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CLINICAL TRIALS

Randomized, controlled, multicentre clinical trial of the antipyretic effect of intravenous paracetamol in patients admitted to hospital with infection

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AIM

No randomized study has been conducted to investigate the use of intravenous paracetamol (acetaminophen, APAP) for the management of fever due to infection. The present study evaluated a new ready-made infusion of paracetamol.

METHODS

Eighty patients with a body temperature onset ≥38.5°C in the previous 24 h due to infection were randomized to a single administration of placebo ($n = 39$) or 1 g paracetamol ($n = 41$), and their temperature was recorded at standard intervals. Rescue medication with 1 g paracetamol was allowed. Serum samples were collected for the measurement of APAP and its metabolites. The primary endpoint was defervescence, defined as a core temperature ≤37.1°C.

RESULTS

During the first 6 h, defervescence was achieved in 15 (38.5%) patients treated with placebo compared with 33 (80.5%) patients treated with paracetamol 1 g ($P < 0.0001$). The median time to defervescence with paracetamol 1 g was 3 h. Rescue medication was given to 15 (38.5%) and five (12.2%) patients allocated to placebo and paracetamol, respectively ($P = 0.007$); nine (60.0%) and two (40.0%) of these patients, respectively, experienced defervescence. No further antipyretic medication was needed for patients becoming afebrile with rescue medication. Serum glucuronide-APAP concentrations were significantly greater in the serum of patients who did not experience defervescence with paracetamol. The efficacy of paracetamol was not affected by serum creatinine. No drug-related adverse events were reported.

CONCLUSIONS

The 1 g paracetamol formulation has a rapid and sustainable antipyretic effect on fever due to infection. Its efficacy is dependent on hepatic metabolism.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The antipyretic effect of intravenous paracetamol for fever due to infections has not been studied previously in a randomized study.
- Intravenous paracetamol provides rapid relief of fever in humans subjected to endotoxaemia.

WHAT THIS STUDY ADDS

- The efficacy of a new formulation of 1 g paracetamol in comparison with placebo was studied for fever due to infections.
- Median time to defervescence with paracetamol was 3h.
- Efficacy is modulated by hepatic metabolism.

Tables of Links

TARGETS
Enzymes
Cyclooxygenase

LIGANDS
Aspirin
Ibuprofen
IL-6
Paracetamol

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Fever is the most common symptom of infection but its importance seems to be neglected. This is underscored by the lack of published clinical trials for the management of fever as a symptom of an infection. A web search from 2000 until the present day disclosed a limited number of clinical studies on the evaluation of the safety and efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for fever that develops during infection. Four of these studies have been conducted in adult populations [3–6] and another seven in paediatric populations [7–13]. From the clinical studies conducted in adults, the first referred to a comparison of orally administered acetaminophen with aspirin for upper respiratory tract infections [3]; the second referred to the intravenous administration of ibuprofen compared with placebo in patients with malaria [4]; the third compared intravenous ibuprofen with placebo in critically ill patients [5]; and the fourth compared zaltoprofen with loxoprofen in patients with types A and B influenza [6].

Paracetamol (acetaminophen, APAP) is one of the most frequently used antifebrile medications. Its mechanism of action varies widely from the other NSAIDs because it readily diffuses through the blood–brain barrier in the central nervous system, where it inhibits the action of the COX-3 isoenzyme of cyclooxygenase (COX) [14]. Paracetamol is administered intravenously in hospitalized patients. However, there are limited clinical data available on the safety and efficacy of intravenously administered paracetamol. Only two double-blind, randomized studies have been conducted. In both of these studies, the study population comprised healthy volunteers subject to endotoxaemia, rather than patients. These studies found intravenous paracetamol to have a rapid antipyretic effect [15, 16]. The only available publication on the antipyretic effect of intravenous paracetamol in infections described a population of 71 Greek patients enrolled in a prospective, open-label, single arm trial [17]. These patients were administered 1 g paracetamol intravenously within 15 min. Defervescence was achieved in 73.2% of patients within 3 h [17].

A new formulation for intravenous administration is now available, in which 1 g paracetamol is provided in polypropylene bags with a volume of 100 ml, with the possibility of immediate connection with the patient's infusion device. The present study compared the efficacy of this new formulation *vs*. placebo for the management of fever due to infection.

Patients and methods

Study design

This was a double-blind, randomized, placebo-controlled clinical study, conducted in patients admitted to five internal medicine departments across Greece (EudraCT number 2014-002588-14). The study protocol was approved by the ethics committees of the participating hospitals, by the National Ethics Committee of Greece (approval 81/14) and by the National Organization for Medicines of Greece (approval IS-78/14). All patients provided written informed consent for participation in the study. The study is registered (ClinicalTrials.gov NCT identifier: NCT02283203). There was no change of protocol until study completion.

Adult patients of both genders could be enrolled, provided that they met all of the following inclusion criteria: (a) fever onset within the previous 24 h; (b) body core temperature ≥38.5°C; and (c) infection of the upper or lower respiratory tract, acute pyelonephritis or infection of the skin and soft tissues.

Exclusion criteria were: (a) age below 18 years; (b) refusal to give written consent; (c) intake of paracetamol for any reason (orally, intravenously or intramuscularly) in the previous 12 h; (d) intake of any NSAID in the previous 8 h; (e) intake of any steroidal anti-inflammatory drug in the previous 12 h; (f) cirrhosis of the liver; (g) serum creatinine >3 mg dl^{-1}; (h) aspartate aminotransferase more than three times greater than the upper normal limit; (i) known allergy to NSAIDs or to paracetamol; (j) pregnancy or lactation; (k) active bleeding of the upper or lower gastrointestinal tract; and (l) thrombocytopenia, defined as an absolute platelet count below 50 000 mm^{-3}.

