Acta Poloniae Pharmaceutica – Drug Research, Vol. 79 No. 3 pp. 401-407, 2022
DOI: 10.32383/appdr/152216
Received 25 May 2022, Received in revised form 16 June 2022, Accepted 19 July 2022

ISSN 2353-5288
Polish Pharmaceutical Society

PHARMACOLOGY

THE METABOLIC CONVERSION OF METAMIZOLE (DIPYRONE) IN MALE AND FEMALE PATIENTS AFTER TOTAL GASTRECTOMY FOR STOMACH CANCER

EDYTA SZAŁEK[1], ARKADIUSZ SPYCHAŁA[2]*, PATRYCJA KOZANECKA[1], HANNA URJASZ[1], TOMASZ GRABOWSKI[3,4], ANNA WOLC[5,6], ELŻBIETA DŁUGOSZ[2], WITOLD KYCLER[2], EDMUND GRZEŚKOWIAK[1], and AGNIESZKA KARBOWNIK[1]

[1]Department of Clinical Pharmacy and Biopharmacy, Karol Marcinkowski University of Medical Sciences, Rokietnicka 3, 61-861 Poznań, Poland
[2]Gastrointestinal Surgical Oncology Department, Wielkopolska Cancer Centre, Garbary 15, 61-866 Poznań, Poland
[3]Polpharma Biologics, Trzy lipy 3, 80-172 Gdańsk, Poland
[4]Department of Inorganic Chemistry, Faculty of Pharmacy, Medical University of Gdańsk, 80-210 Gdańsk, Poland
[5]Department of Animal Science, Iowa State University, 239E Kildee Hall, Ames, IA 50011, USA
[6]Hy-Line International, 2583 240th Street, Dallas Center, IA 50063, USA

Abstract: Metamizole (dipyrone) is a non-opioid analgesic drug used to treat postoperative pain. The pharmacological activity of metamizole is determined by two metabolites: N-methyl-4-aminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA). The conversion of metamizole to metabolites may be impaired in patients who underwent total gastrectomy due to pathophysiological lesions. Moreover, there may be differences in the metabolism of metamizole between men and women. The aim of the research was to analyze the pharmacokinetics of 4-MAA and 4-AA in patients after total gastrectomy, allowing for their sex. The research was carried out on patients with Roux-en-Y reconstruction after gastrectomy. Male (n = 25) and female patients (n = 13) received a single oral dose of 500 mg of metamizole. The plasma concentrations of 4-MAA and 4-AA were measured with high-pressure liquid chromatography with UV detection. The $AUC_{0\text{-}t}$ of 4-MAA in the female group was higher than in the male group (22.90 ± 17.65 *vs.* 15.37 ± 15.12 μg×h/mL), but the difference was not statistically significant (p = 0.0561). The $AUC_{4\text{-}AA}/AUC_{4\text{-}MAA}$ and $C_{max,4\text{-}AA}/C_{max,4\text{-}MAA}$ ratios in the male and female groups were comparable (p = 0.2464 and p = 0.7441, respectively). The greater exposure of the women after gastrectomy to the more potent metabolite 4-MAA may indicate that the analgesic therapy was more effective than in the men. The lack of statistically significant differences in the values of $C_{max,4\text{-}AA}/C_{max,4\text{-}MAA}$ and $AUC_{4\text{-}AA}/AUC_{4\text{-}MAA}$ indirectly indicates that there were no sex-dependent changes in the demethylation of metamizole.

Keywords: metamizole, 4-MAA, 4-AA, metabolism, gastrectomy, sex

Metamizole (dipyrone) is a non-opioid analgesic that relieves fever and muscle spasms. It has been available on the market for over 100 years, however, in the United States, the United Kingdom, Japan, Australia, Sweden, and Iran, the drug was withdrawn from treatment (1). The drug can be purchased in the form of tablets, suppositories, and injections (i.m., i.v.). Metamizole is used to treat acute and chronic pain, including postoperative pain (2, 3). According to the recommendations of the European Medicines Agency (EMA) published in 2019, the maximum single and daily oral doses administered to patients aged over 15 years are 1000 mg and 4000 mg, respectively. When administered intramuscularly or intravenously, the dosage should not exceed 5000 mg/24 h. The drug should not be administered during pregnancy, especially in the last trimester because of its adverse effects on the kidneys and blood circulation in the fetus (4).

