

# The pharmacokinetics of oral oxycodone in patients after total gastric resection

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**Abstract. – OBJECTIVE:** Oxycodone is a semi-synthetic opioid with a stronger analgesic effect than morphine and codeine. The efficacy of this opioid in the treatment of postoperative pain has been proved in different groups of patients. The drug has a favourable adverse reaction profile, which encourages doctors and patients to use it more and more widely. The drug is also used in the patients who underwent an abdominal surgery, e.g. stomach resection. Gastrectomy leads to pathophysiological changes within the gastrointestinal tract, which may cause changes in the drug absorption. In consequence this leads to a change in the pharmacokinetics and effect of the drug. The aim of the research was an analysis of the pharmacokinetics of oxycodone from prolonged release tablet in patients after total gastrectomy.

**PATIENTS AND METHODS:** The research was carried out on patients after gastrectomy with Roux-en-Y reconstruction. The patients (n=24; mean [SD] age, 67.6 [9.8] years; weight, 69.1 [13.6] kg; and BMI, 25.2 [4.0] kg/m<sup>2</sup>) received oxycodone in a prolonged release tablet in a single orally administered dose of 10 mg. Blood samples were collected within 12 h after the drug administration. The plasma concentrations of oxycodone and noroxycodone were measured with validated high-pressure liquid chromatography coupled with triple tandem mass spectrometry method.

**RESULTS:** The main pharmacokinetic parameters for oxycodone in men (n = 14) and women (n = 10) were as follows: C<sub>max</sub>, 14.40 (3.76) and 11.54 (6.98) ng/ml (p = 0.2066); AUC<sub>0-∞</sub>, 157.87 (56.89) and 106.44 (61.31) ng·h/ml (p = 0.0460); t<sub>max</sub>, 2.18 (0.58) and 2.15 (0.58) h (p = 0.8008), respectively.

**CONCLUSIONS:** Total gastrectomy did not affect the pharmacokinetics of oxycodone administered in prolonged release tablets, but the exposure to the drug was significantly lower in women.

*Key words:*

Oxycodone, Pharmacokinetics, Prolonged release tablet, Gastrectomy.

## Introduction

Oxycodone is a semi-synthetic opioid, which along with morphine, proves to be an efficacious analgesic in moderate and severe pain. Its efficacy has been proved in numerous laboratory investigations<sup>1-12</sup>. The effects of the drug, i.e. analgesia and sedation, result from its influence on mi-, kappa- and delta receptors in the brain and spinal cord<sup>13</sup>. The strength of the effect of oxycodone results from the rapid penetration of the drug through the blood-brain barrier and reaching three times higher concentrations in the target tissue than in the blood<sup>14</sup>. The analgesic effect of oxycodone is stronger than that of morphine or codeine<sup>15</sup>. Originally oxycodone was available in combination with other drugs such as non-steroidal anti-inflammatory drugs or paracetamol. Nowadays, the drug is available in a separate intravenous form and in immediate and prolonged release tablets. After an oral administration oxycodone has better bioavailability than morphine (60-87% vs. 20-

