



## ORIGINAL PAPER

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# Intravenous paracetamol vs. ketoprofen for pain management after the abdominal aortic surgery – pharmacokinetics and therapeutics

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### ABSTRACT

**Introduction.** Acute postoperative pain continues to be a dilemma to patients and clinicians.

**Aim.** To define the efficacy, tolerability and pharmacokinetics of paracetamol and ketoprofen in patients after the abdominal aortic surgery. Setting and design in University hospital – intensive therapy unit (clinical part), clinical pharmacy and biopharmacy unit (biochemical part), and pharmaceutical company (statistical part). Prospective randomized study.

**Material and Methods.** 40 adult patients (50–84 years) undergoing abdominal aortic surgery were randomized equally into two groups. After extubation the patients in group 1 (G1) were administered a 1 g paracetamol infusion, and in group 2 (G2) – a 100 mg ketoprofen infusion, both within 15 minutes. All the patients received an epidural infusion of bupivacaine with fentanyl. The following parameters were recorded: mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), plasma concentration of paracetamol and ketoprofen. Postoperative pain was assessed with the visual analogue scale (VAS).

**Results.** The mean values of the MAP, HR and CVP were within normal limits in the both groups. No significant differences were noticed in the assessment of postoperative pain and total use of an opioid. The mean therapeutic plasma concentration of paracetamol and ketoprofen remained up to 180 minutes and up to 120 minutes, respectively.

**Conclusions.** The study enabled us to conclude that intravenous paracetamol as well as ketoprofen have good effectiveness and tolerability. There is no need to modify dosage of these drugs to elderly patients. After paracetamol infusion the therapeutic plasma concentration remains longer than after the ketoprofen infusion.

**Keywords:** paracetamol, ketoprofen, postoperative pain, pharmacokinetics.

## Introduction

In spite of considerable progress in pain therapy the effective treatment of acute postoperative pain continues to be a dilemma to patients and clinicians. It is estimated that in about two thirds of patients the alle-

viation of postoperative pain is insufficient and pain becomes the cause of unnecessary suffering [1].

The intensive development of pharmacology enabled the introduction of multimodal analgesia. This is a method of analgesic treatment which consists of connecting different techniques of local anaesthesia

with combination pharmacotherapy. It enables both the use of the additive and synergistic effects of individual drugs, considerable reduction in the dosage of those drugs as well as reduction in the frequency of adverse reactions occurrence [2].

In view of those facts, apart from opioids the clinical practice of postoperative pain treatment also applies non-steroidal anti-inflammatory drugs and paracetamol, the latter of which is widely used in outpatient medical practice. At present, thanks to the new intravenous formula it can also be applied to patients after surgeries. The recommendations for postoperative pain treatment after the surgeries with considerable tissue trauma include intravenous patient controlled analgesia (PCA) and the techniques of regional analgesia, such as continuous epidural analgesia [3].

Intravenous paracetamol (also known as acetaminophen) is an analgesic and antipyretic substance, recommended worldwide as a first-line agent for the treatment of pain and fever in adults and children [4]. The availability of intravenous paracetamol (Perfalgan®, Ofirmev®) has greatly extended the use of this drug in the intensive care settings [5].

Ketoprofen is a non-steroidal anti-inflammatory drug with a strong anti-inflammatory, analgesic and antipyretic effect. In chemical terms it is a 2-(3-benzoylphenyl)-propionic acid, available in the intravenous, intramuscular, oral, rectal and percutaneous form [6]. The intravenous form is the most suitable and practical for administration in the postoperative period. Ketoprofen was synthesised by the chemists from Rhone-Poulenc company in 1967, 3 years after its prototype – ibuprofen [7]. Intravenous ketoprofen is chiefly used for short-term treatment of postoperative pain.

In spite of the fact that intravenous paracetamol is more and more widely applied in clinical practice, the data comparing the clinical efficacy, safety and clinical pharmacokinetics of this drug with other analgesics are limited [8]. Vascular surgery patients present a formidable challenge to the practising intensivist. These patients are often at an advanced age and carry significant cardiac, respiratory, and renal co-morbidities [9]. Among different types of non-cardiac surgery, peripheral vascular surgery is likely to have the highest cardiac morbidity and overall mortality.

The purpose of this study was to define the clinical tolerability of paracetamol and ketoprofen in patients after the abdominal aortic surgery, the dosage profile of these drugs to this population of patients and the clinical pharmacokinetics with influence on the postoperative analgesic effect.

