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Bioequivalence and Safety of Twice-Daily Sustained-Release Paracetamol (Acetaminophen) Compared With 3- and 4-Times-Daily Paracetamol: A Repeat-Dose, Crossover Pharmacokinetic Study in Healthy Volunteers

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Abstract

Twice-daily sustained-release (SR) paracetamol (acetaminophen) offers convenient administration to chronic users. This study investigated at steady state (during the last 24 hours of a 3-day dosing period) the pharmacokinetics, bioequivalence, and safety of twice-daily SR paracetamol compared with extended-release (ER) and immediate-release (IR) paracetamol. In this open-label, randomized, multidose, 3-way crossover study, 28 healthy subjects received paracetamol SR (2 × 1000 mg twice daily), ER (2 × 665 mg 3 times daily), and IR (2 × 500 mg 4 times daily). At steady state, twice-daily SR paracetamol was bioequivalent to ER and IR paracetamol. The 90% confidence intervals for the ratios of geometric means were within the acceptance interval for SR/ER paracetamol (AUC_{0-t}, 0.973–1.033; AUC_{0-24}, 0.974–1.034; $AUC_{0-\infty}$, 0.948–1.011; C_{max}, 1.082–1.212; C_{av}, 1.011–1.106) and SR/IR paracetamol (AUC_{0-t}, 0.969–1.029; AUC_{0-24}, 0.968–1.027; $AUC_{0-\infty}$, 0.963–1.026; C_{max}, 0.902–1.010; C_{av}, 1.004–1.098). Given twice daily, the SR formulation demonstrated SR properties as expected. Mean time at or above a 4 μg/mL plasma concentration of paracetamol from 2 daily doses of the SR formulation was significantly longer than that from 4 daily doses of IR paracetamol. SR formulation also had a greater T_{max}, a longer half-life, and lower C_{min} compared with ER and IR paracetamol. All formulations were well tolerated.

Keywords

paracetamol, acetaminophen, bioequivalence, steady state, sustained release, twice daily

International guidelines recommend paracetamol (acetaminophen) as a first-line therapy in knee and hip osteoarthritis.[1–3] Manufacturer-recommended paracetamol dosing is 500 to 1000 mg of standard immediate-release (IR) paracetamol every 4 to 6 hours, not to exceed 4000 mg in a 24-hour period. The need to take up to 4 doses per day to sustain relief from chronic pain may reduce compliance, which is known to be inversely related to daily dosing frequency.[4] Failure to continue with a recommended duration of therapy with paracetamol can also compromise pain relief in osteoarthritis.[5] A twice-daily sustained-release (SR) paracetamol formulation has been developed to reduce the dosing frequency, which some chronic users may find more convenient.

Several extended-release (ER) forms of paracetamol are already available, including Panadol Extend (GlaxoSmithKline Consumer Health Care, Weybridge, UK) and Tylenol 8 HR ER caplets (Tylenol; McNeil Consumer Healthcare, Fort Washington, Pennsylvania). These products are taken 3 times daily (maximum,

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6 tablets in 24 hours). The new SR paracetamol has a pharmacokinetic (PK) profile that includes prolonged exposure, which allows the number of daily doses required to be further reduced to only 2. This formulation, developed with the aid of an in vivo modeling and simulation technique,[6] is a white film-coated, bilayered tablet consisting of a layer of IR paracetamol (10%) and a layer of SR paracetamol (90%) that contains hydroxypropyl methycellulose polymer.[7] Two tablets (2 × 1000 mg) can be taken twice daily, for a maximum of 4000 mg.

We previously reported the single-dose PK profile of the new SR paracetamol compared with currently marketed ER and IR paracetamol formulations in both fasted and fed states.[7] SR paracetamol was well absorbed, with >90% relative bioavailability compared with the IR and ER products. The objective of the current study was to investigate at steady state (during the last 24 hours of a 3-day treatment) the bioequivalence and PK profile of twice-daily SR paracetamol compared with 3-times-daily ER and 4-times-daily IR paracetamol. Safety and tolerability of all 3 formulations during this 3-day repeat-dose study were also investigated.

Methods

Ethical Considerations

The study protocol (registered with US clinicaltrials.gov, NCT01476189) and the informed consent form were approved by the institutional review board at the study site, MDS Pharma Services, Tempe, Arizona. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki 1996[8] and the International Council for Harmonisation Guideline for Good Clinical Practice.[9] All subjects provided written informed consent before enrollment.