30%)<sup>16-18</sup>. The time when the drug reaches its maximum concentration ( $t_{max}$ ) is about 3 h for prolonged release tablets<sup>19,20</sup>. The biotransformation of oxycodone into oxymorphone, noroxycodone and noroxymorphone takes place in the intestine and liver, with the involvement of CYP3A4 and CYP2D6 enzymes. The strongest analgesic effect is caused by the parent drug<sup>19,20</sup>. Oxymorphone exhibits high affinity with  $\mu$  receptors, but it remains in very small amounts. Noroxycodone reveals affinity with  $\mu$  receptors, but it has only 17% of the activity of the parent drug. Noroxymorphone reveals affinity with opioid receptors, but it does not penetrate through the blood-brain barrier<sup>18</sup>. After an intravenous administration the elimination half-life of oxycodone is 2-3 h, whereas it is about 8 h for the prolonged release formulation. The availability of both formulations enables an effective analgesic sequential therapy, i.e. a preliminary non-parenteral therapy followed by an oral therapy<sup>18</sup>. Patients tolerate oxycodone relatively well. Oxycodone causes a smaller number of adverse reactions than morphine<sup>4,13</sup> and it causes less postoperative nausea and vomiting (PONV) than tramadol<sup>5,7</sup> or tramadol combined with metamizole<sup>8</sup>. When a smaller intravenous dose of oxycodone was applied to the patients who underwent a surgery of their abdominal cavity, the analgesic effect was faster than when morphine was applied<sup>2</sup>. The availability of the drug in different oral formulations and different doses and its high efficacy encourages physicians and patients to apply it more and more widely. Oxycodone in prolonged release tablets is an interesting therapeutic option in patients after gastrectomy. However, the pathophysiological changes that take place in the alimentary tract after the surgery<sup>21,22</sup> may cause changes in the pharmacokinetics of orally administered drugs<sup>23-29</sup>.

The aim of the research was an analysis of the pharmacokinetics of oxycodone from a prolonged release tablet in patients after total gastrectomy.

## Patients and Methods

### Reagents

Oxycodone, noroxycodone and codeine D3 (internal standard) were purchased from LGC Standards (Dziekanów Leśny, Poland). Acetonitrile and ethyl acetate, both HPLC grade were

supplied by Merck (Warsaw, Poland). Formic acid, ammonium formate, sodium bicarbonate were of analytical reagent grade and bought from Sigma Aldrich (Poznań, Poland). Water used in the mobile phase was deionized, distilled and filtered through a Milipore system before use. OxyContin® (batch: 10072935, expiration date: 03.2015) from Mundipharma Sp. z o.o., Warszawa, Poland.

### Subjects

The research was conducted at the 1<sup>st</sup> 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 June 2013 and December 2013. 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 oxycodone; if they had pain greater than 4 (VAS); 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 oxycodone exposure, partial gastrectomy, serious functional cardiac, hepatic and renal disorders and age under 18 years. The background of all 24 patients enrolled in the research is shown in Table I.

### Drug Administration and Blood Sampling

The patients (n=24) received 1 prolonged release tablet with oxycodone (OxyContin®) at a dose of 10 mg. The drugs were administered in the morning with 200 mL of water and the patients did not have any meals for 60 minutes before and after the administration of the drug. To determine the concentrations of oxycodone, blood samples were collected before drug administration and after it at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 h. Further collection of samples was limited by the necessity to continue the patients' analgesic treatment. The samples were collected in 5-12 days following the gastrectomy. The blood samples were transferred into heparinized tubes and they were centrifuged at 4000 rpm for 10 min at 4°C. Next the

**Table I.** Patients' characteristics.

| Parameter                  | Men<br>(S ± SD)                             | Women<br>(S ± SD)               |
|----------------------------|---------------------------------------------|---------------------------------|
| vn                         | 14                                          | 10                              |
| Age [years]                | 68.2 ± 8.3                                  | 64.3 ± 11.6                     |
| Body mass [kg]             | 74.7 ± 11.5                                 | 61.3 ± 13.0                     |
| BMI [kg/m <sup>2</sup> ]   | 25.9 ± 3.6                                  | 24.2 ± 4.6                      |
| CL <sub>CR</sub> [ml/min]  | 97.9 ± 32.9                                 | 105.2 ± 42.3                    |
| Albumins [g/dl]            | 3.0 ± 0.5                                   | 2.7 ± 0.4                       |
| Aspat [U/l]                | 18.9 ± 8.9                                  | 22.1 ± 14.4                     |
| Alat [U/l]                 | 16.3 ± 7.5                                  | 20.2 ± 9.5                      |
| Tumour location            |                                             |                                 |
| – Cardia                   | 4                                           | 2                               |
| – Body                     | 10                                          | 8                               |
| – Pylorus                  | –                                           | –                               |
| Lauren's histological type |                                             |                                 |
| – Diffuse                  | 5                                           | 3                               |
| – Intestinal               | 6                                           | 3                               |
| – Mixed                    | 2                                           | 3                               |
| – Other                    | 1                                           | 1                               |
| Stage                      |                                             |                                 |
| – G                        | 3 (n=10);<br>2 (n=3);<br>x (n=1)            | 3 (n=7);<br>2 (n=2);<br>1 (n=1) |
| – T                        | 3 (n=8);<br>2 (n=2);<br>1 (n=3);<br>x (n=1) | 4 (n=3);<br>3 (n=5);<br>1 (n=2) |
| – N                        | 3 (n=1);<br>2 (n=4);<br>1 (n=3);<br>x (n=1) | 3 (n=4);<br>2 (n=3)             |
| – M                        | 1 (n=1);<br>x (n=2)                         | 1 (n=1);<br>x (n=1)             |
| Lymph node metastasis      | n=9                                         | n=7                             |