## Material and Methods

After obtaining institutional Bioethics Committee approval, this research was conducted in the intensive care unit (ICU) of the University Hospital. Written informed consent was obtained from all included patients. Forty patients (50–84 years old, 7 females, 33 males, ASA 3–4) qualified for reconstruction of the abdominal part of the aorta due to aortic aneurysms or chronic aortoiliac occlusive disease were included into the study. The patients were randomly divided into two groups. After the extubation group I (G1) received an intravenous infusion of paracetamol (Perfalgan®, Bristol-Myers Squibb, Anagni, Italy) and group II (G2) received ketoprofen (Ketonal®, Lek, Ljubljana, Slovenia). The patients with liver and renal dysfunction or with a documented allergy to the medication were excluded from the survey. All the patients received 10–20 mg of temazepam 60 minutes before the surgery. Anaesthesia was induced intravenously by infusion of etomidate 0.1 mg/kg and fentanyl 3 µg/kg, with muscle relaxation induced by pancuronium 0.1 mg/kg. Then the patients were intubated and received one dose of fentanyl 0.1 mg in 10 ml 0.9% NaCl and constant infusion of 0.125% bupivacaine 5 ml/h into the lumbar epidural space (L2-L3 or L3-L4) through a catheter (16G) inserted to all the patients the day before anaesthesia.

Anaesthesia was maintained with up to 1.5 MAC of volatile anaesthetic isoflurane in a mixture of oxygen and air (FiO<sub>2</sub> 0.4) in a low-flow circuit (fresh gas flow of 1 l/min), with fentanyl in boluses of 0.1 mg and pancuronium 0.03 mg/kg and with a constant infusion of bupivacaine into the epidural space.

Just after the operation the patients were admitted into the ICU. After the extubation G1 (20 patients) received an intravenous infusion of paracetamol (1 g within 15 minutes) and G2 received an intravenous infusion of ketoprofen (100 mg in 100 ml of 0.9% NaCl within 15 minutes). Apart from the above-mentioned medications the patients in both groups were applied a constant infusion of 0.125% bupivacaine with fentanyl 2 µg/ml into the epidural space at a rate of 5–8 ml/h. An opioid (pethidine) was also applied in the patient-controlled anaesthesia (PCA) system. This protocol has been applicable according to therapeutic standard in the department.

All the patients were constantly monitored for the mean arterial pressure (MAP), heart rate (HR) and central venous pressure (CVP). In G1 the concentration of paracetamol and in G2 the concentration of ketoprofen were measured. All the measurements listed above

were made before the infusion of the medications under study (paracetamol and ketoprofen) after extubation – T0, immediately after the end of the infusion – T1, and 5 – T2, 15 – T3, 30 – T4, 60 – T5, 120 – T6, 180 – T7, 240 – T8, 300 – T9 and 360 minutes – T10 after the end of the infusion. The pharmacokinetic parameters of the medications were assessed. The total dose of an opioid used in the PCA system was also measured during the study.

Apart from that, the side effects of the early post-operative period were also monitored, such as the haemodynamic changes (with a cardiac monitor IntelliVue MP60, Phillips), allergic reactions and others.

Arterial blood (3 ml) was taken from an arterial cannula in the radial artery. After centrifuging the plasma was frozen and stored at -20°C until all the material from a particular cycle of the research was collected.

At each point of time (T0–T10) the mean, minimum and maximum concentrations of the medications were analysed. The correlations between the main concentration of paracetamol and the visual analogue scale (VAS) median in G1 and between ketoprofen and the VAS median in G2 were estimated. The values of the pharmacokinetic parameters of paracetamol and ketoprofen were calculated on the basis of a model-independent pharmacokinetic approach. The multifactor analysis of covariance based on the linear model of coexisting variables was used to estimate the influence of body weight and age on the pharmacokinetic parameters of the medications.

The paracetamol plasma concentrations were measured with a TDx apparatus (Abbott Diagnostic Division USA, 1996; Abbott/Shaw Lifecare Infusion

Pump, Model 3) by means of the fluorescence polarisation immunoassay (FPIA).

The ketoprofen concentration in the plasma was measured by means of high-performance liquid chromatography with an ultraviolet detector [10]. The quantification limit was estimated at 0.05 mg/l. The within-day and between-day coefficients of variation were lower than 10%.

