

*Full Paper***Intravenous Paracetamol as an Antipyretic and Analgesic Medication: the Significance of Drug Metabolism**

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Abstract. One prospective, open-label, non-randomized study was conducted in 100 patients to define the antipyretic and analgesic effect of a new intravenous formulation of 1 g of paracetamol; 71 received paracetamol for the management of fever and 29 received paracetamol for pain relief after abdominal surgery or for neoplastic pain. Serial follow-up measurements of core temperature and of pain intensity were done for 6 h. Additional rescue medications were recorded for 5 days. Blood was sampled for the measurement of free paracetamol (APAP) and of glucuronide-APAP and *N*-sulfate-APAP by an HPLC assay. Defervescence, defined as core temperature below or equal to 37.1°C, was achieved in 52 patients (73.2%) within a median time of 3 h. Patients failing to become afebrile with the first dose of paracetamol became afebrile when administered other agents as rescue medications. Analgesia was achieved in 25 patients (86.4%) within a median time of 2 h. Serum levels of glucuronide-APAP were greater among non-responders to paracetamol. The presented results suggest that the intravenous formulation of paracetamol is clinically effective depending on drug metabolism.

Keywords: intravenous paracetamol, fever, pain, analgesia

Introduction

Modern therapeutics does not aim only at prolongation of survival but also at the improvement of the quality of life. Disease hampers quality of life by inducing two major symptoms, fever and pain. As such, part of daily patient management requires the alleviation of these symptoms (1). A variety of compounds have been developed for the management of fever and pain; the most broadly used are non-steroidal anti-inflammatory drugs (NSAIDs) (2). They are available both for oral and for parenteral administration. Those which administered parenterally are considered to achieve some faster effect.

Paracetamol is a well-known antipyretic and analgesic compound available for many years for oral administration since intravenous infusion was hampered by water insolubility. Ready-made paracetamol for intravenous infusion is available in the market in some European countries. Until 2008 when this trial was designed, only four clinical trials had been published testing the efficacy of paracetamol intravenously administered as post-operative analgesia at doses of 1 g after laparoscopic cholecystectomy, after spinal body ectomy, and after third molar surgery. Although in all four trials intravenous paracetamol was superior over placebo for pain relief, results of its efficacy compared to the other studied NSAIDs comparators were conflicting (3 – 6). Part of the explanation for these conflicting results may rely on the pharmacokinetics of paracetamol for which limited data are available in patient populations. No trials were published until 2008 on the antipyretic effect of intra-

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venously administered paracetamol. Since 2008, two trials were published on the antipyretic effect of intravenous paracetamol but they were not conducted in patient populations. Instead, both trials enrolled healthy volunteers in whom fever was induced after experimental endotoxemia (7, 8). In the first trial the efficacy of intravenous paracetamol was compared to placebo (7) and in the second trial it was compared to both placebo and oral paracetamol (8). Results of this second trial showed that the antipyretic effect of the intravenous regimen was greater than the oral regimen (8).

Clinical practice often necessitates the administration of antipyretics and analgesics intravenously due to the severity of the overall condition of the patient. To this end, a new formulation of paracetamol for intravenous infusion of 1 g was introduced in the Greek market in 2007. Taking into consideration the conflicting results on efficacy for pain relief and the lack of data for the antipyretic effect of formulations delivering 1 g of paracetamol intravenously, a non-randomized, open-label clinical trial was conducted. The aim of this trial was to disclose the clinical efficacy of 1 g of intravenous paracetamol as an antipyretic and analgesic medication in relation with pharmacokinetics. Clinical efficacy was studied in medical and surgical patients requiring hospitalization and who had clinical conditions different from those of the populations enrolled in previous studies, e.g., experimental human endotoxemia and post-operative analgesia for elective surgery.

Materials and Methods

Study design

This was a prospective, open-label, non-randomized, multicenter phase IV study that was conducted during the period from January 2009 until January 2010 in two departments of Internal Medicine and in one department of Surgery in Greece (4th Department of Internal Medicine, ATTIKON University Hospital; 2nd Department of Internal Medicine, Sismanogleion Athens General Hospital; and 2nd Department of Surgery, "G. Gennimatas" General Hospital of Thessaloniki). The study was approved by the Institutional Review Boards of the participating hospitals and by the National Organization for Medicines and by the National Ethics Committee of Greece (EUDRA-CT-Number 2008-004807-67; www.clinicaltrials.gov NCT01070732).