Study Population

This study enrolled healthy, nonsmoking volunteers aged 18 to 55 years with a body mass index (BMI) of 19 to 28 kg/m^2. Subjects were screened for eligibility within 15 days prior to dosing. Eligibility was determined on the basis of medical history, physical examination, vital signs, laboratory testing, and electrocardiograms. Female subjects of childbearing potential were eligible only if they were not pregnant or breastfeeding and were willing to practice a reliable method of contraception. Potential subjects were deemed ineligible if they had taken any medications within 14 days of the start of the study or regularly used any drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to study dosing. Persons with liver enzyme levels greater than the upper limit of normal (ULN), bilirubin ≥2× ULN, or international normalized ratio ≥1.5× ULN were excluded. Additional exclusion criteria included known or suspected allergy or intolerance to any of the study materials; abuse of alcohol or other substances within the last 2 years; infection with human immunodeficiency virus or hepatitis B or C; and blood donation or significant blood loss within 56 days or plasma donation within 7 days of the first treatment period. Participants also had to consent to reside at the study site for 2 weeks and then return to the clinic for follow-up approximately 5 days thereafter, and they had to be willing to refrain from consuming alcohol beginning 10 days prior to their stay at the study site and caffeine beginning 24 hours prior to their stay and continuing throughout the remainder of the study.

Study Design and Procedures

This was an open-label, randomized, multiple-dose, 3-way crossover PK study conducted at a single center. Over the course of a 13-day confinement (residential period) divided into 3 study periods, each subject received a daily dose of 4000 mg of paracetamol, administered as either 2 doses of SR paracetamol 2 × 1000 mg tablets taken 12 hours apart, 3 doses of ER paracetamol 2 × 665 mg tablets (Panadol Extend) administered 8 hours apart, or 4 doses of IR paracetamol 2 × 500 mg tablets (Panadol) administered 6 hours apart, each given for 3 consecutive days. Subjects received all 3 paracetamol formulations in 6 sequences according to a randomization schedule based on a Williams design, which is a balanced crossover design that allows for the same number of subjects to be randomized within each sequence.[10,11] All products were manufactured by GlaxoSmithKline Consumer Healthcare, Parsippany, New Jersey.

There was a 48-hour washout separating each treatment period, which was calculated to be at least 5 to 6 times the half-life of the formulation with the longest controlled release of paracetamol. Being that the mean half-life of paracetamol following a 1000-mg oral dose of the IR formulation is approximately 2.3 hours,[12] with steady state reached within 24 hours, and the half-life of paracetamol 1000-mg SR tablets in the fed state is approximately 5 to 6 hours,[7] the 48-hour washout period was considered sufficient to allow for elimination of the study drug and any metabolites between the study sessions. Considering the twice-daily dosing regimen, steady state was expected to be reached within 48 hours, as predicted by an in vivo modeling and simulation approach.[6]

During the residential period, subjects were provided with meals standardized with respect to protein, carbohydrate, and fat content. The same menu and meal schedule were administered uniformly to all subjects and were repeated in each study session. Treatments were administered 30 minutes after the start of the meal on dosing days and were consumed with 200 mL of

noncarbonated water with the subject in an upright position. No food was allowed for at least 4 hours after dosing. Water was allowed as desired except for 1 hour before and after drug administration.

All PK parameters were calculated based on paracetamol concentrations on the third day of each treatment session, which represents steady state. Blood samples of approximately 4 mL were collected from either an indwelling cannula or venipuncture (situated in a forearm vein) into a 4-mL lithium heparin vacutainer. For SR paracetamol (2 × 1000 mg twice daily), blood samples were taken 10 minutes before the first dose on the third day of treatment and at 0, 0.5, 1, 2, 3, 3.5, 3.75, 4, 4.25, 4.5, 5, 6, 7, 8, 9, 11, 11.75, 12, 12.5, 13, 14, 15, 15.5, 15.75, 16, 16.25, 16.5, 17, 18, 19, 20, 21, 22, and 24 hours relative to that dose. For ER paracetamol (2 × 665 mg 3 times daily), blood samples were taken 10 minutes before the first dose on treatment day 3 and at 0, 0.33, 1, 2, 2.5, 2.75, 3, 3.5, 4, 5, 7, 7.75, 8, 8.33, 9, 10, 10.5, 10.75, 11, 11.5, 12, 13, 15, 15.75, 16, 16.33, 17, 18, 18.5, 18.75, 19, 19.5, 20, 21, 23, and 24 hours relative to that dose. For IR paracetamol (2 × 500 mg 4 times daily), blood samples were taken 10 minutes before the first dose on day 3 and at 0, 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5.75, 6, 6.25, 6.5, 7, 7.25, 7.5, 7.75, 8, 9, 10, 11.75, 12, 12.25, 12.5, 13, 13.25, 13.5, 13.75, 14, 16, 17.75, 18, 18.25, 18.5, 19, 19.25, 19.5, 19.75, 20, 21, 22, and 24 hours relative to that dose. These blood sampling times were selected to maximize the information in vivo, particularly on drug absorption and elimination at steady state.[6]