Both ketoprofen and paracetamol pharmacokinetic parameters were calculated by means of the non-compartmental (NCA) model with Phoenix™ WinNonlin® 6.3 (Certara L.P.). The area under the plasma concentration-time curve (AUC) from time 0 to the last sampling point was calculated by means of the linear trapezoidal linear interpolation method. The elimination half-life ( $t_{1/2}$ ) was estimated from the last four plasma concentration time points. The NCA model was used to calculate the following pharmacokinetic parameters for paracetamol and ketoprofen: area under the plasma concentration-time curve from time zero to infinity ( $AUC_{\infty}$ ), elimination half-life ( $t_{1/2}$ ), clearance (CL), volume of distribution (Vd), and mean residence time ( $MRT_{\infty}$ ).

## Statistical analysis

Age, body weight, height, MAP, HR, CVP and the total consumption of an opioid were described as the mean value with the standard deviation (Tables 1 and 2). The Shapiro-Wilk test was used to check the consistence with the normal distribution. The t-Student test was used to compare the two groups of measurements (paracetamol vs. ketoprofen) for independent trials

**Table 1.** The demographic data, classification of physical state, indications for surgery and total dose of an opioid as means with standard deviations

Parameters	G1 (paracetamol)	G2 (ketoprofen)
Age (years)	63.9 ± 7.08	64.7 ± 8.96
Sex (M/F)	15/5	18/2
Body weight (kg)	75.55 ± 16.89	76.8 ± 15.97
Height (cm)	170.94 ± 7.15	171.88 ± 10.47
Body mass index (BMI)	25.6 ± 5.66	25.81 ± 4.96
Classification of physical state (ASA)		
– III	14	15
– IV	6	5
Diagnosis:		
– aneurysm	12	11
– Lerich syndrom	7	7
– aneurysm and Lerich syndrom	1	2
Total consumption of pethidine dose (mg)		
– number of patients (n)	14	16
– mean ± SD	33.1 ± 27.9	30.5 ± 26.8

None p correlations were found between the groups

**Table 2.** The results of hemodynamic parameters as means and standard deviations

Parameters	MAP [mmHg]		HR [beats/min]		CVP [cmH <sub>2</sub> O]	
	G1 (paracetamol)	G2 (ketoprofen)	G1 (paracetamol)	G2 (ketoprofen)	G1 (paracetamol)	G2 (ketoprofen)
T0	105.1 ± 14.6	95.7 ± 11.6 <sup>#</sup>	84.7 ± 14.0	87.7 ± 14.8	6.6 ± 3.1	7.4 ± 2.1
T1	97.7 ± 13.6*	88.6 ± 13.4 <sup>#</sup>	82.6 ± 11.2	84.0 ± 14.2	6.4 ± 3.1	7.2 ± 2.1
T2	94.8 ± 13.0*	86.8 ± 14.4	82.4 ± 11.1	84.8 ± 14.6	6.2 ± 2.8	6.7 ± 2.0
T3	94.1 ± 13.9*	84.8 ± 14.3 <sup>#</sup>	82.7 ± 12.7	82.3 ± 14.1*	5.7 ± 2.5	6.2 ± 2.3
T4	94.3 ± 13.7*	82.3 ± 13.9 <sup>#</sup>	82.9 ± 11.0	83.8 ± 14.1	5.7 ± 2.5	6.1 ± 2.4
T5	90.9 ± 13.1*	83.2 ± 11.7	83.0 ± 11.6	82.3 ± 13.8*	5.8 ± 2.1	6.7 ± 2.4
T6	92.5 ± 14.3*	82.7 ± 11.8 <sup>#</sup>	80.1 ± 11.2	82.7 ± 13.9	5.2 ± 2.7	7.2 ± 2.4 <sup>#</sup>
T7	91.1 ± 14.3*	81.2 ± 13.0 <sup>#</sup>	81.8 ± 11.1	82.2 ± 13.4*	5.5 ± 2.5	7.4 ± 3.2 <sup>#</sup>
T8	93.8 ± 15.4*	83.3 ± 13.7 <sup>#</sup>	83.8 ± 10.1	81.9 ± 13.3*	4.9 ± 2.4	7.6 ± 2.9 <sup>#</sup>
T9	95.2 ± 14.0*	82.3 ± 14.8 <sup>#</sup>	81.5 ± 12.0	81.0 ± 12.8*	5.6 ± 2.4	7.7 ± 3.4 <sup>#</sup>
T10	94.2 ± 14.6*	83.2 ± 12.3 <sup>#</sup>	80.8 ± 10.8	81.5 ± 13.3*	5.2 ± 2.5	8.2 ± 3.7 <sup>#</sup>

MAP – mean arterial pressure, HR – heart rate, CVP – central venous pressure

\* The statistically significant difference within one group ( $p < 0.05$ )

# The statistically significant difference between both groups ( $p < 0.05$ )

when consistence with the normal distribution was present. If not, the Mann-Whitney test was chosen.