Inclusion criteria were the following; a) female or male gender, b) age ≥ 18 years, c) written informed consent by the study participants, and d) medical condition necessitating the administration of antipyretic or analgesic medication. Medical conditions necessitating the administration of antipyretic or analgesic medication

making the patient eligible for this study were defined as follows; a) core temperature $\geq 38.5^{\circ}\text{C}$ due to an infectious disease; b) post-operative pain after open or laparoscopic cholecystectomy or after colectomy of such an intensity that required analgesia. Criterion of the pain intensity necessitating analgesia was any VAS (visual analogue scale) score ≥ 50 mm; and c) pain due to neoplasia of such an intensity that required analgesia. Criterion of the pain intensity necessitating analgesia was any VAS ≥ 50 mm.

Exclusion criteria were; a) age lower than 18 years, b) denial for informed consent, c) history of liver cirrhosis, d) serum creatinine greater than 3 mg/dl, e) serum asparagine aminotransferase greater than 3 times the upper normal limit, f) any history of hypersensitivity to NSAIDs, g) any history of abuse of analgesics, h) pregnancy or lactation, i) fulminant hemorrhage of the upper or lower digestive tract, j) thrombocytopenia defined as less than 50,000 platelets/mm³, k) non-prior administration of any formulation of paracetamol the last two days, and l) non-concomitant administration of any other antipyretic/analgesic during the first 6 h after the end of infusion of the study drug including PCA (patient controlled analgesia) pump.

All patients received one single dose of 1000 mg of paracetamol (APOTEL[®], UniPharma, Athens, Greece). The drug was available at a volume of 6.7 ml; it was dissolved with 100 ml 0.9% sodium chloride and it was infused within 15 min by a catheter inserted under aseptic conditions in a forearm vein.

All patients were under intense follow-up. This comprised of a) measurements of the core temperature before drug infusion and at 0.5, 1, 2, 3, 4, 5, and 6 h after drug infusion. This was done for patients enrolled for fever. Each patient was given one thermometer for individual use and recordings of core temperature were done by mouth; b) patient's impression of pain intensity by VAS score before drug infusion and at 1, 2, 4, and 6 hours after drug infusion. This was done for patients enrolled for pain management. We asked each patient to grade the intensity of his/her pain at a scale from 0 to 100 mm where 0 indicated no pain and 100 mm reflected the worse pain he/she has ever felt (6); c) blood sampling before drug infusion and at 1 and 6 h post drug infusion. A total amount of 3 ml was sampled under aseptic conditions by venipuncture of one forearm vein and collected into sterile tubes without anticoagulant; d) need for rescue medication within the next 5 days either because core temperature relapsed to $\geq 38.5^{\circ}\text{C}$ or VAS relapsed to ≥ 50 mm. The time to antipyresis/analgesia with each rescue dose was recorded by visits every 2 h to each patient. The rescue medication could be either a similar dose of the study drug or any other compound and this

was decided by the attending physician; and f) serious adverse events (SAEs) and non-serious adverse events (non-SAEs). Defervescence was defined as any core temperature less than or equal than 37.1°C. Analgesia was defined as any VAS score less than or equal than 30 mm.

SAE was considered to be any unexpected event that a) led to death, b) put the patients' life in danger, c) prolonged hospitalization, d) was accompanied by permanent or considerable disability, or e) any grade IV laboratory abnormality.

All clinical information was recorded in a clinical report form (CRF). All CRFs were checked by an independent monitor.

Study endpoints and study power

The primary end-point of the study was the efficacy of the new intravenous formulation of 1 g of paracetamol (APOTEL®) as antipyretic and analgesic medication. The secondary study end-points were a) the response of patients to rescue medication, b) pharmacokinetics of paracetamol after the intravenous infusion of the new formulation (APOTEL®), and c) the effect of the new formulation of paracetamol (APOTEL®) on serum inflammatory mediators.

Taking into consideration that the expected ratio of medical indications leading to study enrolment, i.e., fever:pain would be 2:1, to achieve decreases of measured core temperature and pain intensity over-time follow-up at a 5% significance level compared with baseline with 80% power, it was calculated that 100 patients should be enrolled in total.

