.

*Conclusions:* Lower concentrations of ketoprofen in patients after gastrectomy suggest that it might be necessary to apply higher dose of the analgesic.


## Introduction

Gastric cancer is the fourth most common malignancy diagnosed worldwide in men and fifth in women, with a high fatality-to-case ratio (70%) [1]. Total gastrectomy (TG) with lymph node resection is a standard procedure for gastric carcinoma treatment. However, for gastric cancer limited to the lower part of the stomach, distal subtotal gastric resection is possible [2]. There are a few methods of reconstruction of the gastrointestinal tract after total stomach resection. The Roux-en-Y procedure is most often applied. It consists in oesophagojejunal anastomosis. The reconstruction method after partial gastrectomy (PG) includes Billroth's operation II, where the stomach is anastomosed to the first loop of the small intestine. Consequences of the surgery such as reduced gastric volume, decreased gastric secretion or accelerated gastric emptying may influence pharmacokinetics, especially of orally administered drugs [3].

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effect. Its mechanism of action is associated with peripheral COX-1 and COX-2 inhibition, which reduces the synthesis of prostaglandins and thromboxane precursors. [4]

Ketoprofen is a weak acid and it belongs to class II in the Biopharmaceutics Classification System (BCS) [5]. After oral administration of 100 mg ketoprofen achieves its maximum plasma concentration ($C_{max}$) of 6.0–14.3 mg/l within 0.45–2.50 h ($t_{max}$) [6]. The absolute bioavailability is not influenced by food

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intake in spite of significant changes in $t_{max}$ and $C_{max}$. The drug is extensively metabolised in the liver and eliminated predominately through the kidneys as a glucuronide [4,7]

Ketoprofen is widely used in mono- and polytherapy of rheumatoid arthritis, cancer or postoperative pain. From the clinical point of view, it is important to investigate how total and partial gastric resection influence the pharmacokinetics of orally administered ketoprofen.

## Materials and methods

### *Reagents*

Ketoprofen and fenoprofen calcium salt were purchased from LGC Standards (Łomianki, Poland). HPLC (high- performance liquid chromatography) grade acetonitrile, methanol, ether *tert*-butyl methyl, orthophosphoric acid from Merck, and $KH_2PO_4$ from POCH S.A. Water used in the mobile phase was deionized, distilled and filtered through a Milipore system before use. Refastin® (batch: 060115, expiration date: 01.2017) was purchased from Medana Pharma SA, Sieradz, 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 (488/15). The subjects of the research were patients who underwent total and partial gastrectomy for gastric cancer between May 2015 and June 2016. The TG and PG was done by Roux-Y and Billroth II procedures, respectively. The patients were included in the study if they had total or partial gastrectomy; if their age was >18 years; if they had no history of allergy to ketoprofen; if they had pain greater than 4–6 (NRS – Numerical Rating Scale: 0–10 chief criteria for exclusion included previous ketoprofen exposure, serious functional cardiac disorders (cardiomiopathy, cardiac insufficiency, ischemic heart disease, myocardial infraction), severe renal and hepatic insufficiency and age under 18 years. The background of all 20 patients enrolled in the research is shown in Table 1.

### *Administration and blood sampling*

The patients received conventional coated tablets (Refastin®) at a single 100 mg dose. 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. Blood samples (2 mL) were collected before drug administration and: 10, 15, 30, minutes, 1–6 h after administration from central venues catheter (*internal jugular vein*). The samples were collected in 6–11 days following the gastrectomy. The measurement of ketoprofen 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 Roda et al. [4].

### *Pharmacokinetics analysis*

The pharmacokinetic parameters were estimated by means of non-compartmental methods, with validated software (Phoenix® WinNonlin® v. 6.4; Certara L.P., USA). The following pharmacokinetic parameters were calculated: maximum plasma concentration ($C_{max}$), the time to maximum plasma concentration ($t_{max}$), volume of distribution ($V_d$/F), half-life in elimination phase ($t_{1/2kel}$), elimination rate constant ($k_{el}$), clearance (CL/F), mean residence time from zero to the time of infinity ($MRT_{0-\infty}$), area under the plasma concentration-time curve from zero to 0.167 h ($AUC_{0-0.167h}$), area under the plasma concentration-time curve from zero to 0.25 h ($AUC_{0-0.25h}$); area under the plasma concentration-time

**Table 1**
Patients' characteristics.

| Parameter | TG<br>S ± SD | PG<br>S ± SD (*p-value* TG *vs.* PG) |
|---|---|---|
| n | 15 | 5 |
| Men/women | 8/7 | 2/3 |
| Age [year] | 61.86 ± 14.15 | 62.40 ± 16.80 (0.9448) |
| Body mass [kg] | 69.47 ± 11.32 | 72.50 ± 12.25 (0.6168) |
| BMI [kg/m$^2$] | 24.20 ± 3.73 | 23.98 ± 3.45 (0.9113) |
| $CL_{cr}$ [ml/min] | 124.0 ± 50.70 | 130.68 ± 60.36 (0.8100) |
| Albumins [g/dl] | 3.33 ± 0.76 | 3.75 ± 0.59 (0.2809) |
| Aspat [U/l] | 23.73 ± 12.21 | 20.00 ± 4.30 (0.5177) |
| Alat [U/l] | 28.27 ± 15.04 | 17.80 ± 4.87 (0.1495) |
| **Tumor's location** | | |
| Cardia | n = 5 | – |
| Body | n = 7 | n = 1 |
| Pylorus | n = 1 | n = 4 |
| **Louren's histological type** | | |
| Intestinal | n = 2 | n = 2 |
| Diffuse | n = 4 | n = 1 |
| Mixed | n = 6 | – |
| GIST | – | n = 2 |
| **Stage** | | |
| G | 1 (n = 1); 2 (n = 2); 3 (n = 8) | 1 (n = 1); 3 (n = 2) |
| T | 1 (n = 1); 1b (n = 1); 3 (n = 7); 4 (n = 1); 4a (n = 1) | 1 (n = 1); 1b (n = 2) |
| N | 0 (n = 5); 1 (n = 1); 2 (n = 2); 3 (n = 2); 3a (n = 1); | 0 (n = 2); 1 (n = 1) |
| M | 0 (n = 11) | 0 (n = 3) |

$CL_{CR}$ – creatinine clearance estimated by the Cockroft-Gault formula; BMI – body mass index; Aspat – aspartate aminotransferase; Alat – alanine aminotransferase; GIST – gastrointestinal stromal tumor; G – graduation; T – primary tumor; N – regional lymph nodes; M – distant metastasis.