Blood samples were centrifuged at 3000 revolutions per minute at 4°C for 15 minutes. Approximately 1.5 mL of plasma was separated from each sample and transferred equally into 2 5-mL polypropylene screw-top tubes. Plasma samples were stored in tubes labeled with the study number, randomization number, study day, collection date, and time of the blood sample collection and were frozen at approximately -20°C within 1 hour of sampling before the samples were shipped to the central laboratory (Celerion, Lincoln, Nebraska) for analysis.

Safety evaluations included clinical monitoring, recording of adverse events (AEs), vital signs, electrocardiograms, and safety biochemistry tests including liver function tests at screening and at the end of each treatment period.

Bioanalytic Methods and Validation

Validated methods were used to analyze plasma samples.[13] High-performance liquid chromatography–mass spectrometry was used to quantify plasma concentrations of paracetamol in an assay developed by Celerion (Lincoln, Nebraska). Liquid–liquid extraction was performed using methyl tertbutyl ether as the extraction solvent. Sample extracts were injected into an isocratic reversed-phase chromatography system that used an Aquasil C18 (50 × 3 mm, 5 μm; Thermo Electron Corporation, Beverly, Massachusetts) and a polar organic mobile phase (15:85 acetonitrile:1% HCOOH in water). An API 4000 (Applied Biosystems/MDS Sciex, Foster City, California) was used to detect positive ions in multiple-reaction monitoring mode. The m/z transitions were 152.1→110.2 for paracetamol and 156.1→114.1 for the internal standard (d_4-paracetamol). The assay had a lower limit of quantitation of 50.0 ng/mL. Its intrabatch accuracy (% bias) ranged from −2.4% to 6.0%, and its precision (% coefficient of variation) ranged from 1.9% to 6.8%. The interbatch accuracy ranged from 0.4% to 3.6%, and precision ranged from 2.2% to 6.4%.

Approximately 10% of the analyzed samples were reassayed for the purpose of incurred sample reproducibility (ISR). The paired analyses were considered acceptable if the repeat analysis had a difference ≤20%. The ISR testing was considered acceptable if >66.7% of the reassayed values met pair-matching criteria.

PK Outcomes

The primary variables were area under the plasma concentration–time curve (AUC) from 0 to time of the last quantifiable concentration (AUC_{0-t}), AUC from 0 and extrapolated to infinity ($AUC_{0-\infty}$), and maximum plasma paracetamol concentration at steady state (C_{maxSS}). We conducted additional post hoc analyses of AUC from 0 to 24 hours (AUC_{0-24}), average plasma paracetamol concentration during the 24 hours of the third day of dosing (C_{avSS}), and minimum plasma concentration during this period (C_{minSS}). The prespecified primary outcomes and these additional PK outcomes were used to assess bioequivalence between the SR paracetamol formulation and the IR and ER paracetamol formulations.

Secondary PK end points were used to further describe the PK profiles of the 3 formulations. These end points included time to reach maximum plasma paracetamol concentration (T_{max}), duration of time when plasma paracetamol concentration was equal to or greater than 4 μg/mL ($T_{c\geq 4\mu g/mL}$) during the third day of dosing (hours 48 to 72), minimum plasma concentration during this period (C_{minSS}), half-life ($T_{1/2}$), and elimination rate constant. Additional post hoc analyses to further characterize the PK profile of the SR formulations included fluctuation index and swing.

A plasma paracetamol concentration of 4 μg/mL was chosen as a threshold to compare the SR properties of 2000 mg SR paracetamol (2 daily doses) with the effects of the ER (3 doses daily) and IR (4 doses daily) formulations in maintaining this level of plasma paracetamol. This threshold may be an indication of

minimum therapeutic level of paracetamol. Previous studies[14,15] have used indirect methods that suggest the level of 3–5 μg/mL paracetamol as a minimum therapeutic concentration.