Laboratory analysis

Blood samples were transported on the same day by a courier service to the central lab at the Research Laboratory of Immunology of Infectious Diseases at the 4th Department of Internal Medicine of ATTIKON University Hospital of Athens. After centrifugation, serum was stored at -70°C until analysis.

For the measurement of paracetamol (acetaminophen, APAP) and its metabolites, a 0.15 ml aliquot of serum was mixed with 0.3 ml of 6% v/v perchloric acid aqueous solution containing the internal standard, theophylline (Sigma Co., St. Louis, MO, USA), in a centrifuge tube and vortexed vigorously for 5 s. The tube was then centrifuged at $1,700 \times g$ and 4°C for 5 min. A 50- μ l aliquot of the supernatant fraction was injected into an HPLC system using a reversed phase column (4.6 \times 250 mm, C18; Waters, Milford, MA, USA). The mobile phase was acetonitrile/0.05 mM sodium sulfate solution (2:98, v/v) at a flow rate of 1.5 ml/min at 30°C and the detection wavelength was 254 nm. The detection times

for APAP, the *N*-sulfate-APAP metabolite, and the glucuronide-APAP metabolite were 13.17, 7.81, and 8.49 min, respectively. The concentrations of APAP and the metabolites were calculated by generating a standard curve with known concentrations (Eastmann, Rochester, NY, USA). The inter-day variation of the assay was 3.2%.

Concentrations of interleukin-6 (IL-6) were measured in serum by an enzyme immunoassay (R&D Inc., Minneapolis, MN, USA). The lower detection limit was 20 pg/ml.

Statistical analyses

Core temperature, VAS, APAP, and serum metabolites were expressed as the means \pm S.E.M. because they followed normal distribution. IL-6 was expressed as the median and interquartile range (IQR) because they followed linear distribution. Comparisons of core temperatures and of VAS scores over-time follow-up compared with the baseline before start of drug infusion were done by the paired *t*-test. Time until apyrexia and time until analgesia after drug infusion was calculated by Kaplan-Meier analysis. Comparisons of the time until apyrexia for patients asking for diverse rescue medications due to relapse of fever were done by the Mantel-Cox log-rank test. Comparisons of serum APAP and serum metabolites between responders and non-responders to paracetamol treatment were done by Student's *t*-test. Changes of core temperature and of VAS from the baseline were calculated; correlations between these changes and serum APAP and metabolites were done according to Spearman. Comparison of IL-6 over-time follow-up to the baseline was done by Wilcoxon's rank sum test. Any value of *P*-value below 0.05 after adjustment for multiple comparisons by Bonferroni was considered significant.

Results

Study population

The study flow-chart is shown in Fig. 1. From the 100 patients, 71 were enrolled for fever management and 29 patients were enrolled for pain management. The demographic characteristics of the enrolled patients in relation with the medical condition for study enrolment are shown in Table 1. Because only five patients were enrolled for neoplastic pain management, these were considered in the analysis together with those patients enrolled for post-operative pain management.