S: arithmetic mean; SD: standard deviation; CL<sub>CR</sub>: creatinine clearance estimated by the Cockcroft-Gault formula; Aspat: aspartate aminotransferase; Alat: alanine aminotransferase; G: graduation; T: primary tumour; N: Regional lymph nodes; M: distant metastasis<sup>30</sup>.

plasma was transferred to propylene tubes and stored at -20°C until analysis. The oxycodone concentrations in the plasma were measured within two months by high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry.

### Assays

Plasma samples were analyzed for oxycodone and noroxycodone by validated method according to European Medicines Agency, HPLC (Agilent 1200 series, Waldbronn, Ger-

many) coupled with triple quadrupole mass spectrometer, equipped with electrospray ionization source (Agilent 6410B, Wilmington, DE, USA). Mass spectrometer was working in MRM mode and two reactions for each compound were recorded. The column used was Poroshell 120 EC-18 3.0 × 75 mm, 2.7 µm (Agilent, USA). Mobile phase were: formate buffer pH 3.2 [A] and 0.1 % formic acid in acetonitrile [B]. The flow rate was 0.5 mL/min. Gradient was programmed as follows: 90% [A] and 10% [B] for 1 min, followed by a linear change to 60% [A] and 40% [B] in 5 min, then 60% [A] and 40% [B] was held for 2 min, then by a linear change to 90% [A] and 10% [B] for 2 min. then 90% [A] and 10% [B]. Extraction of oxycodone and metabolite was performed using liquid-liquid extraction (LLE) at an alkaline pH. Samples were alkalized with 0.15 M/L NaHCO<sub>3</sub>, mixed with acetonitrile and extracted with ethyl acetate. Extraction recovery (% ± SD) was 88.1±4.0 and 87.7±3.8 for oxycodone and noroxycodone respectively. Inter- and intra-day coefficients of variation were less than 10%. The lower limit of quantification was 1 ng/mL for both analytes. Method was linear from 1 to 20 ng/mL. No significant matrix effect was observed.

### Pharmacokinetics Analysis

Pharmacokinetic parameters were estimated by non-compartmental methods using software (Phoenix<sup>TM</sup> WinNonlin® v. 6.3, Certara L.P.). The following pharmacokinetic parameters were calculated for oxycodone and noroxycodone: area under the plasma concentration-time curve from time zero to infinity (AUC<sub>0-∞</sub>), area under the plasma concentration-time curve from zero to the time of last measurable concentration (AUC<sub>0-t</sub>), maximum observed plasma concentration (C<sub>max</sub>), time to first occurrence of C<sub>max</sub> (t<sub>max</sub>), half-life in elimination phase (t<sub>1/2kel</sub>), Cl – clearance; MRT – mean residence time, AUMC<sub>0-t</sub> – area under the first moment curve from zero to the time of last measurable concentration.

### Statistical Analysis

The differences in the values of pharmacokinetic parameters were analyzed by means of Student's *t*-test using PROC TTEST in SAS (SAS Institute Inc. 2002-2010). The SAS System for Windows version 9.3. Cary, NC 27513-2414 USA). The differences that generated *p*-values < 0.05 were considered statistically significant.