The analysis of variance (ANOVA) was used for repeatable measurements at the 11 time periods with the Tukey post-hoc test for the distribution of data compatible with the normal distribution.

The parameters presented on a serial scale as VAS were described with the median, minimum and maximum values. For confirmation of the two groups the Student t-test or Mann-Whitney test were used for independent trials.

For the assessment of consistence between the concentration of the drug and the VAS the Spearman factor of non-parametric correlation was used.

The statistical analysis was made with specific software (Statistica, version 8.0.), p-values <0.05 were considered statistically significant.

The influence of body weight and age on the pharmacokinetic parameters of the drugs was estimated by means of the multifactor analysis of covariance based on a linear model including the patient's body weight and age as coexisting variables. The measurements were made with the PROC GLM procedure of the statistical package SAS (SAS Institute Inc. 2002-2003. The SAS System for Windows v. 9.1.3, Service Pack 4, Cary, NC, USA).

## Results

No one of 40 patients resigned or was excluded from the study. The assessed groups were homogeneous. There were no differences in the demographic param-

eters or the risk of operation. The majority of patients was categorized as the class III of ASA scale. The mean of total PCA pethidine consumption in G1 and G2 was 33.1 mg and 30.5 mg respectively, and did not significantly differ between both groups (Table 1).

The mean values of hemodynamic parameters (MAP, HR and CVP) are presented in (Table 2). The distinguish changes between both groups were observed for MAP (throughout the whole sampling time) and CVP (from T6 to T10 sampling time). With respect to HR, the only few results in the ketoprofen group were recognized as statistically significant within that group.

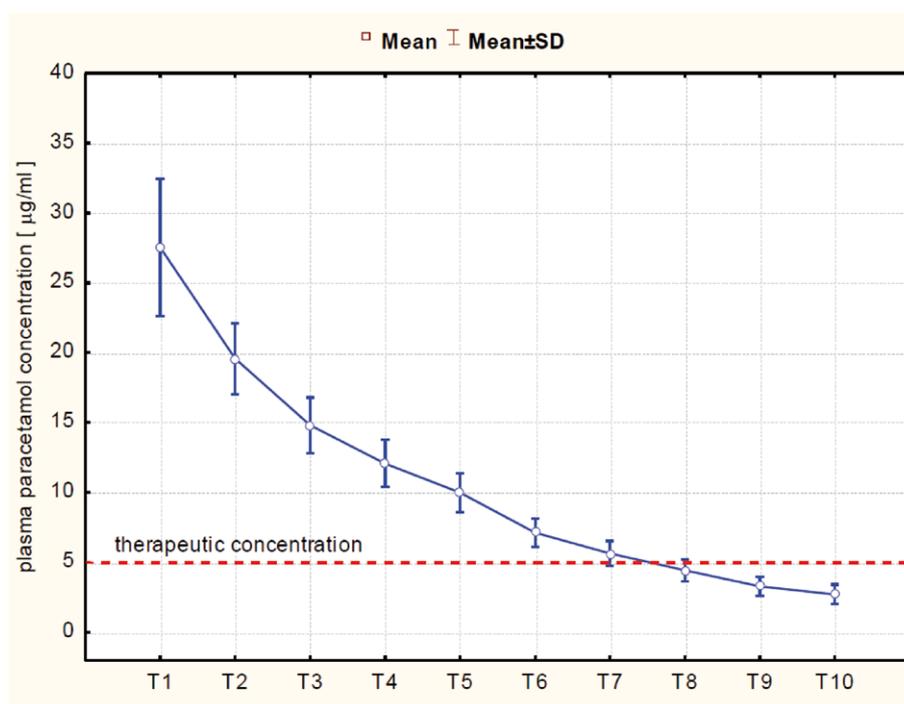
The values of VAS score obtained from patients' interview are described in (Table 3) as median, minimum and maximum measurements, for both group and at each sampling time (T0 – T10). The median of VAS values decreased in similar way in both groups throughout the whole sampling time. It reduced from 4.5 to 2.0 and 5.5 to 1.0 for G1 and G2, respectively. The minimum values were almost the same in both groups at corresponding sampling points. Of note, the maximum results were comparable only from T0 to T4. Maximum values at T5, T6, T9 and T10 were lower for paracetamol group, whereas results at T7 and T8 slightly favored ketoprofen. Increase of maximum VAS results in both groups at the last sampling time points (T9 and T10) may be related with the end of therapeutic concentrations estimated for both drugs (Figures 1, 2 and 3).

