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PHARMACEUTICAL TECHNOLOGY

THE EFFECT OF TOTAL AND PARTIAL NEPHRECTOMY ON THE PHARMACOKINETICS OF INTRAVENOUS PARACETAMOL IN HUMANS

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Abstract: Paracetamol is one of the most common analgesic and antipyretic drugs. Recently intravenous paracetamol has been widely used to treat moderate postoperative pain. Surgery is the main method of treatment of renal cancer. Total or partial nephrectomy can be performed, depending on the size and location of the tumor. Pharmacokinetics of drugs may depend on the type of surgery. The aim of the study was to compare the postinfusion pharmacokinetics of paracetamol in patients after total nephrectomy (TN) and nephron sparing surgery (NSS). The research was carried out on two groups of patients after nephrectomy: total (TN n = 37; mean [SD], age, 60.4 [10.9] years; BMI, 26.5 [3.8] kg/m^2; creatinine clearance, Cl_{cr}, 80.9 [37.1] mL/min) and nephron sparing surgery (NSS n = 17; 57.9 [16.5] years; BMI, 29.5 [5.3] kg/m^2; Cl_{cr}, 97.6 [27.8] mL/min). The patients were treated with paracetamol (*Perfalgan*®, Bristol-Myers Squibb) at an intravenous dose of 1.000 mg, which was infused for 15 minutes after surgery. The concentrations of paracetamol in the patients' plasma were determined by the HPLC method with UV detection (λ = 261 nm). The main pharmacokinetic parameters of paracetamol in the TN *vs*. NSS group were as follows: C_{max} 29.08 [17.39] *vs*. 27.54 [15.70] µg/mL (p = 0.6692); $AUC_{5stop-t}$ 29.24 [13.86] *vs*. 34.85 [14.28] µg·h/mL (p = 0.2896); $AUMC_{5stop-t}$ 47.58 [26.08] *vs*. 62.02 [27.64] µg·h^2/mL (p = 0.1345); $t_{0.5}$ 2.34 [0.96] *vs*. 1.93 [0.50] h (p = 0.1415), respectively. In both groups the exposure to paracetamol was comparable. The $t_{1/2}$ after nephron sparing surgery was shorter than after total nephrectomy. Therefore, these patients may demand more frequent drug administration. In the NSS group the C_{max} of the analgesic was considerably reduced in men.

Keywords: paracetamol, pharmacokinetics, total nephrectomy, nephron sparing surgery

Patients undergoing nephrectomy are a special group, because their pharmacokinetic (PK) parameters may be different than in healthy patients. Drug PK may also depend on the type of surgery. Partial kidney resection may have different influence on PK parameters than total kidney resection. NSS has minimal influence on the glomerular filtration rate, whereas total nephrectomy reduces creatinine clearance (1, 2). Monitoring PK parameters in these patients would enable precise dosage. The aim of therapeutic drug monitoring (TDM) is to measure the drug concentration in the patient's blood and adjust dosage to their individual needs so as to make the therapy effective and to cause as few adverse reactions as possible. The concomitance of diseases which changes PK and polypharmacy is an indication for TDM. This situation can be observed in patients after kidney resection.

Paracetamol is one of the most common analgesics and antipyretics applied in inpatient and outpatient health care. In recent years special attention has been given to the intravenous form of paracetamol, which guarantees a quick and efficacious therapeutic effect. It is more and more widely used for treatment of moderate pain, especially in the postoperative period in intensive care units and depart-

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ments of surgery (3). Apart from the quick effect, intravenous administration enables elimination of differences resulting from individually varying rate of absorption. The biotransformation and excretion of paracetamol are processes which depend on the patient's age, activity of hepatic enzymes and renal function. Acetaminophen is chiefly eliminated in the form of metabolites, with urine – as glucuronate and sulfate (90-95%), and with bile – as cysteinate and mercaptopurinate (5-10%). About 1-4% of the dose is eliminated in an unchanged form by kidneys – it is the consequence of the chemical structure of the compound (4, 5). Paracetamol is only minimally bound by plasma proteins and it is easily filtrated in the glomeruli. It is reabsorbed in the distal part of the nephron. Glucuronates and sulfates are high-polarity compounds and they are eliminated by kidneys in the process of glomerular filtration and tubular secretion.