## Results

Twenty four subjects (14 men, 10 women; 48-84 years of age) were enrolled in and completed the research (first subject visit: March 1, 2013; last subject visit: November 2, 2013). Their demographics and baseline characteristics are summarized in Table I. In the analysed groups, the mean ages of subjects were similar. Mean subjects' BMI were similar in the two groups. The patients were characterized by the normal hepatic function, except for one patient, whose Alat and Aspat were 197 and 115 [U/l], respectively. In 7 patients the calculated creatinine clearance value was under the limit. All patients showed hypoalbuminaemia, which was probably caused by the neoplastic disease and disordered absorption after the surgery. As required by protocol all the subjects had total gastrectomy. The tumour was located in the proximal (25%), in the middle (75%) part of the stomach. The histological type was classified by Laurén's classification<sup>31</sup>. In the patients 33.3% of tumours were diffuse, 37.5% intestinal, 20.8% mixed type, and 8.4% other. During the course of the research there were no serious or unexpected adverse events.

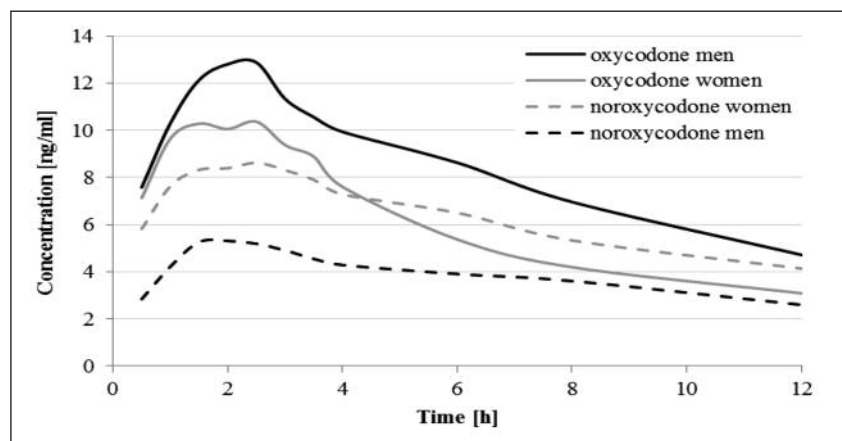
The main aim of our pharmacokinetic study was to characterize the plasma concentration-time course of oxycodone and its active metabolite after a single oral dose in patients after gastrectomy. There were measurable oxycodone and metabolite concentrations within 30 min after dosing and they remained quantifiable at all of the following time points for all the subjects. Figure 1 shows mean plasma concentration-time profile for oxycodone and its metabolite (noroxycodone) respectively in the two subject groups (men and women) during the twelve-hour period after single oral administration of oxycodone. Ta-

bles II presents the results of noncompartmental analysis of the plasma concentration-time data from the study shows the pharmacokinetic values of oxycodone and its metabolite. All the data was expressed as the mean  $\pm$  standard deviation (SD).

There was wide intersubject variability in the pharmacokinetic parameters, as evidenced by the coefficients of variation (CV%) (Table II). Peak oxycodone concentrations in group of men and women were achieved approximately in 2.18 and 2.15 h after the dosing (mean time to the first occurrence of  $C_{\max}$  [ $t_{\max}$ ]), respectively. The mean oxycodone  $C_{\max}$  was similar for both groups ( $14.40 \pm 3.76$  for men and  $11.54 \pm 6.98$  for women ng/ml; Table II). There were no statistically significant differences between the groups under analysis ( $p = 0.2589$ ). However, the mean  $C_{\max}$  for men tended to be higher. The systemic exposure of oxycodone ( $AUC_{0-\infty}$ ) in women was lower than in men ( $106.44 \pm 61.31$  and  $157.87 \pm 56.89$  ng $\times$ h/ml, respectively; Table II). There were statistically significant differences between the groups under analysis ( $p = 0.0460$ ).