Upper respiratory tract infections were defined as the onset of at least two of the following signs in the previous 24 h: (a) redness and a purulent discharge from the throat; (b) intense nasal discharge; (c) cough; (d) enlargement of the cervical lymph nodes; (e) enlargement of the liver or spleen on deep abdominal palpation; and (f) an absolute lymphocyte count of >4000 mm^{-3} [18]. Lower respiratory tract infections were defined as the onset of at least two of the following signs in the previous 24 h: (a) dyspnoea; (b) a purulent expectoration; (c) auscultatory rales; and (d) new consolidation on a chest X-ray [19]. Acute pyelonephritis was defined as the onset of at least two of the following signs in the previous 24 h: (a) dysuria or frequency in urination; (b) pyuria, defined as more than 10 white blood cells per high-power field of spun urine; (c) pain induced after deep palpation of the right or left costovertebral angle; and (d) ultrasound findings compatible with acute pyelonephritis [20]. Acute bacterial skin and skin structure infections could involve either upper or lower extremities, and were defined as the onset of at least two of the following signs in the previous 24 h: (a) redness, warmth and oedema; (b) a well-circumscribed rim; (c) ultrasound findings compatible with soft-tissue infection; and (d) more than 12 000 white blood cells mm^{-3} [21].

Patients meeting all inclusion criteria and none of the exclusion criteria could be enrolled in the study. The study drugs (placebo or active drug) were constructed by the sponsor to be visually similar. A separate allocation sequence was designed for each study site by an independent statistician, who was the only holder of the allocation sequence. To generate this sequence, each of the five hospitals was given a list of 40 numbers, which were either 0 (placebo) or 1 (paracetamol). The numbers were generated using the Excel pseudorandom number generator, using a different random seed (key) for each hospital, thus converging the total sequence closer to 'true' randomness. The study drug was provided in the form of a polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Patients were randomly assigned to one of the following two groups:

- *Placebo*: receiving inactive vehicles diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific vehicles were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.
- *Active drug*: receiving 1 g paracetamol and inactive vehicles (APOTEL Max®, Uni-Pharma, Athens, Greece) diluted in water for injection at a volume of 100 ml and infused within 15 min. The inactive vehicles were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Follow-up for every patient was carried out for 30 h after the start of the study drug infusion and comprised: (a) measurement of body core temperature from the axilla before the infusion of the study drug, and at 0.5, 1, 2, 3, 4, 5 and 6 h postinfusion. A separate thermometer was provided for each patient; (b) a 3 ml peripheral blood sample before the infusion of the study drug and at 1 h and 3 h postinfusion. After venipuncture of one forearm vein under aseptic conditions, the sampled volume was collected into sterile and pyrogen-free tubes without anticoagulant; (c) administration of 1 g paracetamol as rescue medication (APOTEL Max®) 3 h after the start of the study drug infusion on patient demand or at the discretion of the attending physician. Attending physicians could administer one dose of rescue medication if the patient's body temperature returned to ≥38.5°C within 6 h to 24 h from the start of the study drug infusion, provided that they were not given further dose of this rescue medication. The exact time interval between the start of the study drug and start of the rescue medication was recorded, along with core body temperature, 2, 4 and 6 h after the start of rescue medication; and (d) the need for any other type of antipyretic medication after the administration of the study rescue medication. Adverse events (AEs) were recorded up to 10 days from the start of the study drug administration. A serious adverse event (SAE) was defined as any unexpected event that: (a) led to death; (b) put the patient's life in danger; (c) prolonged hospitalization; (d) was accompanied by a permanent or considerable disability; or (e) any grade IV laboratory abnormality. All other AEs were considered nonserious.

All baseline and follow-up information was recorded on a specific case report form (CRF). All CRFs were source-verified by a monitor blinded to the allocated treatment.

Serum pharmacokinetics

Collected blood samples were centrifuged and serum was stored at –70°C. After thawing, concentrations of free paracetamol (APAP), glucuronide-APAP and N-sulfate-APAP were measured after analysis through a high-performance liquid chromatography system by an assay developed in-house, as described elsewhere [17].

Study endpoints

The primary study endpoint was the comparative efficacy of intravenously administered 1 g paracetamol over placebo for the achievement of defervescence, which was defined as any core body temperature ≤37.1°C at 3 h after the infusion of the study drug.

The secondary study endpoints were: (a) a comparison between the two study groups on the frequency and time to administration of the rescue medication; (b) the correlation between defervescence with the rescue drug and the efficacy of the initially administered type of study drug (placebo over active drug); (c) the correlation between the achievement of defervescence and the concentrations of free active

paracetamol and its metabolites in patients' serum; and (d) the correlation between the achievement of defervescence with the rescue medication and the need for the administration of further antipyretic drugs, at the discretion of the attending physicians.

The antipyretic effect of the study formulation of paracetamol in relation to baseline serum creatinine was the exploratory endpoint. A serum creatinine level less than 1 mg ml^{-1} was set as a cut-off for the validation of this endpoint, as defined elsewhere [22].