Statistical Methods

No sample size calculations were performed for this study. Twenty-eight healthy volunteers were enrolled, with the aim of having at least 24 subjects complete the study. This sample size was considered sufficient to provide adequate information for bioequivalence analyses in compliance with Food and Drug Aministration[16] and Committee for Proprietary Medicinal Products guidelines.[17] Analyses were performed on an intent-to-treat (ITT) population, which included all subjects with evaluable data for at least 1 treatment period. The AUCs were derived from plasma paracetamol concentration and elapsed-time data using the noncompartmental linear trapezoidal method of analysis (WinNonlin v. 4.0; Certera, Princeton, New Jersey). The $AUC_{0–24}$ was calculated by the trapezoidal method. Values for $AUC_{0–\infty}$ were calculated as $AUC_{0–t} + C_t/k$, where C_t is the last quantifiable concentration and k is the terminal elimination rate constant determined by least-squares (LS) regression analysis during the terminal log-linear phase of the concentration–time curve. $T_{c\geq 4\mu g/mL}$ and T_{max} were calculated directly from observed plasma paracetamol concentrations. C_{avSS} was calculated from the observed data based on a subject's mean plasma paracetamol concentration per treatment. Similarly, C_{minSS} was calculated from the observed individual minimum plasma paracetamol concentration. Fluctuation index was calculated as $(C_{maxSS} - C_{minSS})/C_{avSS}$, and swing was calculated as $(C_{maxSS} - C_{minSS})/C_{minSS}$.

Bioequivalence analyses were performed on $AUC_{0–t}$, $AUC_{0–24}$, $AUC_{0–inf}$, C_{maxSS}, C_{minSS}, and C_{avSS}. All data were log-transformed (natural log) and analyzed based on a linear mixed-effects model using Proc Mixed of SAS (SAS v. 8.2; SAS Institute, Cary, North Carolina). Treatment, sequence, and period were included in the model as fixed effects, with subjects (sequence) included as a random effect. The residual variance from the model was used to construct 90% confidence intervals (CIs) for LS mean differences between treatments. These differences were back-transformed to obtain point estimates (ratios) of geometric means and the corresponding 90%CIs. Bioequivalence was accepted if the 90%CIs for the treatment mean ratio were within a range of 0.80–1.25.

T_{max} was analyzed nonparametrically using Wilcoxon signed rank tests for the median of differences between treatments, whereas $T_{c\geq 4\mu g/mL}$ was analyzed using a paired *t* test on the mean of differences between treatments. The significance level for both tests was 5%. Half-life, fluctuation index, and swing were summarized using descriptive statistics.

Table 1. Demographic Characteristics of the Study Population

Demographics	Participants (N = 28)
Race, n (%)	
White	28 (100)
Sex, n (%)	
Female	17 (61)
Male	11 (39)
Age, mean (range), years	33.3 (22–45)
Weight, mean (range), kg	67.3 (51.0–84.5)
Height, mean (range), cm	162.3 (142.7–178.1)
BMI, mean (range), kg/m^2	25.5 (22.1–27.5)

BMI, body mass index.

Results

Participants

Of 85 subjects screened, 57 did not meet inclusion criteria, and 28 were randomized. All 28 had evaluable data for at least 1 treatment period (ITT population), and 24 completed all periods of the study. The other 4 subjects discontinued early because of treatment-related AEs; 2 of these subjects missed treatment with SR paracetamol, and the other 2 missed treatment with ER paracetamol. Thus, all 28 subjects provided data for treatment with the IR formulation, whereas 26 provided data for the SR formulation and 26 for the ER formulation. The 28 healthy volunteers enrolled in the study were between 22 and 45 years of age (mean, 33.3 years) and had an average BMI of 25.5 kg/m^2 (range, 22.1–27.5 kg/m^2). All were white. Eleven (39%) were male, and 17 (61%) were female (Table 1).

Primary Pharmacokinetic Parameters

Mean plasma paracetamol concentration–time curves at steady state in the last 24 hours of 3-day dosing with SR, ER, and IR paracetamol are shown in Figure 1. Maximum paracetamol concentration peaks from the SR formulation were similar to those observed for the IR and ER formulations but at the same time were wider, demonstrating that SR paracetamol concentrations remained higher for longer periods.