The elimination of paracetamol and its metabolites is longer in patients with acute renal failure. The elimination rate in these patients is three times slower than in the control group.

It has also been proved that when therapeutic doses of paracetamol are applied to patients undergoing hemodialysis, $t_{1/2}$ is reduced by 40-50% (4, 5). From the clinical point of view it is important to acquire information how strongly kidney resection may influence drug elimination.

Apart from total nephrectomy (TN), nephron sparing surgery (NSS) is increasingly being used to treat patients with solid renal lesions. The technical success rate of nephron sparing surgery is excellent and operative morbidity and mortality are low. For renal cell carcinoma, long-term cancer-free survival is comparable to that after radical nephrectomy, particularly for low-stage disease (6, 7).

In order to obtain this information we scanned the databases of Medline and PubMed with the following entries: paracetamol, intravenous paracetamol, total and/or partial kidney resection. We found no publications concerning relations between the PK of intravenous paracetamol and kidney resection surgeries.

EXPERIMENTAL

Reagents

Paracetamol, HPLC grade acetonitrile, perchloric acid, theophyllinum were purchased from Sigma-Aldrich (Poland), 85% orthophosphoric acid, methanol from Merck (Poland), anhydrous sodium sulfate from Fluka (Poland). Water used in the mobile phase was deionised, distilled and filtered through a Millipore system before use. *Perfalgan*® was purchased from Bristol-Myers Squibb Polska Sp. z o.o., Warsaw, Poland (batch number 1K67394).

Subjects

This study was performed in cooperation with Urology Clinic, Medical University of Gdańsk, (Poland), and at the Department and Unit of Clinical Pharmacy and Biopharmacy, Poznań University of Medical Sciences, (Poland). All the described procedures were reviewed and approved by the Institutional Review Board at the Poznań University of Medical Sciences and by the local ethics committee at the Medical University of Gdańsk. This study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was carried out on 54 patients (29 men and 25 women), who were hospitalized for surgical treatment due to renal tumor. The inclusion criteria were as follows: patients with renal masses qualified for total or partial nephrectomy; age > 18 years; no history of allergy to paracetamol; pain greater than 1-3 (VAS; Visual Analogue Scale); consent to take part in the research; suitability for surgery; no kidney failure confirmed by creatinine level and eGFR (estimated glomerular filtration rate). The research was explained to the patients, and those who consented to the drug administration and blood collection were enrolled as subjects. All the patients gave their informed consent prior to inclusion in the study. The exclusion criteria were as follows: previous paracetamol exposure, allergy to paracetamol, serious functional cardiac, kidney and hepatic disorders, patients with polycystic kidneys, age under 18 years. Creatinine clearance for each patient was calculated using the Cockroft-Gault formula from creatinine concentration value obtained on the day of measurement of paracetamol concentration (2).

Drug administration and blood sampling

Paracetamol was administered to patients in a single intravenous infusion at the dose of 1000 mg (100 mL of solution; *Perfalgan*® 10 mg/mL, Bristol-Myers Squibb), on a 1st day after the nephrectomy. It was the one and only dose of paracetamol that patients received during the study. The time of infusion was 15 min. Blood samples were collected immediately before infusion (0') and after infusion termination, at the following time points: 5, 15 min and 0.5, 1, 2, 3, 5, 4, 6 h. The blood samples (1 mL) were transferred into heparinized tubes and they were centrifuged at 4,000 rpm for 10 min at

4°C. Next, the plasma was transferred to propylene tubes and stored at -20°C until analysis.

Drug assay

The concentration of paracetamol was assayed using the high-performance liquid chromatography (HPLC) method with UV-Vis detection (8). Separation was achieved by isocratic elution of the mobile phase, sodium sulfate 0.05 M pH 2.2 (adjusted with 85% orthophosphoric acid) – acetonitrile (93 : 7, v/v), at a flow rate of 1.5 mL/min through an ODS Hypersil® C18 column (150 mm × 4.6 mm, 5.0 µm particle size) (Thermo Electron Corporation®). The column temperature was maintained at 25°C, the UV–Vis detection wavelength was set at 261 nm, and the injection volume was 50 µL. The total analysis time for each run was 5 min. The lower limit of quantification (LLOQ) was 0.15 µg/mL. Intra- and inter-day precision and accuracy of the LLOQ, low quality control (0.3 µg/mL), medium quality control (30.0 µg/mL), and high quality control (60.0 µg/mL) were well within the acceptable limit of 10% coefficient of variation (CV%). The calibration for paracetamol was linear, ranging within 0.15-75.0 µg/mL (r = 0.999).