Power of the study

The study was powered for the study primary endpoint. This was a multicentre study, in which data would be collected from five centres, with a roughly equal number of patients from each, with a 1:1 ratio in the two groups, separately randomized for each centre. It was anticipated that, in each centre, defervescence would be achieved in 10% of patients allocated to the placebo arm. If the true within-centre odds ratio for achievement of defervescence in the paracetamol group relative to the placebo group was 7, based on a previous publication [17], then the study required 40 subjects in each group to be able to reject the null hypothesis that this odds ratio equals 1, with a probability (power) of 0.9. The Type I error probability associated with this test of the null hypothesis is 0.05 using a continuity-corrected Mantel–Haenszel chi-squared statistic.

Statistical analysis

Unblinding to study drugs A and B was done after all CRFs data were verified for data enrolment. Final unblinding to placebo and paracetamol arms was done at the end of the analysis. Baseline quantitative variables followed normal distribution, as assessed by Kolmogorov–Smirnov's statistics, and were expressed as means ± standard deviations. Baseline comparisons between groups were done by the Fisher exact test for the qualitative variables and by the Student's t-test for the quantitative variables. Core temperature and concentrations of APAP and APAP metabolites at 1 h and 3 h were expressed as means ± standard errors, and compared using the Mann–Whitney U test. Comparisons of the advent of defervescence and of the need for rescue medication between the groups were carried out using the Fisher exact test. Comparison of the antipyretic effect of paracetamol within subgroups of creatinine was carried out using the Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated according to Mantel–Haenszel's statistics. The homogeneity of the ORs between study sites was studied using the Breslow–Day test. The median and interquartile ranges of time to the advent of defervescence and to the need for rescue medication were measured after Kaplan–Meier analysis; comparisons between groups were done by the log-rank test. Any two-sided *P*-value below 0.05 was considered significant.

Results

In total, 231 patients were asked to provide written consent for assessment of eligibility, and 185 provided this. The study flow chart is shown in Figure 1. As intense follow-up of enrolled patients was mandated as per the protocol, once a patient had been enrolled, no screening was run in parallel,

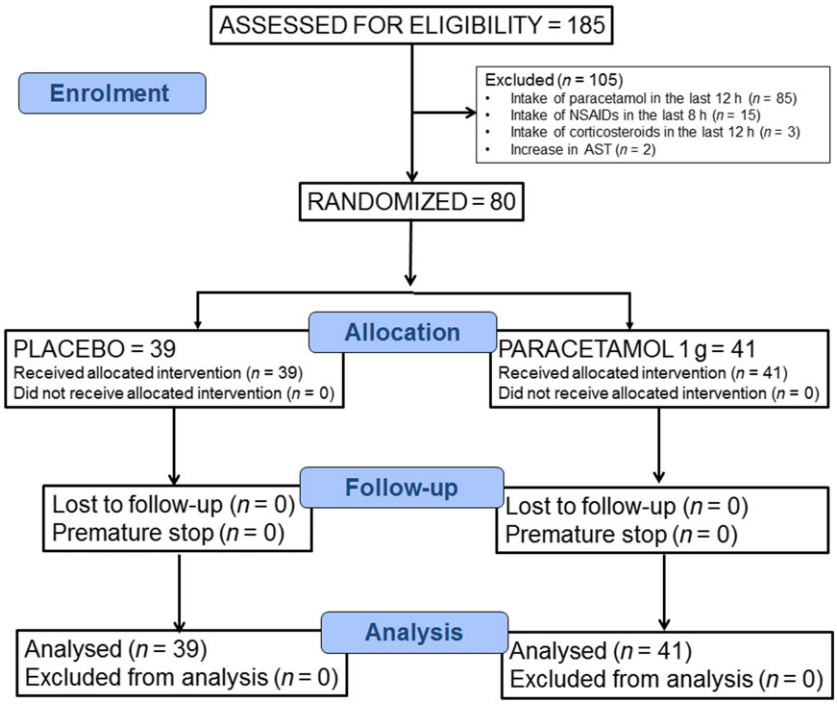

Figure 1

Study flow chart. AST: aspartate aminotransferase; NSAIDs: nonsteroidal anti-inflammatory drugs

to avoid mistakes by the study personnel during follow-up. This may have resulted in the loss of eligible patients. The first patient was enrolled on 18 February 2015, and the last on 19 March 2016. In total, 39 patients were randomized to the placebo arm and 41 to the paracetamol arm. No patients were lost during follow-up; all patients finished the study completely, with no dropouts. Baseline demographics did not differ between the two treatment groups (Table 1).

Primary study endpoint

The core body temperature was already lower in the overall patient population 1 h after administration of paracetamol 1 g compared with placebo (mean core temperature 37.89°C *vs*. 38.36°C; $P = 0.019$; Figure 2A). The rate of defervescence was greater in the paracetamol arm from the first hour (Figure 2B). Overall, during the 6-h follow-up, sustained defervescence was found in 15 (38.5%) patients treated with placebo compared with 33 (80.5%) patients treated with paracetamol 1 g ($P < 0.0001$). The OR for defervescence with paracetamol 1 g was 6.60 (95% CI 2.41, 18.05). This OR, as confirmed by the Breslow–Day test ($\chi^2 = 5.8$, df = 4, $P = 0.215$), was spread homogeneously in the five study sites. The median time to defervescence with placebo was 6 h (interquartile range 3–6 h); this was 3 h after treatment with paracetamol 1 g (interquartile range 1–5 h; ($P < 0.0001$ between groups) (Figure 2C).