Basic pharmacokinetic parameters for both drugs were investigated (Table 4). With respect to paracetamol, of note, much higher values of AUC<sub>∞</sub>, Vd, CL and MRT<sub>∞</sub>

**Table 3.** Values of VAS score in the paracetamol group (G1) and ketoprofen group (G2)

Parameter	VAS score					
	Median		Minimum		Maximum	
Group Time points	G1 (paracetamol)	G2 (ketoprofen)	G1 (paracetamol)	G2 (ketoprofen)	G1 (paracetamol)	G2 (ketoprofen)
T0	4.5	5.5	1.0	1.0	10.0	9.0
T1	4.0	5.0	1.0	1.0	10.0	9.0
T2	3.5	5.0	1.0	1.0	9.0	9.0
T3	3.0	4.5	1.0	1.0	9.0	8.0
T4	3.0	3.0	1.0	1.0	8.0	8.0
T5	3.0	3.0	0.0	1.0	6.0	8.0
T6	2.0*	2.0*	0.0	0.0	5.0	8.0
T7	2.0*	1.5*	0.0	0.0	5.0	4.0
T8	2.0*	1.0*	0.0	0.0	5.0	4.0
T9	2.0*	1.0*	0.0	0.0	7.0	8.0
T10	2.0*	1.0*	0.0	0.0	6.0	8.0

\* The statistically significant difference within one group ( $p < 0.05$ )



**Figure 1.** The mean values of paracetamol concentration

were observed for paracetamol than ketoprofen, whereas elimination phase  $t_{1/2}$  was similar for both drugs.

The statistic analysis (ANOVA variation) of an influence of the age and body weight of patients to the above-mentioned parameters were calculated (Table 5). The only significant relation in the paracetamol group was found between body weight and MRT. In contrast, the statistically important dependence were

shown between age and  $AUC_{\infty}$  or  $MRT_{\infty}$ , body weight and CL, Vd or  $MRT_{\infty}$  in the ketoprofen group.

Mean values of pharmacokinetic parameters obtained in our study were similar to those presented in the Flouvat survey (Table 6).

The mean concentration values of paracetamol and ketoprofen at each sampling time, and their direct comparison are presented in Figures 1, 2 and 3.