There were no statistically significant differences between the two groups under analysis for the following pharmacokinetic parameters of noroxycodone:  $AUC_{0-t}$  ( $p = 0.0696$ ),  $AUC_{0-\infty}$  ( $p = 0.2658$ ), and  $t_{\max}$  ( $p = 0.8008$ ), but there were significant differences observed for  $C_{\max}$  ( $p = 0.0198$ ).

The plasma concentrations of noroxycodone was comparable to or exceeded the parent drug concentration in some patients. The mean noroxycodone/oxycodone ratios for  $AUC_{0-t}$  in men and women were  $0.59 \pm 0.48$  and  $1.67 \pm 1.46$ , respectively. There were statistically significant differences proved for the noroxycodone/oxycodone ratios for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{\max}$  ( $p = 0.0157$ ,  $p = 0.0240$ ,  $p = 0.0151$ , respectively).



**Figure 1.** Mean oxycodone and noroxycodone plasma concentration vs. time profiles following a single 10 mg oral dose of oxycodone in prolonged release tablet.

## Discussion

The manner of effective drug dosage in post-operative patients is difficult due to a wide range of factors which may additionally influence changes in the pharmacokinetics of drugs administered. These factors are both physiological, e.g. age, gender, and pathophysiological, i.e. the factors related with renal failure, motility of the gastrointestinal tract and multipharmacy. All of these factors may cause a significant problem in a safe dosage of opioid analgesics, because there is a high risk of serious adverse reactions (e.g. respiratory depression, bradycardia, hypotonia). Thus, the application of opioid drugs requires that medical staff should be particularly alert. An intravenous administration of the drug guarantees a rapid reaction (including adverse reactions) and the possibility of effective titration. However, on the other hand, due to the short duration of the effect frequent administration is necessary. Therefore, prolonged-release analgesics are an interesting therapeutic option. Due to the impossibility to titrate drugs in this formulation they are not applied during the first days after surgery.

Oxycodone is ranked as a step 3 strong opioid in the World Health Organisation pain ladder. The drug is recommended to treat pain of moderate or severe intensity. Due to the AcroContin™ system the sustained-release formulation guarantees rapid and long release of the therapeutic substance, which enables pain relief during the first hour and stable pain control within 12 hours. At present it is known that a few factors may influence the pharmacokinetics of oxycodone, although not all of them are clinically important. Due to the lower clearance of the drug (30%) in elderly people the exposure to oxycodone is even 80% higher than in younger patients. The AUC and  $C_{max}$  of this opioid were respectively 41% and 35% higher in older women than in young men<sup>17,18,32</sup>. Differences in the pharmacokinetics of oxycodone are also gender-dependent. Andreassen et al<sup>33</sup> observed lower oxycodone plasma concentrations in women. Oxycodone binds with blood albumins in 45%. Therefore, hypoalbuminaemia, which is characteristic of oncological patients, may lead to intensified effect. Gastrectomy is another factor which may change absorption of the drug. In spite of the fact that most

**Table II.** Plasma pharmacokinetic parameters for oxycodone and metabolite (noroxycodone) following a single 10-mg oral dose of oxycodone in prolonged release tablet.