Secondary endpoints

Paracetamol 1 g rescue medication was given to 15 (38.5%) patients allocated to the placebo arm and five (12.2%) allocated to the paracetamol arm ($P = 0.007$) (Figure 3A). Treatment with paracetamol was preventive of the need for rescue medication (OR 0.22, 95% CI 0.07, 0.69). The median time to rescue medication for those patients in the placebo group who needed it was 3 h (interquartile range 3–24 h) and for patients in the paracetamol group needing this medication was 4.5 h (interquartile range 3–24 h; $P = 0.013$ between groups). Core temperature follow-up for patients in each group not requiring and requiring rescue medication is shown in Figures 3C and 3D, respectively. From the 15 patients originally allocated to placebo, nine (60.0%) experienced defervescence with the rescue medication; defervescence was experienced with the rescue medication by two (40.0%) of five patients originally allocated to paracetamol ($P = 0.617$).

Serum APAP and metabolites were below the limit of detection in all 80 patients before infusion of the study drug. They were also below the lower limit of detection in serum sampled 1 h and 3 h after administration of placebo. However, serum concentrations of the glucuronide-APAP metabolite were significantly greater in the serum of patients who did not experience defervescence with paracetamol 1 g (Figure 4).

In total, 20 patients were administered paracetamol rescue medication. Eleven of these experienced defervescence, none of whom needed another drug for fever management over the following 24 h (0%). The remaining nine did not experience defervescence, and another drug was needed for fever management in seven (77.8%) over the next 24 h ($P < 0.0001$).

Exploratory endpoint

From the 41 patients allocated to treatment with paracetamol 1 g, 17 had a serum creatinine level lower than 1 mg dl^{-1} and

Table 1

Demographics of patients assigned into each treatment group

	Placebo ($n = 39$)	Paracetamol 1 g ($n = 41$)	*P*-value
Male (*n*, %)	18 (46.2)	20 (48.8)	0.827
Age (years, mean ± SD)	50.1 ± 24.7	53.0 ± 20.8	0.584
Serum creatinine (mg dl^{-1}, mean ± SD)	0.97 ± 0.41	1.00 ± 0.32	0.713
Type of infection (*n*, %)			
Upper respiratory tract infection	12 (30.8)	14 (34.1)	0.814
Lower respiratory tract infection	12 (30.8)	14 (34.1)	0.814
Acute pyelonephritis	7 (17.9)	9 (22.0)	0.782
ABSSSI	8 (20.5)	4 (9.8)	0.220
Co-existing disorders (*n*, %)			
Type 2 diabetes mellitus	3 (7.7)	5 (12.2)	0.713
Chronic heart failure	3 (7.7)	3 (7.3)	1.000
COPD	3 (7.7)	3 (7.3)	1.000
Malignancy	3 (7.7)	2 (4.9)	0.671
Nephrolithiasis	3 (7.7)	2 (4.9)	0.671

ABSSSI, acute bacterial skin and skin structure infection; COPD, chronic obstructive pulmonary disease; SD, standard deviation