Results of the bioequivalence analysis are presented in Table 2. Paracetamol exposure from 2 doses of SR paracetamol (2 × 1000 mg) was bioequivalent to that of 3 doses of ER paracetamol (2 × 665 mg). The ratio of geometric means comparing the SR and ER formulations for $AUC_{0–t}$ was 100.2% (1.002; 90%CI, 0.973–1.033), for $AUC_{0–24}$ was 100.4% (1.004; 90%CI, 0.974–1.034); for $AUC_{0–inf}$ was 97.9% (0.979; 90%CI, 0.948–1.011), and for C_{maxSS} was 114.5% (1.145; 90%CI, 1.082–1.212). All these CIs were within the acceptance

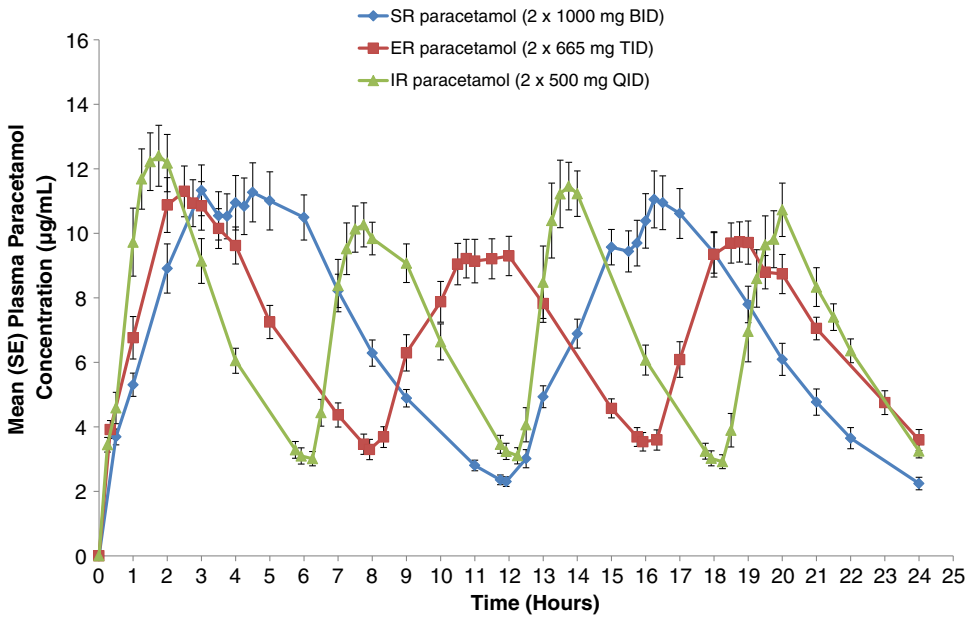

Figure 1. Mean plasma paracetamol (acetaminophen) concentration versus time at steady state in the last 24 hours of 3-day dosing with twice-daily SR, 3-times-daily ER, and 4-times-daily IR paracetamol.

Table 2. Bioequivalence at Steady State of Sustained-Release With Extended-Release and Immediate-Release Paracetamol (Acetaminophen) Formulations

	Arithmetic Mean (SD)			Ratio of Geometric Means[a] (90%CI)[b]	
PK End Point	SR Paracetamol (2 × 1000 mg Twice Daily)	ER Paracetamol (2 × 665 mg 3 Times Daily)	IR Paracetamol (2 × 500 mg 4 Tmes Daily)	SR vs ER Paracetamol	SR vs IR Paracetamol
AUC_{0-24}, µg·h/mL	164.4 (39.22)	167.3 (43.65)	167.5 (43.90)	1.004 (0.974–1.034)	0.997 (0.968–1.027)
AUC_{0-t}, µg·h/mL	165.4 (39.47)	168.4 (43.78)	168.2 (44.11)	1.002 (0.973–1.033)	0.999 (0.969–1.029
$AUC_{0-\infty}$, µg·h/mL	174.6 (41.53)	183.1 (52.66)	176.6 (47.94)	0.979 (0.948–1.011)	0.994 (0.963–1.026)
C_{maxSS}, µg/mL	12.8 (3.97)	11.2 (2.98)	13.3 (3.62)	1.145 (1.082–1.212)	0.955 (0.902–1.010)
C_{avSS}, µg/mL	7.6 (1.95)	7.3 (1.93)	7.4 (1.99)	1.057 (1.011–1.106)	1.050 (1.004–1.098)
C_{minSS}, µg/mL	2.2 (0.71)	3.0 (1.14)	2.7 (1.04)	0.770 (0.713–0.831)	0.831 (0.770–0.897)