Metamizole is a prodrug whose concentrations in the blood and urine are not detectable after oral administration. When the drug is ingested

* Corresponding author: e-mail: spychala@me.com

orally, in the gastrointestinal tract it rapidly undergoes non-enzymatic hydrolysis into its main active metabolite, i.e. N-methyl-4-aminoantipyrine (4-MAA). Next, 4-MAA can undergo two processes: demethylated into active 4-aminoantipyrine (4-AA) or oxidation to N-formyl-aminoantipyrine (4-FAA). On the other hand, 4-AA is converted into N-acetyl-4-aminoantipyrine (4-AAA) by means of N-acetyltransferase type 2 (NAT2). Undergoes oxidation and gives the inactive metabolite N-formyl-4-aminoantipyrine (4-FAA). 4-AA is also acetylated into inactive N-acetyl-4-aminoantipyrine (4-AAA) (5). Bachmann et al. showed that the following isoenzymes are involved in the process of 4-MAA demethylation: CYP3A4, 2B6, 2C8, and 2C9 (6).

The rate of 4-AA acetylation into 4-AAA, which affects the risk of hypersensitivity to metamizole, especially the risk of developing anaphylaxis (7), is slower in NAT2-slow acetylators, in drinkers and in men, whereas 4-MAA oxidation is slower in carriers of the CYP2C19*2 allele (7, 8). The influence of sex on metamizole metabolism still has not been determined. However, the differences in the pharmacokinetics of individual metamizole metabolites observed in different groups of patients did not affect the individualization of the drug dosage. The mechanism of action of metamizole is multidirectional. It includes the inhibition of COX-1 and COX-2 as well as COX-independent pathways (including interaction with the adrenergic nervous system, modulation of potassium channels, stimulation of the endogenous opioid system, and interaction with endocannabinoid/endovanilloid system) (5, 9). The most serious adverse effect of metamizole is agranulocytosis, the risk of which may be higher in some populations (e.g. the British, Irish, and Scandinavians) (10). Additionally, Bachmann et al. show that N-demethylation of 4-MAA may also take place in the precursors of granulocytes and granulocytes in the bone marrow and the formation of free radicals by myeloperoxidase, which may be associated with the myelotoxicity of metamizole. Moreover, Bachmann et al. (11) showed that metamizole is a broad inducer of CYP, due to the activity of 4-MAA, as well as an inhibitor of CYP1A2.

Researchers have already proved the influence of gastrectomy on the pharmacokinetics of analgesics in several studies (12-15). Patients after gastrectomy suffer from pathophysiological changes in the gastrointestinal tract, which may affect the pharmacokinetics of orally administered drugs and they include a reduced surface of the stomach, gastrointestinal motility disorders, reduced gastric emptying rate (GER), impaired lipid absorption, increased pH of gastric juice and changes in the intestinal flora (16). The activity of drug-metabolizing enzymes may also be altered (17). As metamizole needs to be converted into active metabolites in the lumen of the gastrointestinal tract, it seems important to determine its metabolism in patients with gastric homeostasis disorders caused by gastrectomy. Therefore, the main aim of the study was to assess the influence of total gastrectomy on the pharmacokinetics (PK) of two active metabolites of metamizole, i.e. 4-MAA and 4-AA, in male and female patients receiving the analgesic to treat postoperative pain.

EXPERIMENTAL

Chemicals

4-MAA (CAS 519-98-2), 4-AA (CAS 83-07-8) were purchased from LGC Standards (Łomianki, Poland) and Internal Standard – Phenacetin (CAS 62-44-2) from Merck. HPLC (high-performance liquid chromatography) mobile phase methanol (CAS 67-56-1) and glacial acetic acid (CAS 64-19-7) from Merck. Water used in the mobile phase was deionized, distilled, and filtered through a Millipore system Direct Q3 before use. The extractive mixture consists of ethyl acetate (CAS 141-78-6) and chloroform (CAS 67-66-3) from Merck.