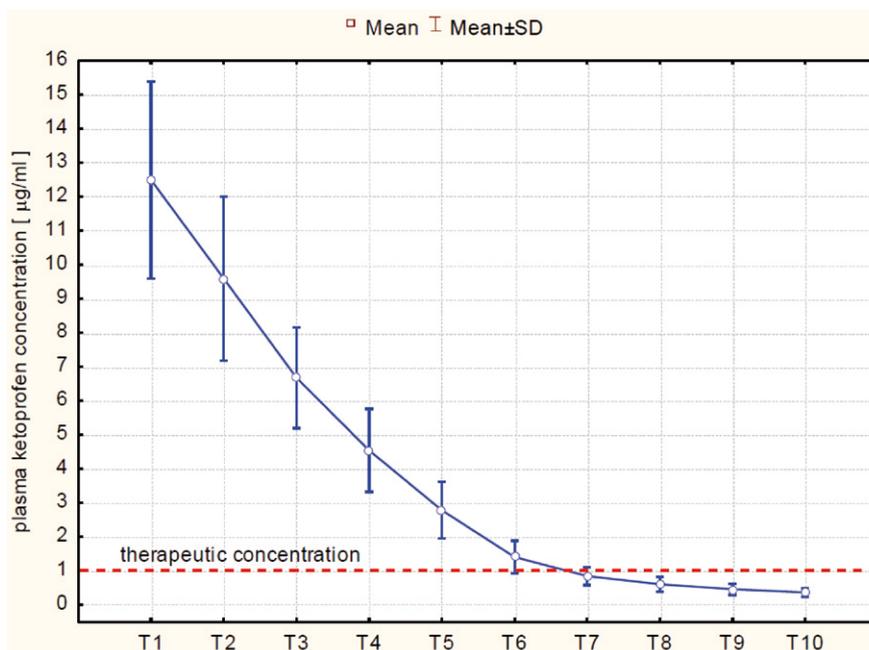


Figure 2. The mean values of ketoprofen concentration

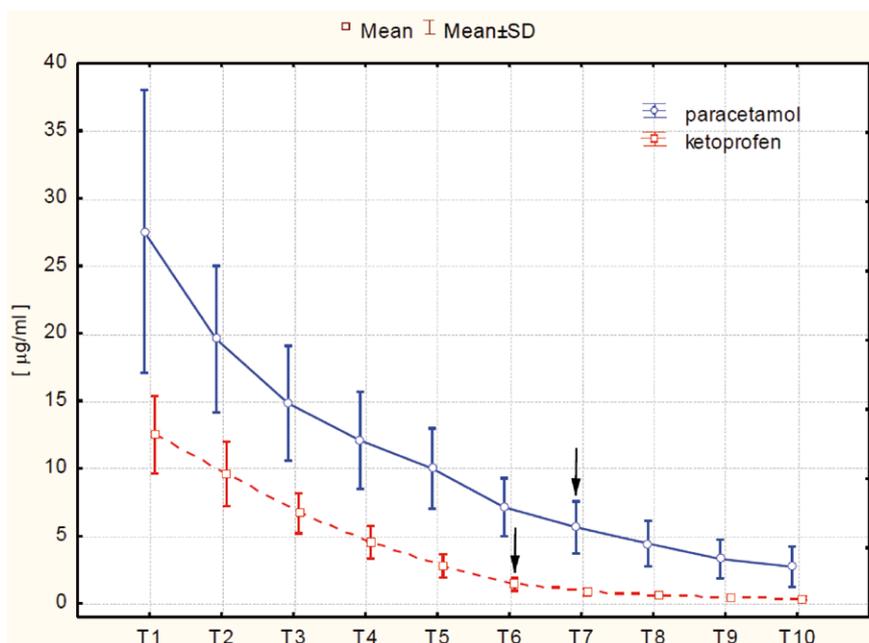


Figure 3. The mean concentration of paracetamol and ketoprofen (the pointers indicate the end of therapeutic concentration)

Table 4. The mean values of pharmacokinetic parameters of paracetamol and ketoprofen

Parameter	paracetamol			ketoprofen		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
AUC <sub>∞</sub> [mg·h/l]	55.01 ± 25.88	23.78	135.91	13.11 ± 3.25	8.25	23.78
Vd [l]	84.88 ± 33.15	26.02	186.93	27.76 ± 11.13	12.90	54.68
CL [l/h]	21.74 ± 9.46	7.36	60.89	8.02 ± 1.81	4.20	12.13
t <sub>1/2</sub> [h]	2.85 ± 1.36	1.42	6.45	2.36 ± 0.07	1.44	3.64
MRT <sub>∞</sub> [h]	4.04 ± 1.84	2.06	9.27	2.23 ± 0.45	1.64	3.05

AUC<sub>∞</sub> – the area under the plasma concentration-time curve, Vd – volume of distribution, CL – the apparent total clearance, t<sub>1/2</sub> – terminal phase half-life, MRT<sub>∞</sub> – mean residence time

**Table 5.** The statistic assessment ANOVA – the influence of body weight and patient’s age on pharmacokinetic parameters of paracetamol and ketoprofen

Parameter	paracetamol		ketoprofen	
	Age (p-value)	Body weight (p-value)	Age (p-value)	Body weight (p-value)
AUC <sub>∞</sub>	> 0.05	> 0.05	0.0104	> 0.05
CL	> 0.05	> 0.05	> 0.05	0.0124
Vd	> 0.05	> 0.05	> 0.05	< 0.0001
t <sub>1/2</sub>	> 0.05	> 0.05	> 0.05	> 0.05
MRT <sub>∞</sub>	> 0.05	< 0.05	< 0.05	< 0.05

AUC<sub>∞</sub> – the area under the plasma concentration-time curve, Vd – volume of distribution  
 CL – the apparent total clearance, t<sub>1/2</sub> – terminal phase half-life, MRT<sub>∞</sub> – mean residence time  
 The p-values <0.05 indicate statistical significance

**Table 6.** The mean values of chosen pharmacokinetic parameters of paracetamol in our research in comparison to Flouvat survey

Parameter	Minimum	Maximum	Mean ± SD	Mean ± SD
	Our research	Our research	Our research	Flouvat survey
AUC <sub>∞</sub> [mg·h/l]	23.78	135.91	55.01 ± 25.88	57.6 ± 10.4
Vd [l]	26.02	186.93	84.88 ± 33.15	69.2 ± 8.6 l
CL [l/h]	7.36	60.89	21.74 ± 9.46	17.9 ± 3.4 l
t <sub>1/2</sub> [h]	1.42	6.45	2.85 ± 1.36	2.72 ± 0.35

AUC<sub>∞</sub> – the area under the plasma concentration-time curve, Vd – volume of distribution,  
 CL – the apparent total clearance, t<sub>1/2</sub> – terminal phase half-life

## Postoperative period

The groups did not differ significantly in the number of perioperative side effects and complications. In G1 two patients (10%) suffered from postoperative complications, i.e. haemorrhagic shock and iatrogenic pneumothorax. In G2 three patients (15%) had postoperative side effects or complications, i.e. supraventricular arrhythmia, iatrogenic pneumothorax, acute ischemia of the lower extremity. None of local side effects or complications caused by the use of analgesic medications was noted in either group.