| Pharmacokinetics parameters <sup>a</sup>    | Men (n=14)             | Women (n=10)           | p-value |
|---------------------------------------------|------------------------|------------------------|---------|
| <b>Oxycodone</b>                            |                        |                        |         |
| AUC <sub>0-t</sub> (ng×h/ml)                | 97.53 ± 32.62 (33.4)   | 72.42 ± 49.09 (67.8)   | 0.0885  |
| AUC <sub>0-∞</sub> (ng×h/ml)                | 157.87 ± 56.89 (36.0)  | 106.44 ± 61.31 (57.6)  | 0.0460  |
| t <sub>1/2kel</sub> (h)                     | 8.00 ± 2.77 (34.7)     | 8.22 ± 3.55 (43.3)     | 0.8657  |
| Cl (l/h)                                    | 72.72 ± 31.58 (43.4)   | 132.45 ± 86.27 (65.1)  | 0.0611  |
| C <sub>max</sub> (ng/ml)                    | 14.40 ± 3.76 (26.1)    | 11.54 ± 6.98 (60.5)    | 0.2589  |
| t <sub>max</sub> (h)                        | 2.18 ± 0.58 (26.4)     | 2.15 ± 0.58 (27.0)     | 0.9059  |
| MRT (h)                                     | 11.94 ± 3.69 (30.9)    | 11.42 ± 4.78 (41.9)    | 0.7658  |
| AUMC <sub>0-t</sub> (ng×h <sup>2</sup> /ml) | 495.39 ± 187.87 (37.9) | 340.39 ± 251.46 (73.9) | 0.0973  |
| <b>Noroxycodone</b>                         |                        |                        |         |
| AUC <sub>0-t</sub> (ng×h/ml)                | 48.03 ± 26.47 (55.1)   | 71.79 ± 34.66 (48.3)   | 0.0696  |
| AUC <sub>0-∞</sub> (ng×h/ml)                | 106.60 ± 75.01 (70.4)  | 148.86 ± 106.83 (71.8) | 0.2658  |
| C <sub>max</sub> (ng/ml)                    | 6.12 ± 2.83 (46.2)     | 9.74 ± 4.25 (43.6)     | 0.0198  |
| t <sub>max</sub> (h)                        | 2.39 ± 1.15 (47.9)     | 2.50 ± 0.78 (31.3)     | 0.8008  |
| <b>Noroxycodone/oxycodone<sup>b</sup></b>   |                        |                        |         |
| AUC <sub>0-t</sub> (ng×h/ml)                | 0.59 ± 0.48 (81.5)     | 1.67 ± 1.46 (87.1)     | 0.0157  |
| AUC <sub>0-∞</sub> (ng×h/ml)                | 0.81 ± 0.68 (83.8)     | 2.07 ± 1.79 (86.3)     | 0.0240  |
| C <sub>max</sub> (ng/ml)                    | 0.50 ± 0.37 (73.6)     | 1.34 ± 1.12 (83.7)     | 0.0151  |

CI: confidence interval; AUC<sub>0-t</sub>: area under the plasma concentration-time curve from zero to the time of last measurable concentration; AUC<sub>0-∞</sub>: area under the plasma concentration-time curve from zero to infinity; t<sub>1/2kel</sub>: elimination half-life time; Cl: clearance; C<sub>max</sub>: maximum observed plasma concentration; t<sub>max</sub>: time to reach maximum concentration; MRT: mean residence time; AUMC<sub>0-t</sub>: area under the first moment curve. <sup>a</sup>Arithmetic means ± standard deviations (CV%) are presented with CV (%) in the brackets. <sup>b</sup>Ratio of noroxycodone/oxycodone exposure.

substances are absorbed in the small intestine, total resection of the stomach may influence the processes related with the preparation of a therapeutic substance for absorption, whereas the functional and anatomical changes in the gastrointestinal tract after gastrectomy (lower pH in the stomach lumen, changes in the motoric function, reduced absorption area, lipid absorption disorders)<sup>34</sup> may be decisive to the degree and rate of absorption. In this group of patients reduced drug concentration has also been proved for cyclosporine<sup>26</sup>, imatinib<sup>24</sup>, propranolol<sup>28</sup> and cefcapene<sup>35</sup>. In the previous study Szałek et al<sup>25,36</sup> found lower mean  $C_{\max}$  values for paracetamol and tramadol in patients after gastrectomy than in healthy volunteers.