Subjects

The research was conducted at the Gastrointestinal Surgical Oncology Department, Wielkopolska Cancer Center, Poznan and the Department of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznan, Poland with the approval from the Bioethics Committee, University of Medical Sciences, Poznan, Poland (993/18). The subjects of the research were patients who underwent total gastrectomy between October 2018 and February 2020. The patients were included in the study if they met the following criteria: total gastrectomy; age > 18 years; no history of allergy to metamizole; pain ≤ 4 (NRS – Numerical Rating Scale: 0–10). The chief criteria for exclusion included previous metamizole exposure, partial gastrectomy, serious functional cardiac disorders, severe renal and hepatic insufficiency, and age under 18 years. The baseline characteristics of all patients enrolled in the study are shown in Table 1. All patients provided written consent to participate in the study.

Table 1. Patients' characteristics

Parameter	Males (S±SD)	Females (S±SD)
n	25	13
Age [years]	65.68 ± 12.44	60.92 ± 11.88
Body mass [kg]	82.38 ± 15.75	62.31 ± 8.37
BMI [kg/m^2]	26.62 ± 4.68	23.24 ± 3.78
CL_{CR} [mL/min]	99.24 ± 29.95	116.85 ± 39.11
Albumins [g/dl]	3.21 ± 0.51	3.10 ± 0.41
Aspat [U/I]	34.08 ± 17.48	21.72 ± 9.47
Alat [U/I]	30.5 ± 21.51	24.17 ± 16.11
Lauren's histological type		
Diffuse	2	7
Intestinal	11	3
Mixed	8	2
Other	4	1
Lymph node metastasis	n = 10	n = 9

S, arithmetic mean; SD, standard deviation; CL_{CR}, creatinine clearance estimated by the Cockroft-Gault formula; AspAT, aspartate aminotransferase; AlAT, alanine aminotransferase;

Administration and blood sampling

The patients (n = 38) received 1 tablet with metamizole (Pyralgina®, batch number 70818, expiration date: 31.08.2021, Polpharma S.A., Starogard Gdański, Poland) at a dose of 500 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. Blood samples (2 mL) were collected before drug administration (0) and after it at the following times: 0.5; 1; 1,5; 2; 2,5; 3; 4; 6; 8; 12; and 24 h after administration. The blood samples were transferred into heparinized tubes and centrifuged at 2880 g for 10 min at 4°C. Next, the plasma was transferred to propylene tubes and stored at − 20°C until analysis (max. 3 months). The samples were collected in 7-10 days following the gastrectomy.

Assays

The concentrations of 4-MAA and 4-AA in plasma were assayed using the high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection (18). Phenacetin was used as the internal standard (IS). Samples were analyzed on Alliance 2695 HPLC UV-Vis System with Empower Software No 1154 Waters Corporation. The separation was done using 29 min gradient method. Phase A was 0.2% acetic acid in water, phase C was ultrapure water, and phase D was methanol. The gradient started at 100% C and decreased linearly to 11% C, 1% A and 88% D in 15 min, then changed to 1% D, 99% C and on 25 min it returned to starting condition for column equilibration. The flow rate was 1 mL/min. Chromatography was run on Waters Symmetry C8, 5 µm, 4.6 mm x 250 mm analytical column. The internal standard solution was 30 µg/mL phenacetin in methanol. The retention time of 4-MAA, 4-AA, and phenacetin were 12, 13, and 16 min, respectively. The column temperature was maintained at 25°C, the UV detection wavelength was set at 254 nm and the injection volume was 10 µL.