## Discussion

Our study was comparing intravenous paracetamol with ketoprofen, an NSAID, in terms of clinical pharmacokinetics. Postoperative analgesia is an important factor relieving pain and decreasing complications. The additional use of non-steroidal analgesics decreases pain and it may also reduce the side effects caused by the use of opioids [11, 12]. Sinatra and other authors documented the fact that the intensity of pain decreases significantly in the patients receiving an intravenous infusion of paracetamol or non-steroidal analgesics as a supplement to morphin in the PCA system, as compared with the use of morphine only in a monotherapy [13–15]. However, non-steroidal analgesics, such as ketoprofen, increase the effectiveness of opioid analgesia, but they cause numerous side effects. Ketoprofen

increases the risk of perioperative bleeding and the risk of renal dysfunction in patients with renal insufficiency [16–18].

Both Moller et al. and Sinatra et al. stated in their reports that the infusion of paracetamol did not have any clinically significant influence on the patients' haemodynamic parameters [13, 19, 20]. However, Peduto et al. in their research assessing the drug efficacy in orthopaedic surgery documented the fact that the heart rate in the group of patients receiving propacetamol was lower than in the group receiving a placebo, but the difference was not statistically significant [21]. In our study in the group of patients receiving paracetamol the heart rate ranged within the normal values during all periods of the research and it did not differ significantly between one another either after finishing the infusion or later. The average values of the mean arterial pressure ranged within the normal values during the whole study period, but they decreased after the end of infusion of the drug. However, these values were significantly greater than in the group receiving ketoprofen. Cusson et al. assessed the influence of ketoprofen on the blood pressure of patients suffering from arterial hypertension, who were treated with captopril and they found that it is safe to apply the drug to the patients only in a short-term therapy. The values of the patients' blood pressure were similar to those found in the patients receiving a placebo [22, 23].

Intravenous paracetamol is well tolerated by elderly people, including patients with high perioperative risk

[24]. Our research proves this fact, because the average age in the group of patients who received paracetamol was  $63.9 \pm 7.08$  years, III and IV class according to the ASA scale. Sinatra et al., whose findings were mentioned above, arrived at similar conclusions [13].

In our research the efficacy of paracetamol and ketoprofen as well as other methods of multimodal analgesia (PCA and epidural) was proved by low VAS values. According to the Visual Analogue Scale (VAS), after the infusion of the drug in G1 79.5% of the results reached lower values than 4, which proves the appropriate effectiveness of analgesia. Low VAS values remained until the end of the investigation in spite of the fact that the mean paracetamol concentration from the 240<sup>th</sup> minute to the end of the infusion (T8) was lower than 5 µg/ml (**Figure 1**). The authors are of the opinion that it is the lower limit of the therapeutic concentration [25] On the other hand, in G2 after the infusion of the drug 73.5% of the results reached lower values than 4, according to the Visual Analogue Scale (VAS). The mean concentration of ketoprofen remained within the therapeutic range only until the 120<sup>th</sup> minute after the end of the infusion (T6) and amounted to  $1.41 \pm 0.48$  µg/ml. Głowska et al. estimate the therapeutic concentration of ketoprofen at 1–5 µg/ml (**Figure 3**) [26].

The paracetamol and ketoprofen groups did not differ significantly in the total dose of an opioid the patients applied during the period under investigation. Fletcher et al. arrived at similar conclusions in their study, which was mentioned above [27]. However, our research cannot assess the opioid-sparing effect of those analgesics, because there was no control group with a placebo available. The data from reference books prove the fact that in comparison with a placebo both paracetamol and ketoprofen decrease the demand for opioids [27–29]. Previous studies suggested that action of paracetamol might involve the opioidergic system but Pickering et al. in their pilot trial did not prove that yet [30].

The plasma paracetamol concentration which is required to achieve the necessary analgesia has not been fully investigated. It is thought that the therapeutic antipyretic concentration is 5–20 µg/ml [25]. Probably the plasma concentration which is necessary to achieve the analgesic effect needs to be higher, although both higher and lower values are suggested [31]. In the article by Gibb and Anderson, published in March 2008, it is suggested that the necessary concentration to achieve the antipyretic effect is 5 µg/ml, whereas it is 10 µg/ml for the analgesic effect [32].