Pharmacokinetics and statistics

Pharmacokinetic calculations were based on non-compartmental analysis using Phoenix® WinNonlin® 6.4 software (Certara L.P., US). Since the obtained data do not permit the calculation of a two-compartment model, non-compartmental analysis was conducted. Pharmacokinetics calculation were based on the postinfusion pharmacokinetics. The following pharmacokinetic parameters were calculated for paracetamol: elimination rate constant (k_{el}), area under the plasma concentration-time curve from 5 min after infusion termination to infinity ($AUC_{5min\text{-}inf}$), area under the plasma concentration-time curve from 5 minutes after infusion termination to the time of last measurable concentration ($AUC_{5min\text{-}t}$); maximum observed plasma concentration (C_{max}), time to first occurrence of C_{max} (t_{max}), half-life in elimination phase ($t_{1/2}$), clearance (Cl), volume of distribution (V_d), area under the first moment curve measured between 5 min after infusion termination to the last measurable concentration ($AUMC_{5min\text{-}t}$), mean residence time ($MRT_{5min\text{-}t}$). The elimination half-life ($t_{1/2}$) was calculated with the last 4 points of the curve. The maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (t_{max}) were obtained directly from the concentration – time data.

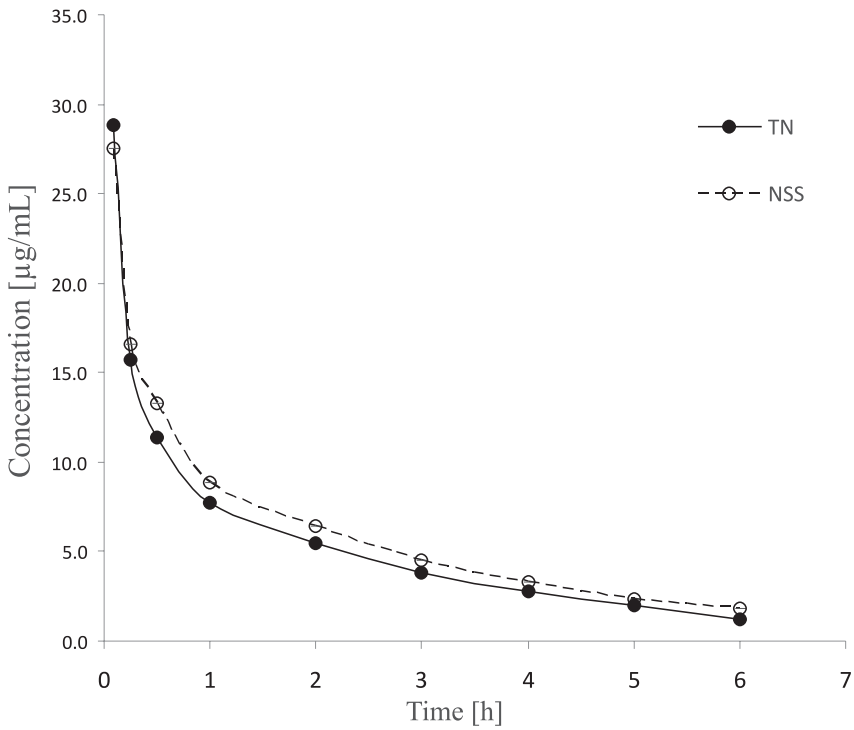

Figure 1. The mean paracetamol plasma concentration *vs*. time profiles following a single 1.000 mg intravenous dose in the patients after total nephrectomy (TN) and nephron sparing surgery (NSS)

Statistical analysis

Statistical calculations were made with SAS software package (SAS Institute Inc. 2002-2010. The SAS System for Windows version 9.3. Cary, NC, USA). Two-way analysis of variance was used to estimate statistical significance of differences between the results obtained in the NSS and TN groups and between men and woman (PROC GLM). The paracetamol Cl and MRT_{5min-t} was correlated with creatinine clearance (Cl_{cr}), eGFR, creatinine level (C_{cr}) (after surgery) at baseline using linear correlation analysis (Pearson correlation coefficient provided). Student's t-test was used to estimate statistical significance of differences between the results obtained in the groups of men and women within the treatment groups. The 90% confidence intervals for the ratio of geometric means were constructed for the treatment groups to evaluate bioequivalence.