Pharmacokinetics analysis

Pharmacokinetic parameters were estimated using software (PhoenixTM WinNonlin® v. 8.0, Certara L.P., Princeton, New Jersey, USA). The following pharmacokinetic parameters were calculated for 4-MAA and 4-AA: area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), 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}), time to first occurrence of C_{max} (t_{max}), half-life in elimination phase ($t_{1/2kel}$), k_{el} – elimination constant, $MRT_{0-\infty}$ – mean residence time from zero to the time of last measurable concentration, $AUMC_{0-t}$ – area under the first moment curve from zero to the time of last measurable concentration. The maximum plasma concentration (C_{max}) and the time to reach the C_{max} (t_{max}) were obtained directly from the measured values. All of the abovementioned parameters underwent statistical analysis. The A-MAA and 4-AA for C_{max}, AUC_{0-t},

and $AUC_{0-\infty}$ parameters were not calculated for dose (4-MAA and 4-AA are metabolites of metamizole).

Statistical analysis

The normality of the distribution of pharmacokinetic parameters was tested with the Shapiro-Wilk test in PROC CAPABILITY in SAS (SAS Institute Inc. 2002-2012. The SAS System for Windows version 9.4. Cary, NC 27513-2414 USA). With very few exceptions the data significantly deviated from normality therefore a non-parametric Wilcoxon exact test in PROC NPAR1WAY was used to evaluate differences in values between the groups. The differences that generated p-values <0.05 were considered statistically significant. Differences in patient characteristics between males and females were evaluated with test for body mass, BMI and CL_{CR} and with a non-parametric Wilcoxon exact test for age, albumins, Aspat, and Alat according to the results of normality of the distribution test.

RESULTS

The HPLC method was validated according to the current guidelines of the European Medicines Agency (EMA) concerning bioanalytical method

Table 2. Plasma pharmacokinetic parameters for 4-MAA and 4-AA, following a single 500-mg oral dose of metamizole.

pharmacokinetics parameters[a]	men (n = 25)	women (n = 13)	p-value
4-MAA			
AUC_{0-t} (μg×h/mL)	15.37 ± 15.12 (98.4)	22.90 ± 17.65 (77.1)	0.0561
$AUC_{0-¥}$ (μg×h/mL)	18.30 ± 17.26 (94.3)	25.59 ± 20.71 (80.9)	0.0873
$t_{1/2kel}$ (h)	5.81 ± 4.31 (74.1)	5.95 ± 4.53 (76.1)	0.5226
k_{el} (l/h)	0.19 ± 0.13 (68.4)	0.16 ± 0.09 (56.3)	0.5153
C_{max} (μg/mL)	2.84 ± 2.77 (97.5)	3.27 ± 1.68 (51.4)	0.2937
t_{max} (h)	1.76 ± 1.02 (58.0)	2.00 ± 0.91 (45.5)	0.2224
$MRT_{0-¥}$ (h)	8.72 ± 5.84 (67.0)	8.32 ± 3.78 (45.4)	0.4743
$AUMC_{0-t}$ (μg×h²/mL)	92.81 ± 127.35 (137.2)	152.69 ± 170.62 (111.7)	0.0454
4-AA			
AUC_{0-t} (μg×h/mL)	6.68 ± 6.85 (102.5)	6.28 ± 4.06 (64.6)	0.6203
$AUC_{0-¥}$ (μg×h/mL)	8.92 ± 7.87 (88.2)	7.73 ± 4.51 (58.3)	0.9369
C_{max} (μg/mL)	0.86 ± 1.12 (130.2)	1.08 ± 0.84 (77.8)	0.3306
t_{max} (h)	3.35 ± 4.63 (138.2)	2.31 ± 1.74 (75.3)	0.3201
4-AA/4-MAA			
C_{max}	0.43 ± 0.60 (139.5)	0.64 ± 1.01 (157.8)	0.7441
AUC_{0-t}	0.62 ± 0.50 (80.6)	0.40 ± 0.35 (87.5)	0.2464

AUC_{0-t} – area under the plasma concentration-time curve from zero to the time of last measurable concentration; $AUC_{0-¥}$ – area under the plasma concentration-time curve from zero to infinity; $t_{1/2kel}$ – half-life time; k_{el} – elimination constant; C_{max} – maximum observed plasma concentration; t_{max} – time to reach maximum concentration; MRT – mean residence time; $AUMC_{0-t}$ – area under the first moment curve.