Efficacy of 1 g intravenous paracetamol in fever management

Core temperature was considerably decreased after

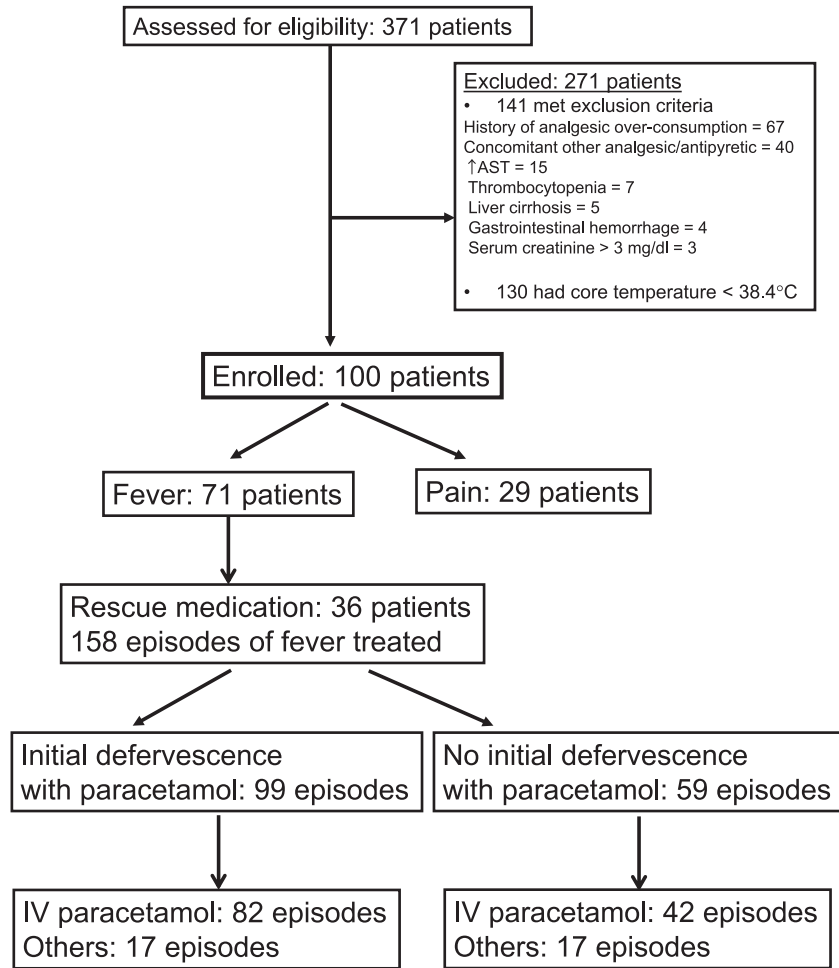


Fig. 1. Study flow-chart. AST, asparagine aminotransferase; IV, intravenous.

Table 1. Demographic characteristics of 100 patients enrolled in the study

	Patients enrolled for fever (n = 71)	Patients enrolled for pain (n = 29)
Gender (male/female)	44/27	12/17
Age (years, mean ± S.D.)	57.5 ± 22.1	59.6 ± 13.8
Underlying diseases (n, %)	Community-acquired pneumonia = 29 (40.8)	Laparoscopic cholecystectomy = 18 (62.1)
	Acute pyelonephritis = 14 (19.7)	Open cholecystectomy = 2 (6.9)
	Skin and soft tissue infections = 9 (12.7)	Metastatic tumor malignancy = 5 (17.2)
	Intraabdominal infections = 5 (7.1)	Colectomy = 4 (13.8)
	H1N1-related pneumonia = 4 (5.6)	
	Infectious mononucleosis = 4 (5.6)	
	Other infections = 6 (8.5)	

the first 0.5 h (Fig. 2). Defervescence was achieved in 52 patients (73.2%) within a median time of 3 h. After the end of the infusion of the study drug, a total of 36 patients (50.7%) required at least one more dose of rescue medication because core temperature relapsed to $\geq 38.5^{\circ}\text{C}$. The median time until requirement of a second dose of antipyretic was 6.5 h. As expected, this

time was shorter for patients who did not become afebrile with the first dose of paracetamol (median of 5 h vs. 7.0 h, $P = 0.041$). In total within the next 5 days after the first dose of 1000 mg of paracetamol, these patients needed 122 intravenous doses of 1 g paracetamol (APOTEL[®]); 18 doses of intravenous 400 mg parecoxib; and 16 oral doses of paracetamol (1 g) or mefenamate

(750 mg). Analysis showed that all other rescue agents were more effective than rescue paracetamol to achieve defervescence when administered to patients who failed to become afebrile with the first intravenous dose of

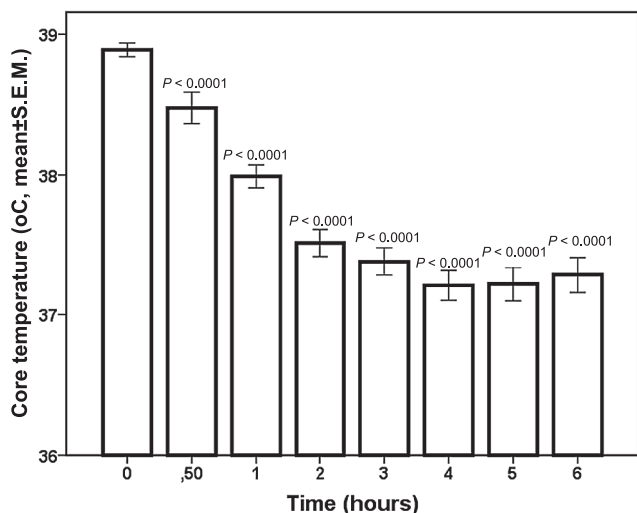


Fig. 2. The antipyretic effect of 1000 mg of intravenous paracetamol. Changes of core temperature within the first 6 h after infusion of the study drug in 71 patients. $N = 71$ for all time intervals. P -values compared with baseline time 0 before the start of paracetamol infusion are provided and they are corrected by Bonferroni for multiple testing.

paracetamol (Fig. 3).