This study analyzes the pharmacokinetic parameters of oxycodone and its active metabolite (noroxycodone) after single administration of a prolonged-release tablet to patients after total gastrectomy. A dose of 10 mg of oxycodone was applied, because the initial dose applied to a patient who has not received opioids yet is usually 10 mg. Patients received the drug on an empty stomach although prolonged-release tablets may be administered during meals or independent of them, drinking a sufficient amount of liquid afterwards. The patients were instructed not to break or chew OxyContin tablets, because the application of broken, chewed or crushed tablets leads to the absorption of a potentially lethal dose of oxycodone. OxyContin is not recommended to be used within 12 to 24 hours after the surgery<sup>37</sup>. Therefore, the patients received the drug in the treatment of post-operative pain only after 5-12 days following the gastrectomy. The potential variation in pH in the gastrointestinal tract after gastrectomy should not affect the release of the drug, because the release of oxycodone from OxyContin tablets is independent of pH<sup>37</sup>.

The authors compared the obtained results with the data from reference publications. In the analyzed patients  $t_{\max}$  is slightly lower in comparison with the healthy volunteers (2.2 vs. 3 h)<sup>37,38</sup>. The change can be caused by reduced gastric emptying time in patients after gastrectomy<sup>39</sup>. In comparison with the healthy volunteers the patients from the group under analysis exhibited similar values of  $C_{\max}$  (12.97 vs. 10.6 ng/ml)<sup>37</sup>. Slightly higher concentrations of the drug in the patients under analysis may have been caused by the concomitant hypoalbuminaemia and age. 14 out of the 24 patients were aged over 65. In view of the information that the concentrations of oxycodone in women is low-

er than in men<sup>33</sup> the authors compared the obtained pharmacokinetic parameters of the drug for both sexes. In the conducted study the mean value of  $C_{\max}$  for women is approximately 20% lower than in men, but it had no clinical meaning. No statistically significant differences for most pharmacokinetic parameters were observed between the men and women under analysis (Table II), but significant differences were noted for the  $AUC_{0-\infty}$  value. Therefore, women may have greater demand for analgesic therapy. This demand was not observed in the research, but this may have resulted from the small number of women. The authors of numerous studies suggest that severe liver disease may influence the pharmacokinetics of oxycodone<sup>40,41</sup>. Our data set included liver biochemistry (Aspat and Alat). In the group of patients under analysis one patient had very high Aspat and Alat values, i.e. 197 and 115 [U/I], respectively. However, the maximum oxycodone concentration in this patient (5.0 ng/mL) did not diverge from the values obtained from the other patients. The resulting high interindividual variability in the PK parameters of the patients under investigation is consistent with the results reported in the reference publications<sup>16,37,42</sup>.

This study also provides the calculations of pharmacokinetic parameters for the main metabolite of oxycodone, i.e. noroxycodone, which is produced by CYP3A4<sup>42</sup>. Andreassen et al<sup>33</sup> report that the noroxycodone/oxycodone ratio may be 31% lower in men due to the lower activity of this enzyme than in women and due to its slower clearance in some drugs metabolized by CYP3A4<sup>43-46</sup>. In our study the noroxycodone/oxycodone ratios for  $C_{\max}$  and  $AUC_{0-t}$  were significantly lower in the men by about 63% and 65%, respectively.  $C_{\max}$  for noroxycodone was significantly higher in the women (Table II), which may have been caused by reduced renal clearance and accumulation of the metabolite, which is mainly excreted through the kidneys. The high interindividual variability in the noroxycodone/oxycodone ratios may have been caused by the BMI, albumin concentration, drugs applied and renal clearance.

The values obtained in the research are pilot results. It is necessary to continue the research in order to precisely determine the influence of gastrectomy on the pharmacokinetics of oxycodone. Nevertheless, the surgery does not seem to influence the concentration of this opioid. This knowledge considerably facilitates dosage of the drug burdened with serious adverse reactions.

## Conclusions

Total gastrectomy did not affect the pharmacokinetics of oxycodone administered in prolonged release tablets, but the exposure to the drug was significantly lower in the women. Therefore, women may have greater demand for analgesic therapy.

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## Conflict of interest

The Authors declare that there are no conflicts of interest.

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