SR, sustained-release paracetamol 2 × (2 × 1000 mg paracetamol), ER, extended-release paracetamol 3 × (2 × 665 mg paracetamol), IR, immediate-release paracetamol 4 × (2 × 500 mg).
[a]Ratio of least-squares (LS) means of log-transformed data back-transformed to original data.
[b]90% confidence intervals of the ratio of LS means of log-transformed data back-transformed to original data.

range of bioequivalence (0.80–1.25), and most were very close to 1.0, demonstrating a similar paracetamol exposure for the SR and ER formulations at steady state. Bioequivalence of the SR and ER formulations was also proven for C_{avSS} (ratio, 1.057; 90%CI, 1.011–1.106) but not for C_{minSS} (ratio, 0.77; 90%CI, 0.713–0.831).

Paracetamol exposure from 2 doses of SR paracetamol (2 × 1000 mg) was also bioequivalent to 4 doses of IR paracetamol (2 × 500 mg). The ratio of geometric means for AUC_{0-t} was 99.9% (0.999; 90%CI, 0.969–1.029), for AUC_{0-24} was 99.7% (0.997; 90%CI, 0.968–1.027), for AUC_{0-inf} was 99.4% (0.994; 90%CI, 0.963–1.026), and for C_{maxSS} was 95.5% (0.955; 90%CI, 0.902–1.010). All these CIs were within the acceptance range of bioequivalence (0.80–1.25), and their values were very close to 1.0, demonstrating a similar exposure of paracetamol at steady state from the SR and IR formulations. Bioequivalence between these 2 formulations was also proven for C_{avSS} (ratio, 1.050; 90%CI, 1.004–1.098) but not for C_{minSS} (ratio, 0.831; 90%CI, 0.770–0.897).

Secondary Pharmacokinetic Parameters

Summary statistics for the secondary PK parameters of each formulation at steady state are shown in

Table 3. Pharmacokinetic Parameters of Secondary End Points at Steady State of Twice-Daily SR Paracetamol, 3-Times-Daily ER Paracetamol, and 4-Times-Daily IR Paracetamol (Acetaminophen)

PK End Point	SR Paracetamol (2 × 1000 mg Twice Daily)	ER Paracetamol (2 × 665 mg 3 Times Daily)	IR Paracetamol (2 × 500 mg 4 Times Daily)
T_{maxSS}, median (range), h	4.25 (2–6.5)	3.0 (1.6–5.3)	1.78 (1.3–3.5)
$T_{C\geq 4\mu g/mL}$, h	16.74 (2.62)	17.79 (4.29)	15.74 (3.84)
$T_{1/2}$, h	2.77 (0.54)	2.76 (0.84)	1.99 (0.29)
Fluctuation index[a]	1.41 (0.24)	1.15 (0.22)	1.47 (0.21)
Swing[b]	5.22 (2.02)	3.06 (1.42)	4.18 (1.52)

C_{min}, minimum plasma paracetamol concentration; ER, extended release; IR, immediate release; PK, pharmacokinetic; SD, standard deviation; SR, sustained release; $T_{C\geq 4\mu g/mL}$, time spent at or above plasma paracetamol concentration of 4 μg/mL at steady state (ie, hours 48 to 72); T_{maxSS}, time to reach maximum plasma paracetamol concentration at steady state; $T_{1/2}$, time of elimination half-life.
All values are arithmetic means (SD) unless otherwise noted.
[a]Fluctuation index calculated as ($[C_{maxSS} - C_{avSS}]/C_{avSS}$).
[b]Swing calculated as ($[C_{maxSS} - C_{minSS}]/C_{minSS}$).

Table 4. Comparison of Time to Maximum Concentration (T_{max}) and Time at or Above 4 μg/mL Paracetamol Concentration at Steady State From Treatment With Sustained-Release (2 × 1000 mg Twice Daily), Extended-Release (2 × 665 mg 3 Times Daily), and Immediate-Release (2 × 500 mg 4 Times Daily) Paracetamol (Acetaminophen)

	T_{max} (h)			$T_{C\geq 4\mu g/mL}$ (h)		
Treatment Comparison	Median Difference	95%CI[a]	P[b]	Mean Difference	95%CI[c]	P[d]
SR vs ER paracetamol	1.18	0.59–1.74	< .0001	−0.8	−2.13–0.55	.2339
SR vs IR paracetamol	2.31	1.75–2.87	< .0001	1.5	0.51–2.47	.0046