Among the 19 patients who failed to become afebrile, 6 (31.6%) were not started on antibiotics in parallel with the infusion of the study drug, 7 (37.6%) were treated with one β -lactam, 3 (15.8%) were treated with daptomycin, 2 (10.5%) were treated with one fluoroquinolone, and 1 (5.2%) was treated with tigecycline. Among the 52 patients who became afebrile, 29 (55.8%) were not started on antibiotics in parallel with the infusion of the study drug, 11 (21.2%) were treated with one β -lactam, 3 (5.8%) were treated with daptomycin, 3 (5.8%) were treated with metronidazole, 2 (3.8%) were treated with one macrolide, 2 (3.8%) were treated with one aminoglycoside, 1 (1.9%) was treated with one fluoroquinolone, and 1 (1.9%) was treated with tigecycline. No differences in the distribution of administered antimicrobials were found between patients who experienced defervescence and patients who failed to experience defervescence ($P = 0.177$).

Efficacy of 1 g intravenous paracetamol in pain management

Follow-up VAS evaluation of pain showed relief after the first 0.5 h (Fig. 4). Analgesia was achieved in 17 patients (86.4%) within a median time of 2 h. After the end of the infusion of the study drug, additional doses of analgesics were needed by 17 patients (58.6%)

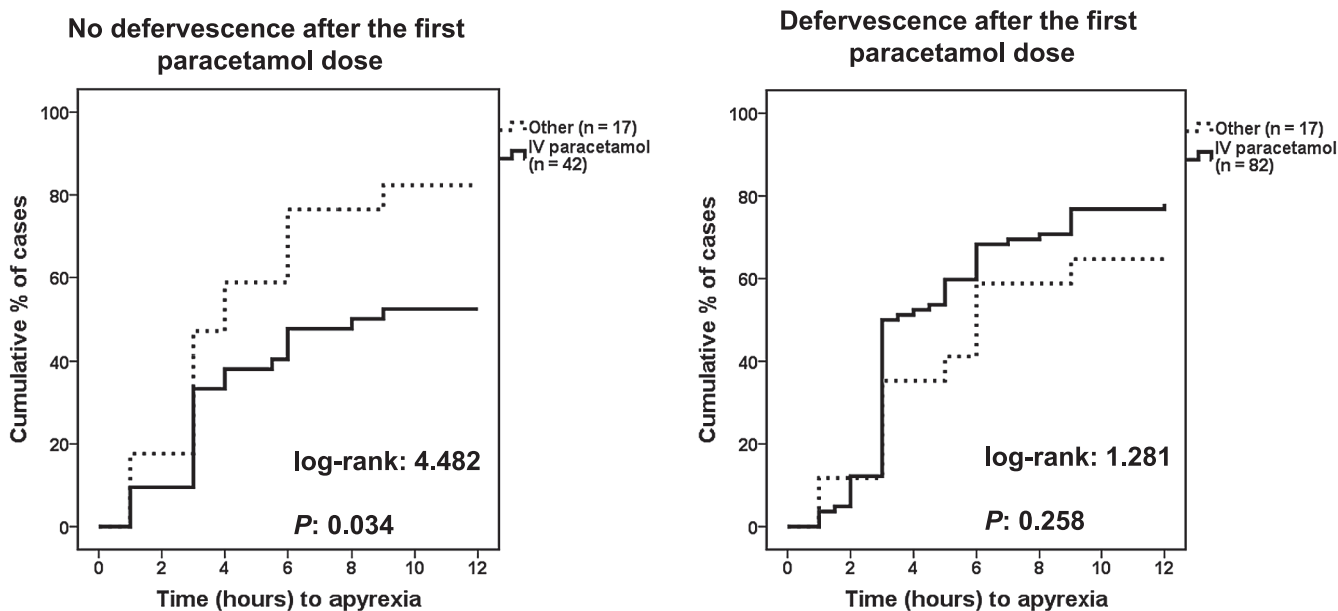


Fig. 3. Time to defervescence among rescue regimens. Some patients asked for rescue medication after relapse of fever 6 h post infusion of the study drug. At the discretion of the attending physicians, intravenous 1000 mg paracetamol or other antipyretics were administered. Results were analyzed separately for those who reached defervescence with the first dose of the study drug (i.e., core temperature $\leq 37.1^\circ\text{C}$) or those who did not. The number of febrile episodes for 5 days after the infusion of the study drug for which rescue medications was given is shown in parenthesis. P -values for comparisons between intravenous paracetamol and other agents by the log-rank test are provided.