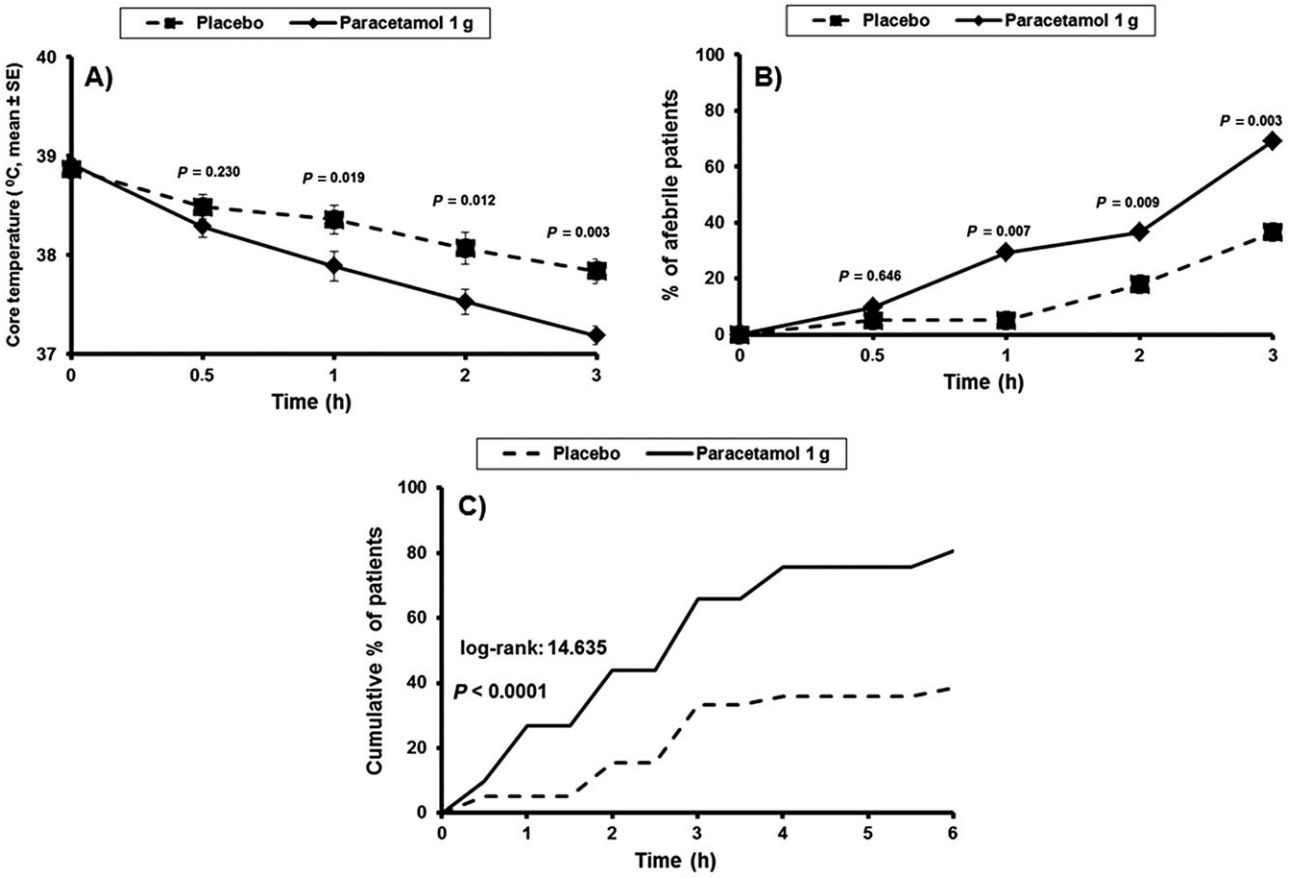

Figure 2

Primary study endpoint. (A) Core temperature over the first 3 h of follow-up of patients enrolled in each group. (B) Percentage of each group being afebrile at the indicated time of follow-up. (C) Time to defervescence within the first 6 h of follow-up. *P*-values represent statistical comparisons between placebo-treated patients (n = 39) and paracetamol 1 g–treated patients (n = 41) at the indicated time intervals. SE, standard error

24 had a serum creatinine level ≥1 mg dl^{-1}; 13 (75.5%) and 20 (83.3%), respectively, experienced defervescence (P = 0.698).

Safety

No (0%) SAEs were reported in the placebo arm and two (4.9%) were reported in the paracetamol arm (P = 0.494). These two SAEs comprised deaths, which occurred more than 24 h after infusion of the study drug; in both cases, this was caused by the underlying infection. No AEs (0%) were reported in the placebo arm and two non-SAEs (4.9%) were reported in the paracetamol arm (P = 0.494). These non-SAEs comprised one episode of nausea and one episode of hypoglycaemia, both of which were not related to the study drug.

Discussion

The present double-blind, placebo-controlled, randomized clinical trial was the first to show the superiority of intravenous paracetamol over placebo for the management of fever due to infection. Using a similar design, the efficacy of intravenous paracetamol has previously been studied in healthy volunteers who were administered intravenous endotoxins [15, 16]. Our study design was superior to studies of human endotoxaemia for two main reasons: (a) it involved patients with infections and evoked a real-life scenario; and (b) fever resulting from endotoxaemia has different characteristics to fever resulting from a real infection because the molecular patterns associated with the released pathogen are not similar in all types of infections, and do not follow the kinetics of circulating endotoxins that are administered intravenously [23]. This also explains why, over time, some patients allocated to placebo became afebrile.

The present study used a preparation of paracetamol provided as a ready-made dilution in bags of 100 ml, with the possibility of immediate connection to the patient's infusion device. This formulation provides the advantage of all ready-to-use dilutions, in that there is a considerable financial benefit; nursing staff are not preoccupied with the preparation of dilutions and there is no cost of consumables to prepare the drug for infusion. The new formulation achieves rapid defervescence in 3 h; when given either as a first treatment or as a rescue medication, it significantly decreased the need for any further antipyretic drug and was free from any AEs.

It should be noted that one original finding described by our group in a previous open-label trial was validated here.