RESULTS

Fifty-four subjects (29 men, 25 women; 32-86 years of age) were enrolled in and completed the research (first subject's visit: 11 May 2011; last subject's visit: 4 April 2013). Patients were divided into two groups: patients after total nephrectomy (TN) and after NSS. TN group consisted of 22 men and 15 women, while NSS group included 7 men and 10 women with average age [years] (S ± SD) 60.35 ± 10.95 and 57.88 ± 16.48, weight [kg] 79.66 ± 13.17 and 82.35 ± 15.70, height [m] 1.73 ± 0.08 and 1.69 ± 0.08, BMI [kg/m^2] 26.51 ± 3.81 and 29.47 ± 5.26, respectively. Mean parameters used to assess renal function were as follows: BUN [mg/dL] 17.79 ± 5.86 and 16.59 ± 5.60; $C_{cr\ (before\ surgery)}$ [mg/dL], 0.93 ± 0.18 and 0.89 ± 0.23; $C_{cr\ (after\ surgery)}$ [mg/dL] 1.22 ± 0.34 and 0.89 ± 0.31; $Cl_{cr\ (before\ surgery)}$ [mL/min] 92.43 ± 26.68 and 100.60 ± 32.5; $Cl_{cr\ (after\ surgery)}$ [mL/min] 80.97 ± 37.06 and 97.61 ± 27.80; $eGFR_{(before\ surgery)}$ 80.22 ± 18.11 and 83.59 ± 21.49; $eGFR_{\ (after\ surgery)}$ 64.96 ± 21.53 and 84.42 ± 27.04 in patients after TN and NSS, respectively. The plasma concentration-time profiles for paracetamol in the patients after total nephrectomy and in the patients after nephron sparing surgery are shown in Figure 1.

No significant differences were found in such parameters as age, weight, height and BMI (Body Mass Index) between both studied groups. In the TN group low C_{cr} was observed in 1 patient. Low Cl_{cr} and eGFR values were observed in 18 and 20 patients, respectively. High Cl_{cr} was observed in 1 patient. In the NSS group low C_{cr} values were observed in 3 patients, whereas a high C_{cr} value was observed in one patient. Low Cl_{cr} and eGFR values were observed in 4 and 5 patients, respectively.

Table 1. Pharmacokinetic parameters for paracetamol in plasma.

Pharmacokinetic parameters[a]	TN (n = 37) S ± SD	NSS (n = 17) S ± SD	p value TN *vs.* NSS	p value male *vs.* female	Gmean ratio[b] (90% CI)
					TN vs NSS
AUC_{5min-t} (µg·h/mL)	29.24 ± 13.86	34.85 ± 14.28	0.2896	0.0780	1.18 (0.94; 1.48)
$AUC_{5min-inf}$ (µg·h/mL)	36.56 ± 17.03	40.40 ± 16.57	0.6320	0.0842	1.10 (0.87; 1.39)
$AUMC_{5min-t}$ (µg·h^2/mL)	47.58 ± 26.08	62.02 ± 27.64	0.1345	0.0343	1.29 (0.98; 1.70)
$AUMC_{5min-inf}$ (µg·h^2/mL)	115.47 ± 80.44	109.60 ± 54.46	0.6447	0.2590	1.01 (0.70; 1.45)
MRT_{5min-t} (h)	2.98 ± 1.27	2.61 ± 0.67	0.2713	0.9127	0.92 (0.76; 1.12)
$t_{1/2}$ (h)	2.34 ± 0.96	1.93 ± 0.50	0.1415	0.4673	0.87 (0.72; 1.05)
Cl (L/h)	41.04 ± 16.81	37.09 ± 25.69	0.7828	0.0173	0.85 (0.68; 1.06)
C_{max} (µg/mL)	29.08 ± 17.39	27.54 ± 15.70	0.6692	0.5289	0.93 (0.71; 1.22)
V_d (L)	63.96 ± 25.51	59.91 ± 29.31	0.8667	0.0405	0.93 (0.75; 1.14)

[a] Arithmetic means ± standard deviations (CV%) are presented with CV (%) in the brackets. [b] Ratio of geometric means (Gmeans) between groups with the lower and upper bounds of a 90% confidence interval in the brackets are presented.