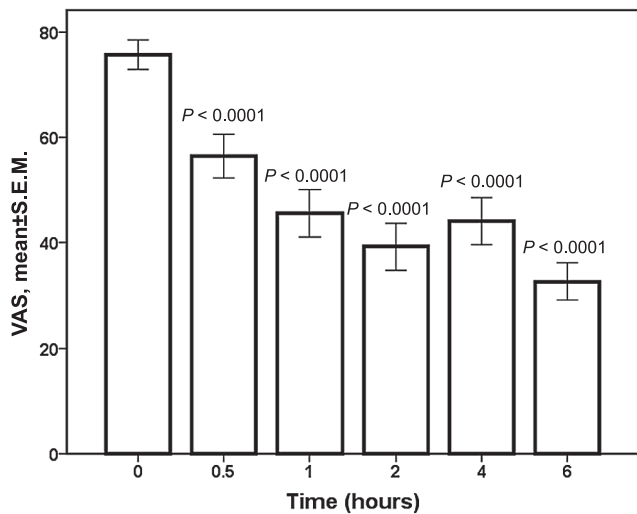


Fig. 4. Analgesic effect of 1000 mg of intravenous paracetamol. Changes of VAS pain scale within the first 6 h post infusion of study drug in 29 patients. $N = 29$ for all time intervals. P -values compared with baseline time 0 before the start of paracetamol infusion are provided and they are corrected by Bonferroni for multiple testing.

because VAS relapsed to ≥ 50 mm. The median time until requirement of rescue medication was 6.5 h. In total within the next 5 days after the first dose of 1000 mg of paracetamol, these patients needed 17 intravenous doses of 1 g of paracetamol (APOTEL®); 4 intravenous doses of 400 mg of parecoxib, and 10 oral doses of tablets containing both paracetamol (500 mg) and codeine (10 mg). Analgesia was achieved in 13 (76.5%), 3 (75%), and 8 (80%) patients, respectively.

Pharmacokinetics of paracetamol

Serum concentrations of APAP, of glucuronide-APAP, and of N -sulfate-APAP were measured in serum 1 h after the end of infusion and 6 h after the end of infusion. The clinical efficacy of paracetamol was correlated with its metabolism. Results showed that circulating concentrations of glucuronide-APAP after 1 h were greater in patients who failed to respond to paracetamol compared to responders (Fig. 5: a – c). To fully confirm these findings in individual patients, the correlations between serum levels of APAP and of both metabolites with changes of core temperature and of VAS from the baseline were explored. Results showed positive correlations between these changes and serum glucuronide-APAP at 1 h (Fig. 5: d and e). No significant correlations were found between serum APAP and these changes (data not shown).

Effect of paracetamol on circulating IL-6

Median (IQR) IL-6 in serum before drug infusion was

431.7 (200.0) pg/ml; it was 327.5 (190.0) pg/ml at 1 h post drug infusion; and 388.2 (90.0) pg/ml at 6 h post drug infusion. No statistically significant differences were found between these time intervals.

Safety

No SAE event was reported. No non-SAE was reported.

Discussion

Intravenous administration of 1 g of paracetamol provided an early decrease of core temperature and early relief from pain. Although the study design was single-arm and no comparator arm was provided, it presented many strong points in design. The first strong point is the significant number of patients with fever who were enrolled that provide robust data for the antipyretic effect of paracetamol. The only available data come from two studies that enrolled healthy volunteers subjected to experimental endotoxemia (7, 8) and from one very recent publication in patients admitted for emergencies (9). In studies of experimental endotoxemia, the effect of paracetamol in core temperature was recorded as early as 30 min after the end of infusion (7, 8) and corroborates the findings of the present study. In a recent study, patients admitted for fever in emergencies were randomized to intramuscular diclofenac, intravenous paracetamol, and oral paracetamol. Intravenous paracetamol achieved earlier decrease of core temperature compared with oral paracetamol (9).