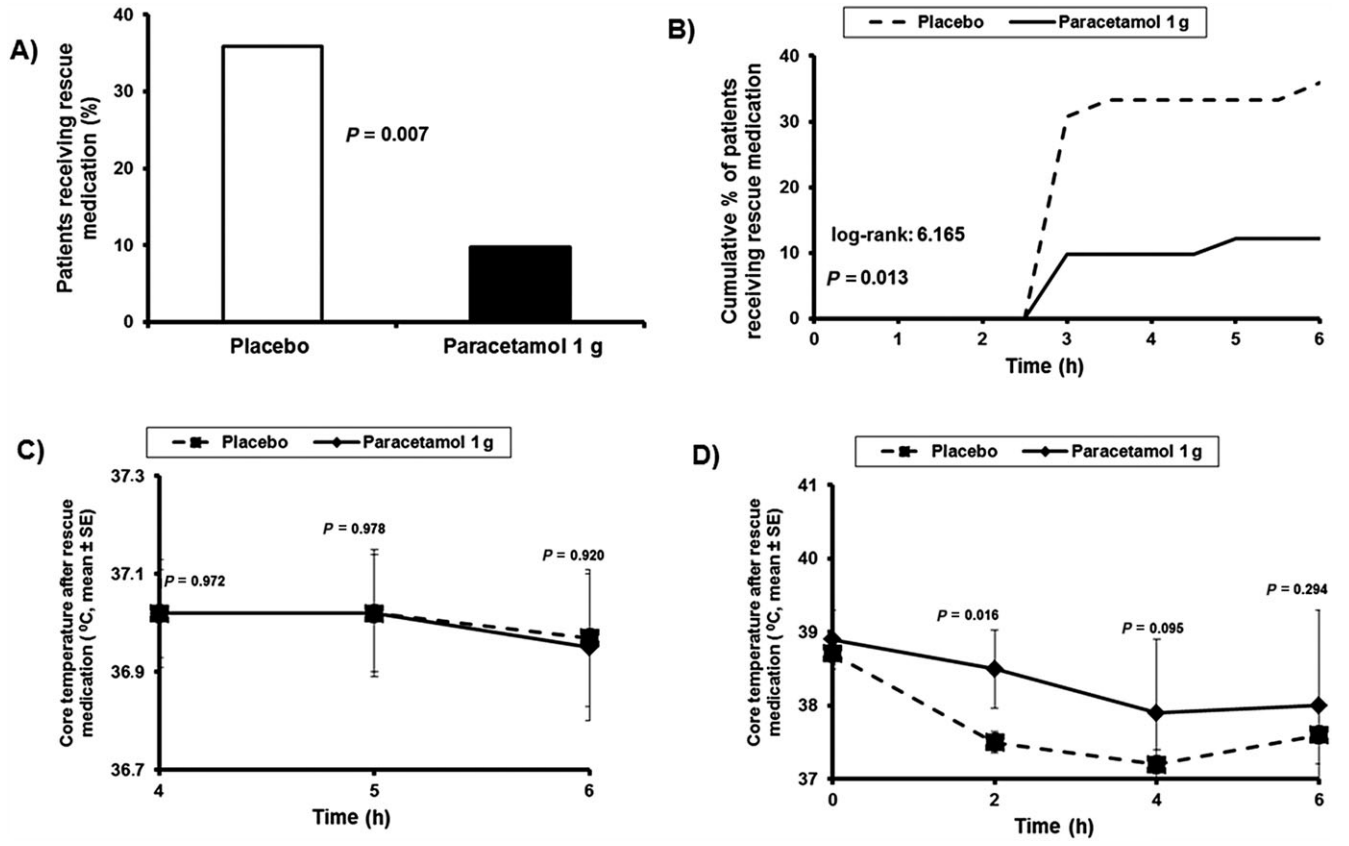

Figure 3

Secondary study endpoints. (A) Percentage of patients requiring one dose of rescue paracetamol 1 g in each treatment group. (B) Time to the need for one dose of rescue paracetamol 1 g from the time of study enrolment for each treatment group. (C) Core temperature in the first 4–6 h of follow-up for patients not requiring rescue medication (n = 24 for the placebo group and n =36 for the paracetamol group). (D) Core temperature over time for patients requiring rescue paracetamol 1 g (n = 15 for the placebo group and n = 5 for the paracetamol group). P-values represent statistical comparisons between placebo- and paracetamol 1 g–treated patients. SE, standard error

In our previous study [17], 1 g paracetamol was administered intravenously for the management of fever and pain in 100 patients. Pharmacokinetic analysis showed that concentrations of the glucuronide-APAP metabolite were greater in the serum of patients who failed to experience relief of their symptoms. This finding was fully replicated here, and suggests that lack of defervescence after intravenous administration of paracetamol is associated with the hepatic metabolism of the drug as conjugation with glucuronides is taking place in the liver. The impact of metabolism is further supported by the fact that the use of paracetamol as a rescue medication following initial treatment with paracetamol was accompanied by a slower decrease in core temperature compared with patients originally treated with placebo.

This was the first double-blind, randomized study assessing the antipyretic effect of paracetamol for fever due to infections. Several other studies of prospective or retrospective design assessed the effect of paracetamol administration among critically ill patients, but using different endpoints to fever. A retrospective analysis of 15 818 patients hospitalized in five different intensive care units (ICUs) in Australia showed that exposure of patients to paracetamol during their ICU stay was an independent protective factor against death. Despite the retrospective nature of the latter study, logistic regression analysis against confounding factors, such as surgery and infection, confirmed the finding [24]. In the prospective Permissive Hyperthermia through Avoidance of Acetaminophen in Known or Suspected Infection in the Intensive Care Unit (HEAT) study, patients aged 16 years or older and hospitalized in an ICU because of infection were randomized to either intravenous placebo (n = 344) or paracetamol 1 g (n = 346) every 6 h for 28 days or until ICU discharge. Although the two groups did not differ in ICU-free days (which was the primary endpoint), the median length of ICU stay of survivors in the placebo group was longer than that of survivors in the paracetamol group (4.3 *vs.* 3.5 days; P = 0.010) [25]. No AEs were noted in that study [25]. One probable explanation for the beneficial effects of paracetamol in critically ill patients comes from two smaller studies. In the first study [26], patients were administered placebo (n = 22) or 1 g paracetamol (n = 18) orally every 6 h for 3 days. Administration of paracetamol decreased circulating F2-isoprostane, indicating an antioxidant effect [26]. In the second study, 10 critically ill patients were administered 650 mg paracetamol intravenously every 6 h for 10 days; they were compared with 10 patients not administered any antipyretic unless core temperature reached 40°C. Circulating concentrations of interleukin