During the course of the research there were no serious or unexpected adverse events. The PK parameters and a summary of the statistical analyses for paracetamol are shown in Table 1.

The mean paracetamol C_{max} was similar for both the TN and NSS groups (29.08 ± 17.39 and 27.54 ± 15.70 µg/mL, respectively). There was no significant difference between the groups under analysis (p = 0.6692). There was no statistically significant difference revealed for $t_{1/2}$, but $t_{1/2}$ in the NSS group tended to be shorter than in the TN group (1.93 ± 0.50 and 2.34 ± 0.96 h, respectively; p = 0.1415). There were no statistically significant differences between the TN and NSS groups under analysis for the following pharmacokinetic parameters: AUC_{5min-t} (p = 0.2896), $AUC_{5min-inf}$ (p = 0.6320), $AUMC_{5min-t}$ (p = 0.1345), V_d (p = 0.8667), MRT_{5min-t} (p = 0.2713), and Cl (p = 0.7828). For all parameters the confidence interval for ratio of geometric means included the value of one which confirms the lack of significant differences in absorption of paracetamol between the TN and NSS groups in this study.

The two-way ANOVA revealed a significant difference between men and women for Cl (p = 0.0173), $AUMC_{5min-t}$ (p = 0.0343), and V_d (p = 0.0405). A more detailed analysis within the treatment groups revealed that the mean paracetamol C_{max} was similar in the TN group both in men and women (29.05 ± 16.19 and 29.14 ± 19.95 µg/mL, respectively; p = 0.9876). The systemic exposure of paracetamol ($AUC_{5min-inf}$) in men was lower than in women (33.03 ± 16.70 and 41.73 ± 16.71 µg·h/mL, respectively). There was no statistically significant difference between the groups under analysis (*p* = 0.1288). The $AUMC_{5min-t}$ in men was lower than in women (40.10 ± 21.73 and 58.56 ± 28.71 µg·h^2/mL, respectively). There was statistically significant difference between the groups under analysis (p = 0.0343). There were no statistically significant differences between men and women in the TN group under analysis for the following PK parameters: AUC_{5min-t} (p = 0.1013), V_d (p = 0.1621), $t_{1/2}$ (p = 0.3886), and Cl (p = 0.0751).

The mean paracetamol C_{max} in the NSS group was lower in men than in women (22.27 ± 14.09 and 31.24 ± 16.40 µg/mL, respectively). There was no statistically significant difference between the groups under analysis (p = 0.2592). The systemic exposure to paracetamol ($AUC_{5min-inf}$) in men was lower than in women (36.45 ± 21.94 and 43.17 ± 12.11 µg·h/mL, respectively). There was no statistically significant difference between the groups under analysis (p = 0.4279). The V_d value tended to be higher in men than in women (102.28 ± 59.79 and 69.67 ± 28.57 L). There was no statistically significant difference between the groups under analysis (p = 0.2216). The Cl value tended to be higher in men than in women (44.08 ± 36.63 and 24.65 ± 6.06 L/h, p = 0.2213). There were no statistically significant differences between men and women in group NSS under analysis for the following pharmacokinetic parameters: AUC_{5min-t} (p = 0.4863), $t_{1/2}$ (p = 0.8036), and $AUMC_{5min-t}$ (p = 0.5283).

A significant negative correlation was identified in the TN group between $t_{1/2}$ and Cl_{cr} (r = -0.4293, p = 0.0322), and between MRT_{5min-t} and Cl_{cr} (r = -0.4271, p = 0.0332) . Correlations between $t_{1/2}$ and other parameters of creatinine clearance were not significantly different from zero eGFR (r = -0.11912, p = 0.5706), C_{cr} (r = -0.06879, p = 0.7439), as were the correlations between MRT_{5min-t} and eGFR (r = -0.08131, p = 0.6992) and C_{cr} (r = -0.1502, p = 0.4736). In the NSS group correlations between $t_{1/2}$ and Cl_{cr} (r = 0.3408, p = 0.2545), eGFR (r = 0.3532, p = 0.2366), C_{cr} (r = -0.2204, p = 0.4693) and between MRT_{5min-t} and Cl_{cr} (r = 0.1925, p = 0.5286), eGFR (r = 0.1268, p = 0.6798), C_{cr} (r = -0.0943, p = 0.7592) were not significantly different from zero.