The second strong point of the present study is the criteria for enrolment of patients necessitating pain relief. These were well-defined patients necessitating post-operative analgesia or analgesia for neoplastic pain who were not under the parallel influence of other analgesics and who had not experienced over-consumption of analgesics, as shown from the study flow-chart (Fig. 1). This allowed us to document that the administered formulation of paracetamol may be an effective first line management for pain. The third strong point of this study is that enrolled patients had medical or surgical disorders requiring hospitalization (Table 1). To our knowledge, this patient population is far more severe than those enrolled in previous studies, e.g., of experimental endotoxemia and of elective surgery.

Three randomized studies are available providing results for the efficacy of the 1-g intravenous formulation of paracetamol for the management of pain after abdominal surgery. The results of these studies corroborate the described efficacy of paracetamol in pain relief of the present study. More precisely, in a randomized trial, 88 patients were treated with 2 doses of 1 g of paracetamol for pain after laparoscopic surgery; efficacy was com-

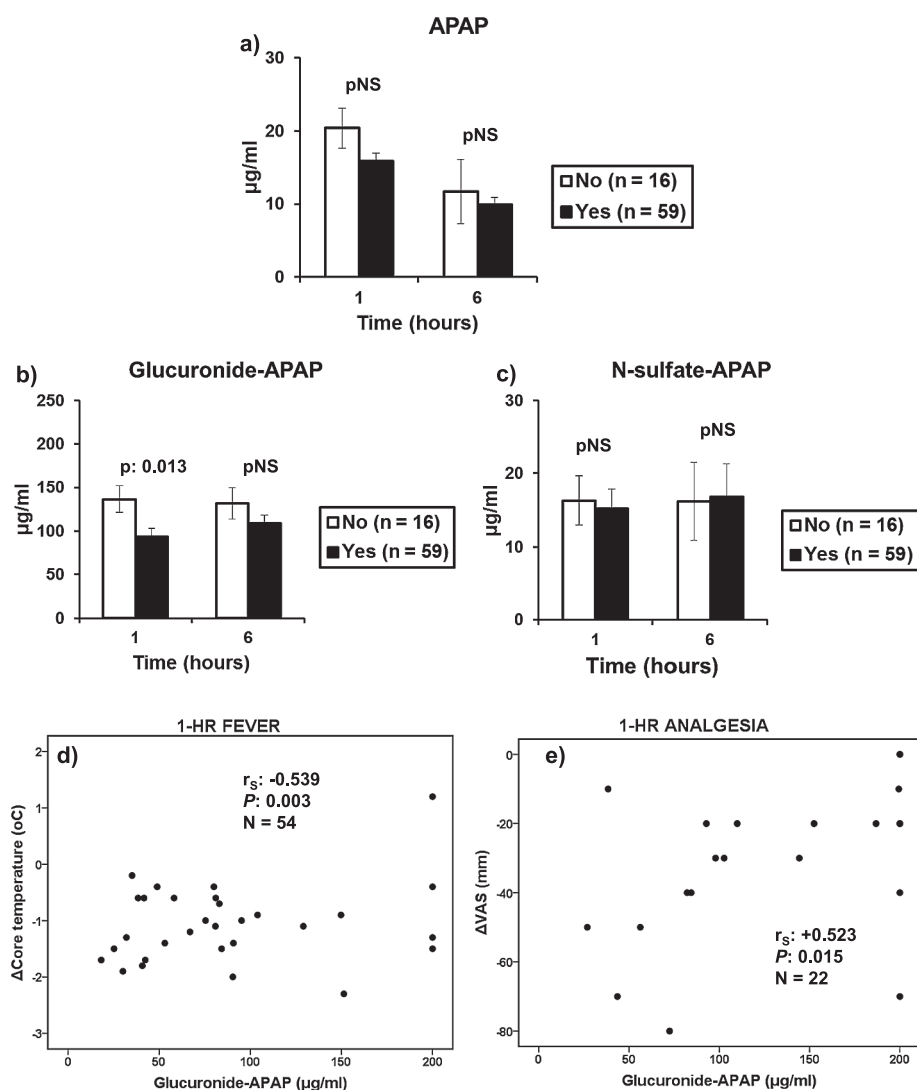


Fig. 5. Serum pharmacokinetics of paracetamol. a – c: Concentrations of active paracetamol (APAP) and of glucuronide and N-sulfate metabolites were measured in serum after the intravenous administration of 1000 mg of paracetamol. Results are given separately for patients experiencing alleviations of fever or pain (indicated by Yes) and for patients not experiencing alleviations of fever or pain (indicated by No). *P*-values indicate differences between patients who experienced and patients who did not experience alleviations of their symptoms. NS: non-significant. d and e: scatterplots of changes of core temperature and of the visual analogue scale for pain (VAS) from the baseline to serum concentrations of the glucuronide metabolite at 1 h. Correlation coefficients, *P*-values, and the absolute number of observations for each correlation are provided.