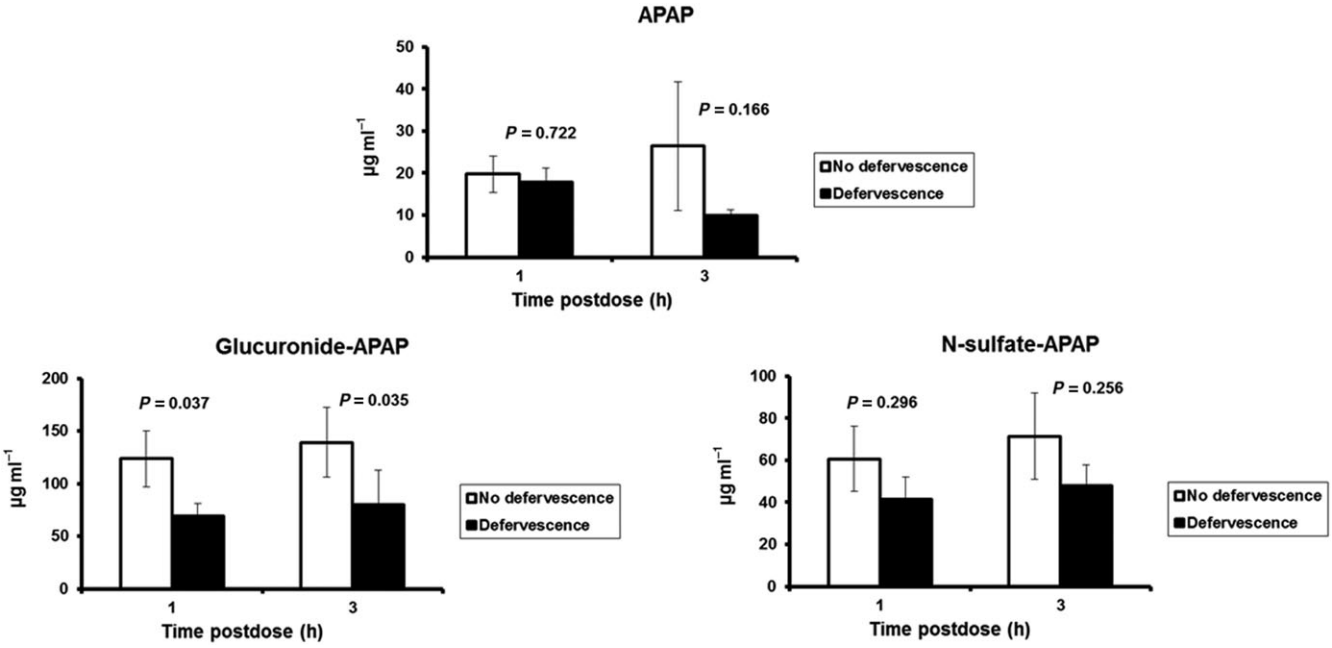

Figure 4

Relationship between serum paracetamol metabolites and defervescence. Concentrations of circulating acetaminophen (APAP) and of the glucuronide-APAP and N-sulfate metabolites are shown for the 41 patients allocated to treatment with 1 g paracetamol. Concentrations are provided in relation to the advent of defervescence (Yes, $n = 26$) or not (No, $n = 15$) within the first 3 h after the administration of paracetamol 1 g. *P*-values refer to statistical comparisons between patients with and without defervescence

6 were significantly decreased from baseline in the paracetamol group but not in the control group, which was in agreement with our previous observations [17, 27]. However, two other prospective studies found that aggressive antipyretic treatment was not of benefit for critically ill patients with sepsis [28, 29]. This observation was the same for all types of antipyretic treatment, not just for paracetamol.

Our results suggest that the new formulation of 1 g paracetamol in a ready-made 100 ml bag for infusion has a rapid antipyretic effect when given in patients with fever due to infection. This effect appears to be sustainable over time as most patients are not in need of rescue medication or of another antipyretic. Efficacy is dependent on the hepatic metabolism of paracetamol.

Competing Interests

The study was sponsored by Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., Athens, Greece. It was designed by both the sponsor and the coordinating investigator, Evangelos J. Giamarellos-Bourboulis, who are holders of the data, jointly carried out the analysis and made the decision to publish. Evangelos J. Giamarellos-Bourboulis has received honoraria for providing scientific advice to AbbVie, Chicago, IL, USA; Astellas, Athens, Greece; Biotest AG, Dreieich, Germany; and ThermoFisher Scientific GmbH, Henningdorf, Germany. He has received unrestricted educational funding by ThermoFisher Sceintific GmbH, Henningdorf, Germany; Sanofi SA, Athens, Greece; and by the Seventh Framework European Program HemoSpec. He has not received any financial support for the submitted study. The other authors have no competing interests to declare.

Contributors

T.T. and N.T. contributed to patient enrolment and the measurement of paracetamol and metabolites, and critical review of the manuscript for intellectual content, and they provided consent to publish. M.K., A.P., K.A., C.G., N. Ts., A.K. and S.S. contributed to patient enrolment and critical review of the manuscript for intellectual content, and they provided consent to publish. I.K.T. and G.S.S. contributed to study design and critical review of the manuscript for intellectual content, and they provided consent to publish. E.J.G.B. wrote the study protocol, drafted the manuscript and provided consent to publish.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44 (Database Issue): D1054–D1068.

2 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

3 Bachert C, Chuchalin AG, Eisebitt R, Netayzhenko VZ, Voelker M. Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose-ranging study. Clin Ther 2005; 27: 993–1003.

4 Krudsood S, Tangpukdee N, Wilairatana P, Pothipak N, Duangdee C, Warrell DA, *et al*. Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated *Plasmodium falciparum* malaria but prolongs parasitemia. Am J Trop Med Hyg 2010; 83: 51–5.