DISCUSSION

Intravenous paracetamol (also known as acetaminophen) is one of the more commonly used analgesics and antipyretics in intensive care units and surgical departments. It guarantees a quick and efficacious therapeutic effect and enables elimination of differences resulting from individually varying rates of absorption (9, 10). Comparing the early bioavailability of rectal, effervescent oral and intravenous paracetamol, only intravenous and effervescent paracetamol were found in therapeutic concentrations one day after surgery (11).

A major benefit of intravenous administration of paracetamol is the fact that the median time to reach t_{max} is much faster than typically reported for oral or rectal formulations (> 45 min) (4). C_{max}, which occurs at the end of a 15-minute infusion of paracetamol, is up to 70% higher than that observed with the same dose of oral acetaminophen, although the overall exposure (area under the concentration time curve) is very similar (12).

However, caution must be used when administering paracetamol to patients with liver dysfunction, active liver disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe kidney dysfunction (i.e., creatinine clearance = 30 mL/min) (13).

Despite its beneficial analgesic properties, some data indicate that paracetamol induces cell death with features of apoptosis in proximal tubular epithelial cells (14) and elicits chronic long-term renal toxicity (13).

As mentioned above, the harmful influence of paracetamol is especially important in patients with acute renal failure (15), where the elimination time of paracetamol and its metabolites is longer (up to three times slower elimination rate than in the control group). It has also been proved that when therapeutic doses of paracetamol are administered to patients undergoing hemodialysis, $t_{1/2}$ is reduced by 40-50%. Additionally, surgical removal of all or part of the kidney may influence drug elimination, because it: 1) reduces the number of active nephrons, 2) alters permeability of capillaries (by causing migration of fluids to extravascular areas) and 3) causes hypoalbuminemia (by inducing local inflammation) (16).

There is no available data on the PK of paracetamol in nephrectomized patients. Therefore, this study was designed to acquire information on how strongly kidney resection (total or partial) may influence the PK of intravenous administration of paracetamol.

After collecting blood samples (Fig. 1), we observed similar time-dependent decreases in the mean paracetamol plasma concentration in both groups. While both types of nephrectomy cause a decrease in renal function (by reducing either a small or large amount of active nephrons), the plasma concentration of paracetamol changes in a similar way. Data from the literature suggest that there are structural and functional adaptations of the remaining renal tissue, even at an early stage after surgery (17).

The plasma concentrations of paracetamol (described above) in the TN and NSS groups were similar and independent of gender. However, when we compared $AUMC_{5min-t}$, there was a significant decrease in men in the TN group only. This effect may have been induced by gender differences in drug elimination (including body surface area, renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption) (18). However, as far as paracetamol is concerned, data from the literature are poor and inconsistent. In rats, large dosages of paracetamol cause kidney necrosis, which is more severe in young adult female rats (19). In elderly patients, the elimination half-life is associated with gender, since females have increased paracetamol concentrations after intravenous paracetamol (20). In accordance with our observations, previous data showed that gender differences in drug clearance were minor and not significant (21).

Another, more significantly altered parameter is the elimination half-life of paracetamol. In the TN group, it was similar to that reported in the literature (approximately 2.24 to 3.30 h) (22) and was relatively short. However, in several diseases like renal failure (41.3 ± 2.2 h *vs*. 26.8 ± 1.1 h the half-life of protein-derived acetaminophen-cysteine APAP-CYS in patients with renal failure compared with healthy controls, respectively) (23) or liver failure (1.72 days) (24, 25), it is prolonged. Surprisingly, our results indicated that $t_{1/2}$ was shorter after NSS than after TN (1.93 ± 0.50 *vs*. 2.34 ± 0.96 h, respectively). These data suggest that the type of nephrectomy is important in determining the half-life of paracetamol. This observation could be helpful in planning analgesic treatment after renal surgeries. Further investigations are required to determine the cause of these differences.

CONCLUSIONS

Exposure to paracetamol was comparable in both groups under analysis. The $t_{1/2}$ after nephron sparing surgery was shorter than after total nephrectomy. Therefore, these patients may demand more frequent drug administration. In the NSS group the C_{max} of the analgesic was considerably reduced in men.

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