pared with 83 placebo-treated patients. Paracetamol achieved early relief from pain and the rate of decrease of VAS was similar to the one described in the present study (10). In another randomized study, 40 patients undergoing laparoscopic cholecystectomy were administered 1 g of intravenous paracetamol every 6 h on the first postoperative day followed by a similar oral dose regimen for 7 days. These patients were compared with another 40 patients treated with intravenous parecoxib followed by oral valdecoxib. The efficacy of the paracetamol regimen in pain relief was similar to the efficacy of the coxib regimen (5). Similar efficacy was also found between intravenous formulations of paracetamol, parecoxib, and dipyrrone in the postoperative pain relief after mild to moderate abdominal surgery (11).

Despite the lack of randomized design and the absence of a comparator arm, some comparisons were made possible regarding the efficacy of paracetamol over

other analgesics. These comparisons were done when both agents were used in the study population as rescue medication. The efficacy of intravenous paracetamol was similar to other analgesics comprising coxibs and codeine tablets. This similar efficacy corroborates findings of two previous clinical studies with a randomized design (5, 11). It should however be underscored that in the present study setting of patients with limited past experience of analgesics, paracetamol had similar efficacy to the other agents. This finding indicates that intravenous paracetamol may be a first-line analgesic providing an opioid-sparing effect. The opioid-sparing effect of intravenous paracetamol has also been described by the findings of a randomized study in women undergoing breast surgery. In this study, cumulative consumption of morphine was lower within women administered paracetamol as post-operative analgesia compared to those administered metamizol and placebo (12).

The most striking finding of the present study was the relationship between the clinical efficacy of paracetamol and pharmacokinetics. In general, serum levels of the free drug were within the expected range of concentrations achieved after the infusion of 1 g of paracetamol as described by others (13). However, serum concentrations of the glucuronide metabolite drug were greater among patients who failed to respond compared with responders. This is the first study describing the impact of metabolism on the clinical efficacy of the intravenous 1-g regimen of paracetamol. This finding may probably be expected since not all people metabolize paracetamol in a similar way. Four haplotypes of the *UTG1A6* gene encoding for the UTG1A6 enzyme have been described according to the carriage of major or minor frequency alleles of single nucleotide polymorphisms at positions 19, 315, 541, and 552 of the gene. UTG1A6 is catalyzing the glucuronidation of paracetamol and these haplotypes encode for enzymes with different activity (14, 15). Other factors, like age, seem also to impose considerably on the rate of formation of *N*-sulfate-APAP (16). The presented findings indicate that patients who failed to become afebrile with the first dose of paracetamol, reached defervescence with paracetamol as a rescue medication much slower compared to those administered other agents. This signifies that defervescence with paracetamol is difficult to achieve in some patient populations. The independency of this finding from any confounding factors is supported by two observations: a) patients who experienced defervescence and patients who did not experience defervescence did not differ in the distribution of antimicrobial agents administered, where necessary, for their underlying infection; and b) circulating IL-6 did not alter during the time of administration of paracetamol, indicating that achieved defervescence did not result from some attenuation of the inflammatory response of the host. The constant lack of defervescence with paracetamol in some patients and the absence of any anti-inflammatory effect render more probable that the only factor that explains why some patients respond to paracetamol treatment more efficiently than others is the rate of metabolism. The positive correlations of the change of body temperature and of VAS with the glucuronide metabolite (Fig. 5: d and e) suggest that a greater effort towards more rapid metabolism is done among non-responders compared to responders. The exact driver of this phenomenon remains to be defined.

The presented results clearly indicated that the studied intravenous formulation of paracetamol was clinically effective and achieved early defervescence and early relief from pain. The clinical efficacy of paracetamol is dependent on the rate of drug metabolism.

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Conflicts of Interest

The authors indicated no potential conflicts of interest.

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