[a] arithmetic means ±standard deviations (CV%) are presented with CV (%) in the brackets.

validation. The lower limit of quantification (LLOQ) for 4-MAA and 4-AA was 0.1 μg/mL and 0.05 μg/mL, respectively. Intra- and inter-day precision and accuracy of the low quality controls (QC), medium QC and high QC were well within the acceptable limit of 15% coefficient of variation (CV%). The calibration curve for 4-MAA was linear within the range of 0.1-13.5 μg/mL (r = 0.999) and for 4-AA within the range of 0.05-3.0 μg/mL (r = 0.999). The high precision (coefficient of variation, CV < 10%) and accuracy (%bias ≤ 13%) for 4-MAA and 4-AA of the applied methodology was obtained.

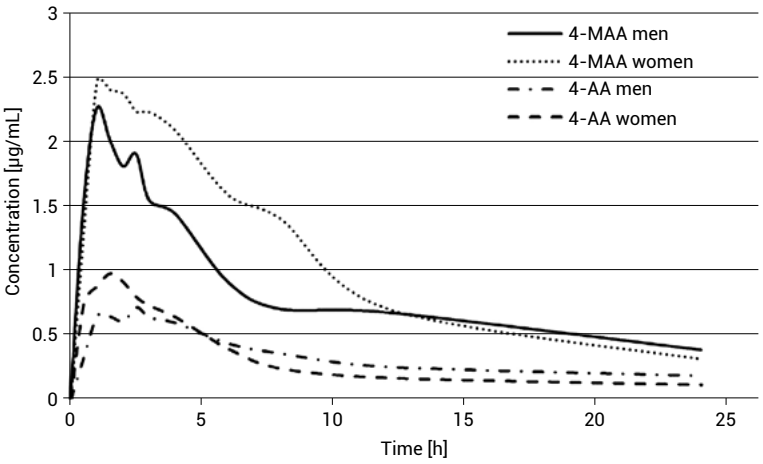

Figure 1. 4-MAA and 4-AA plasma concentration–time profiles following a single oral dose of metamizole 500 mg in male and female patients after gastrectomy (arithmetic means)

The anthropometric and biochemical parameters of analyzed patients are shown in Table 1. The analysed groups were comparable in BMI (p = 0.0651), CL_{CR} (p = 0.1414), albumins (p = 0.3884), Aspat (p = 0.0917), and Alat (p = 0.2928), but males tended to be older (p = 0.0418), and with higher body mass (p = <0.001). Pharmacokinetic parameters for both active metabolites of metamizole 4-MAA and 4-AA were estimated by non-compartmental methods (Table 2). There were no significant differences among the groups for all PK parameters of 4-MAA and 4-AA (p > 0.05).

The arithmetic means of plasma concentrations for 4-MAA and 4-AA after oral administration of metamizole (500 mg) to the groups are shown in Figure 1.

DISCUSSION AND CONCLUSION

The incidence of gastric cancer is gradually decreasing, but it is still one of the most common cancers in the world. This downward trend may have been caused by higher hygiene standards, higher consumption of fresh fruit and vegetables, and the eradication of Helicobacter pylori bacteria (19). Despite the development of numerous cancer treatment methods, gastric resection remains the only chance for a full recovery. Gastrectomy requires analgesic treatment. Oral medications, including metamizole, are used a few days after gastrectomy for postoperative analgesia. Metamizole is an analgesic that effectively alleviates pain, especially in the viscera. The drug is also appreciated as a spasmolytic. It rarely causes adverse reactions. The risk of agranulocytosis is not as high as initially estimated. It is currently believed that metamizole has a relatively positive risk-benefit ratio, especially in comparison with other non-opioid analgesics (20, 21). Additionally, Kötter et al. in a meta-analysis showed that in the analyzed randomized trials, no cases of agranulocytosis were recorded. Moreover, the International Agranulocytosis and Aplastic Anemia Study reported only 9 cases per million per year (22).