ER, extended release; IR, immediate release; $T_{c\geq 4\mu g/mL}$, time spent at or above plasma paracetamol concentration of 4 μg/mL at steady state (ie, hours 48 to 72); SR, sustained release; T_{max}, time to reach maximum plasma paracetamol concentration.
SR paracetamol, 2 × 1000 mg twice daily; ER paracetamol, 2 × 665 mg 3 times daily; IR paracetamol, 2 × 500 mg 4 times daily.
[a]Hodges-Lehmann 95% confidence intervals for median of differences between treatments.
[b]*P* from Wilcoxon signed rank test.
[c]95% confidence intervals for mean of differences between treatments.
[d]*P* from *t* test.

Table 3. A noticeable difference was observed in median T_{max}, which was 4.25 hours with SR paracetamol compared with 3 hours for ER paracetamol and 1.78 hours for IR paracetamol. These differences were statistically significant ($P < .0001$), demonstrating a significantly slower rate of absorption with SR paracetamol compared with the ER and IR formulations (Table 4). At steady state, $T_{c\geq 4\mu g/mL}$ was significantly longer for SR paracetamol (16.74 hours) compared with IR paracetamol (15.74 hours, $P = .0046$), but not compared with ER paracetamol (17.79 hours, $P = .2339$); see Table 4.

The average C_{min} observed for SR paracetamol was lower than that for IR and ER paracetamol (Table 3). As expected, the half-life for SR paracetamol of 2.77 hours was similar to the half-life of ER paracetamol (2.76 hours), and the half-lives of both formulations were noticeably longer than the half-life of IR paracetamol (1.99 hours). The elimination rate constant for SR paracetamol (0.26) was 25% lower than that for standard IR paracetamol (0.35) and comparable to that of ER paracetamol (0.27). At steady state, both SR and IR paracetamol had higher fluctuation indices compared with ER paracetamol. Most noticeably, swing for SR paracetamol (5.22) was higher than that of IR paracetamol (4.18) and ER paracetamol (3.06). This was mostly because SR paracetamol had the lowest C_{min}.

Safety Results

Twenty-one of the 28 participants (75%) in the safety population reported a total of 70 AEs (Table 5). The rate of AEs varied by treatment formulation: 27% occurred during treatment with ER paracetamol, 39% during treatment with SR paracetamol, and 54% during treatment with IR paracetamol. Gastrointestinal disorders were the most common category of AEs (Table 5).

Twelve AEs were considered treatment related. These consisted exclusively of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The incidence of these AEs was the same for SR and ER paracetamol (2 events during each of these treatment periods) and highest with IR paracetamol (8 events). Four subjects discontinued the study because they had elevated levels of AST/ALT that were >3× ULN, including 3 subjects during treatment with IR paracetamol and 1 subject during treatment with SR

Table 5. Adverse Events During 3-Day Treatment With Twice-Daily SR Paracetamol, 3-Times-Daily ER Paracetamol, and 4-Times-Daily IR Paracetamol (Acetaminophen)