5 Morris PE, Promes JT, Guntupalli KK, Wright PE, Arons MM. A multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults. Crit Care 2010; 14: R125.

6 Azuma A, Kudoh S, Nakashima M, Nagatake T. Antipyretic and analgesic effects of zaltoprofen for the treatment of acute upper respiratory tract infection: verification of a noninferiority hypothesis using loxoprofen sodium. Pharmacology 2011; 87: 204–13.

7 Wong A, Sibbald A, Ferrero F, Plager M, Santolaya ME, Escobar AM, *et al*. Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. Clin Pediatr 2001; 40: 313–24.

8 Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. Arch Pediatr Adolesc Med 2006; 160: 197–202.

9 Duhamel JF, Le Gall E, Dalphin ML, Payen-Champenois C. Antipyretic efficacy and safety of a single intravenous administration of 15 mg/kg paracetamol versus 30 mg/kg propacetamol in children with acute fever due to infection. Int J Clin Pharmacol Ther 2007; 45: 221–9.

10 Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al*. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. Health Technol Assess 2009; 13: 11–63.

11 Kokki H, Kokki M. Dose-finding studies of ketoprofen in the management of fever in children: report on two randomized, single-blind, comparator-controlled, single-dose, multicentre, phase II studies. Clin Drug Investig 2010; 30: 251–8.

12 Kokki H, Kokki M. Ketoprofen versus paracetamol (acetaminophen) or ibuprofen in the management of fever: results of two randomized, double-blind, double-dummy, parallel-group, repeated-dose, multicentre, phase III studies in children. Clin Drug Investig 2010; 30: 375–86.

13 Senel S, Erkek N, Karacan CD. Comparison of acetaminophen and ketoprofen in febrile children: a single dose randomized clinical trial. Indian J Pediatr 2012; 79: 213–7.

14 Kumpulainen E, Kokki H, Halonen T, Heikkinen M, Savolainen J, Laisalmi M. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. Pediatrics 2007; 119: 766–71.

15 Kett DH, Breitmeyer JB, Ang R, Royal MA. A randomized study of the safety and efficacy of intravenous acetaminophen *vs*. intravenous placebo for the treatment of fever. Clin Pharmacol Ther 2011; 20: 32–9.

16 Peacock WF, Breitmeyer JB, Pan C, Smith WB, Royal MA. A randomized study of the efficacy and safety of intravenous acetaminophen compared to oral acetaminophen for the treatment of fever. Acad Emerg Med 2011; 18: 360–6.

17 Giamarellos-Bourboulis EJ, Spyridaki A, Savva A, Georgitsi M, Tsaganos T, Mouktaroudi M, *et al*. Intravenous paracetamol as an antipyretic and analgesic medication: the significance of drug metabolism. J Pharm Sci 2014; 124: 144–52.

18 Antonopoulou A, Baziaka F, Tsaganos T, Raftogiannis M, Koutoukas P, Spyridaki A, *et al*. Role of tumor necrosis factor gene single nucleotide polymorphisms in the natural course of 2009 influenza A H1N1 virus infection. Int J Infect Dis 2012; 16: e204–e208.

19 Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, *et al*. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia. A randomized trial. Am J Respir Crit Care Med 2006; 174: 84–93.

20 Pinson AG, Philbrick JT, Lindbeck GH, Schorling JB. Fever in the clinical diagnosis of acute pyelonephritis. Am J Emerg Med 1997; 15: 148–51.

21 Stryjweski ME, Graham DR, Wilson SE, O'Riordain W, Young D, Lentnek A, *et al*. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by Gram-positive organisms. Clin Infect Dis 2008; 46: 1683–93.

22 Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Individualizing pharmacotherapy in patients with renal impairment: the validity of the Modification of Diet in Renal Disease formula in specific patient populations with a glomerular filtration rate below 60 ml/min. A systematic review. PLoS One 2015; 10: e0116403.

23 Kritselis I, Tzanetakou V, Adamis G, Anthopoulos G, Antoniadou E, Bristianou M, *et al*. The level of endotoxemia in sepsis varies in relation to the underlying infection: Impact on final outcome. Immunol Lett 2013; 152: 167–72.

24 Suzuki S, Eastwood GM, Bailey M, Gattas D, Kruger P, Saxena M, *et al*. Paracetamol therapy and outcome of critically ill patients: a multicenter retrospective observational study. Crit Care 2015; 19: 162.

25 Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, *et al*. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 2015; 373: 2215–24.

26 Janz DR, Bastarache JA, Rice TW, Bernard GR, Warren MA, Wickersham N, *et al*. Acetaminophen for the reduction of oxidative injury in severe sepsis: the acetaminophen for the reduction of oxidative injury in severe sepsis trial. Crit Care Med 2015; 43: 534–41.

27 Honarmand J, Abdollahi M, Ahmadi A, Javadi MR, Khoshayand MR, Tabeefar H, *et al*. Randomized trial of the effect of intravenous paracetamol on inflammatory biomarkers and outcome in febrile critically ill patients. DARU J Pharm Sci 2012; 20: 12.

28 Schulma CI, Namias N, Doherty J, Manning RJ, Li P, Elhaddad A, *et al*. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. Surg Infect (Larchmt) 2005; 6: 369–75.

29 Lee BH, Inui D, Suh GY, Lim JY, Kwon JY, Park J, *et al*. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care 2012; 16: R33.