The pharmacological activity of metamizole is determined by two metabolites (mainly 4-MAA and to a lesser extent 4-AA), into which the parent drug is transformed within the gastrointestinal tract. Gastric resection may disturb the metabolic conversion of the analgesic. The pharmacokinetics and ultimately the effect of the drug may also be influenced by the sex of the patient, as was observed in tests on various commonly used drugs, including statins and beta-blockers (23). For example, tramadol and oxycodone are analgesics whose PK differs between men and women (13). Therefore, this study allows for the influence of the patient's sex on the pharmacokinetics of both metamizole metabolites.

After the oral administration of 500 mg of metamizole the maximum concentrations of both of its active metabolites in the male ($C_{max,4\text{-}MAA}$ = 2.84 ± 2.77, $C_{max,4\text{-}AA}$ = 0.86 ± 1.12 μg/mL) and female patients ($C_{max,4\text{-}MAA}$ = 3.27 ± 1.68, $C_{max,4\text{-}AA}$ = 1.08 ± 0.84 μg/mL) were lower than in the healthy volunteers, who received an oral dose of 480 mg of metamizole ($C_{max,4\text{-}MAA}$ = 4.2, $C_{max,4\text{-}AA}$ = 1.4 μg/mL) (24). This may indicate that metamizole had a weaker analgesic effect on the patients after gastrectomy. Therefore, the

pharmacodynamic effect of the drug should be assessed in further research. In earlier studies, the authors of this article also observed reduced concentrations of paracetamol and ketoprofen in patients after gastric resection (12, 15). The t_{max} values of both metabolites were comparable in patients after gastrectomy (Table 2) and in healthy subjects ($t_{max,4\text{-}MAA}$ = 1.3-2.0 h; $t_{max,4\text{-}AA}$ = 1.9-4.6 h) (25). Therefore, the time of the analgesic effect should not change.

In the group under study, where the patient's sex was the factor compared, the mean C_{max} value of both active metabolites in the women was higher than in the men (Table 2). However, these differences were not statistically significant due to the high value of the coefficient of variation. The mean $AUC_{0\text{-}t}$ values of 4-MAA in both groups were 22.9 ± 17.7 *vs*. 15.4 ± 15.1– they were noticeably higher in the female group. But these differences were not statistically significant (p = 0.0561). There were no differences between the sexes in the PK parameters of the weaker metabolite, i.e. 4-AA. Additionally, the $AUC_{4\text{-}AA}/AUC_{4\text{-}MAA}$ values noted in the women (40%) and men (62%) after gastrectomy were higher than in the healthy subjects (25%) (26). This suggests the possible influence of clinical consequences of the surgery alone on the activity of CYP2C19 and metamizole metabolism. According to Ishii et al., after gastrectomy, the increase in the activity of e.g. CYP3A is observed and it is probably caused by an increase in the nuclear translocation of pregnane X receptor, which is triggered by an increase in lithocholic acid-producing bacteria (17).

To sum up, the analysis of data provided in reference publications proved that the patients after total gastrectomy were characterized by lower exposure to the active metamizole metabolites, determined by the C_{max} values, than the healthy subjects. This might suggest the need to verify the dosage of metamizole in a larger group of these patients. The exposure to the active metabolite 4-MAA in the group of women after gastrectomy was noticeably higher – this may indicate that the analgesic therapy was more effective than in the male group. The lack of statistically significant differences in the values of $C_{max,4\text{-}AA}/C_{max,4\text{-}MAA}$ and $AUC_{4\text{-}AA}/AUC_{4\text{-}MAA}$ indirectly indicates that there were no sex-dependent changes in the demethylation of metamizole among the patients after total gastrectomy.

The presented study is a pilot study and has some limitations: it should be continued in a larger group of patients compared to the control group. Additionally, free fractions of the metabolites and the concentrations of inactive metabolites should also be measured. Pain intensity was not assessed in the study, as each patient additionally received 1000 mg paracetamol. Additionally, more men than women were enrolled in the study, which was related to the number of cases and qualification for the procedure.

Conflict of interest

The authors declare no conflict of interest.

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