The mean maximum values of plasma paracetamol concentrations in the patients in this research were comparable with the results obtained by Flouvat et al., Murat et al. and with the values given by the drug manufacturer [33, 34]. After the end of the infusion the mean maximum concentration of the drug was 27.53 µg/ml in our research, 29.9 µg/ml in Flouvat's and 30 µg/ml in Murat's. The latter value is the same as the one given by the manufacturer. Also, such pharmacokinetic parameters as: the total area under curve for time-dependent variations in the drug concentration ( $AUC_{\infty}$ ), the mean volume of distribution (Vd), the mean total clearance (CL) or the half-life at the elimination stage ( $t_{1/2}$ ) did not differ significantly from the values obtained by Flouvat (**Table 6**). Flouvat researched a group of young healthy volunteers (aged 19–37 years), who neither received other drugs nor were anaesthetised immediately before the investigation. Hence the conclusion that the pharmacokinetic parameters and metabolism of paracetamol in elderly patients (the mean age of the patients in group I was  $63.9 \pm 70.8$  years) with numerous preoperative burdens do not change and it is not necessary to modify the drug dosage to those patients.

Immediately after the end of the infusion the plasma paracetamol concentration was higher than 40 µg/ml (40.84 µg/ml, 48.3 µg/ml and 53.08 µg/ml) in three patients from group I. Prins et al. suggest that if the values of paracetamol concentration reach such a high level, this may potentially result in the hepatotoxic effect from the increased production of the toxic metabolite NAPQI involving the cytochrome P450 isoenzyme CYP2E1. However, Jackson et al. think that the risk of damage to the liver appears only when the plasma concentration exceeds 150 µg/ml, which is much higher than the concentration from therapeutic doses [25].

Debruyne et al. studied the pharmacokinetics of ketoprofen after the intravenous administration of 100 mg of the drug and they obtained the following values of pharmacokinetic parameters:  $AUC_{\infty}$  – about 14 mg·h/l,  $t_{1/2}$  – about 2.5 h and CL – about 5.1 l/h [36]. These results are similar to the values obtained in this research, which may indicate that after the reconstructive surgery of the abdominal aorta the elimination of ketoprofen is not impaired. The statistical analysis proved the influence of body weight on the Vd parameter value. When the volume of distribution per kg of body weight value is calculated, a decrease in the inter-individual variation can be observed. The correlation between the  $AUC_{\infty}$  parameter and the patient's age was also proved. The bioavailability of the drug

increases by 0.21 along with each consecutive year of life in the age group under investigation. On the other hand, the clearance value and the elimination half-life were not observed to decrease as the age increased.

Advenier et al. compared the pharmacokinetics of ketoprofen after the oral administration to younger and elderly people. They proved a significant increase in the values of the total area under the curve of variations in the time-dependent concentration of the drug ( $AUC_{\infty}$ ) and  $t_{1/2}$ , but there was a decrease in CL. The patients' age span was much larger in that study, i.e. on average  $24 \pm 1.3$  years in the group of younger patients and  $86 \pm 2.4$  in the group of geriatric patients [37].

Our research findings do not point to the correlation between the patient's age and  $AUC_{\infty}$ , Vd, CL or  $t_{1/2}$  parameters for paracetamol. This is in agreement with the earlier data from reference books, which do not indicate the need to modify the dosage of the drug to elderly people [38].

Further clinical investigations are necessary to specify the place of intravenous paracetamol in pain therapy in different groups of patients. The drug has a wide range of advantages, which are particularly useful in the postoperative period. Our research findings also confirm the fact that after an intravenous administration the effect begins as soon as 5–10 minutes [8, 13, 39].

To sum up, intravenous paracetamol and ketoprofen administered to patients with moderate or severe postoperative pain after the reconstructive surgery of the abdominal aorta are effective, safe and well tolerated procedure.

The investigations in this study point to the fact that intravenous paracetamol and ketoprofen are useful components of multimodal analgesia in the treatment of postoperative pain in patients after the reconstructive surgery of the abdominal aorta.

## Conclusion

The study enabled the following conclusions: intravenous paracetamol as well as ketoprofen has good tolerability; there is no need to modify dosage to elderly patients and the therapeutic drug plasma concentration remains longer after a paracetamol infusion than after a ketoprofen infusion.

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### Conflict of interest statement

The authors declare no conflict of interest.

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