	SR Paracetamol (2 × 1000 mg Twice Daily), n = 26		ER Paracetamol (2 × 665 mg 3 Times Daily), n = 26		IR Paracetamol (2 × 500 mg 4 Times Daily), n = 28	
Adverse Event	n (%)[a]	Total TEAEs, n[b]	n (%)[a]	Total TEAEs, n[b]	n (%)[a]	Total TEAEs, n[b]
All TEAEs	10 (38.5)	20	7 (26.9)	17	15 (53.6)	33
Treatment-related TEAEs	1 (3.8)	2	1 (3.8)	2	5 (17.9)	8
Serious TEAEs	0	0	0	0	0	0
TEAEs by MedDRA Preferred Class/Term						
Gastrointestinal TEAEs	3 (11.5)	4	4 (15.4)	6	10 (35.7)	13
Abdominal pain	2 (7.7)	2	3 (11.5)	3	6 (21.4)	6
Dyspepsia	1 (3.8)	2	2 (7.7)	2	2 (7.1)	2
Nausea	0	0	1 (3.8)	1	2 (7.1)	2
Nervous system disorders	6 (23.1)	8	3 (11.5)	3	4 (14.3)	4
Headache	3 (11.5)	5	3 (11.5)	3	4 (14.3)	4
Somnolence	2 (7.7)	2	0	0	0	0
Paresthesia	1 (3.8)	1	0	0	0	0
General disorders	4 (15.4)	4	1 (3.8)	1	3 (10.7)	3
Vessel puncture-site pain	3 (11.5)	3	0	0	1 (3.6)	1
Chest pain	1 (3.8)	1	1 (3.8)	1	0	0
Asthenia	0	0	0	0	1 (3.6)	1
Thirst	0	0	0	0	1 (3.6)	1
Psychiatric disorders	0	0	1 (3.8)	1	2 (7.1)	2
Insomnia	0	0	1 (3.8)	1	1 (3.6)	1
Anxiety	0	0	0	0	1 (3.6)	1
Eye disorders	1 (3.8)	1	0	0	1 (3.6)	1
Eye pruritus	0	0	0	0	1 (3.6)	1
Photophobia	1 (3.8)	1	0	0	0	0
Musculoskeletal disorders	0	0	1 (3.8)	1	1 (3.6)	1
Flank pain	0	0	1 (3.8)	1	1 (3.6)	1
Renal and urinary disorders	0	0	1 (3.8)	2	0	0
Dysuria	0	0	1 (3.8)	1	0	0
Urinary hesitation	0	0	1 (3.8)	1	0	0
Respiratory TEAEs	1 (3.8)	1	0	0	1 (3.6)	1
Nasal congestion	1 (3.8)	1	0	0	1 (3.6)	1
Laboratory abnormalities	1 (3.8)	2	2 (7.7)	3	5 (17.9)	8
Increased ALT	1 (3.8)	1	1 (3.8)	1	5 (17.9)	5
Increased AST	1 (3.8)	1	1 (3.8)	1	3 (10.7)	3
Urine color abnormal	0	0	1 (3.8)	1	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
[a]Number (%) of subjects with at least 1 TEAE.
[b]Number of events.

paracetamol. The other 3 subjects experienced elevated ALT/AST >2× ULN but <3× ULN; all these subjects continued treatment because their ALT/AST levels returned to within the normal range during the washout period between treatments. Liver enzyme levels also returned to normal by the time of the scheduled follow-up visit for the 4 subjects who discontinued the study.

There were no deaths or serious AEs during the study, and there were no clinically relevant changes in vital signs.

Discussion

In this study, a new formulation of SR paracetamol (2 × 1000 mg twice daily) was bioequivalent to currently marketed ER paracetamol (2 × 665 mg 3 times daily) and IR paracetamol (2 × 500 mg 4 times daily) in healthy volunteers for exposure of paracetamol at steady state as measured by AUC_{0-t}, AUC_{0-24}, AUC_{0-inf}, C_{max}, and C_{avSS}. This repeat-dose study showed that twice-daily SR paracetamol maintains plasma paracetamol concentrations at or above

4 μg/mL significantly longer than currently marketed IR product. During treatment at steady state with SR paracetamol (2 × 1000 mg twice daily), plasma paracetamol concentration remained at or above 4 μg/mL for a significantly longer duration of time compared with the same total daily dose of IR paracetamol (2 × 500 mg 4 times daily). The average plasma paracetamol concentration at this level was 1.5 hours longer for the SR formulation, and this difference was significant. There were no significant differences among daily doses of SR and ER paracetamol formulations for the time during which plasma paracetamol was at or above 4 μg/mL. Findings of this study show that the twice-daily SR paracetamol formulation is bioequivalent to the ER and IR products used 3 and 4 times daily and provides SR properties that allow maintenance of daily plasma paracetamol concentrations at or above an important threshold for a similar or longer duration than existing paracetamol products. As a result, SR paracetamol can be substituted for these formulations, allowing for a twice-daily dosing regimen. Such a reduction in dosing frequency compared with ER and IR paracetamol without loss of PK effects may help to improve compliance as a result of greater convenience.

The SR formulation had a significantly slower rate of paracetamol absorption compared with both IR and ER formulations. Time to reach maximum plasma paracetamol concentration was significantly longer for the SR compared with the IR and ER formulations. At steady state, SR paracetamol demonstrated a longer half-life than IR paracetamol. Half-life of the SR formulation was similar to that of ER paracetamol. All these findings consistently demonstrate the SR properties of the SR formulation.

The PK profile of standard IR paracetamol is well established. Oral paracetamol is rapidly absorbed but undergoes first-pass metabolism and is therefore incompletely bioavailable[12,18]; absolute systemic bioavailability is dose related, such that it is 63% for a single dose of 500 mg, 79% for a single dose of 650 mg, and ≥87% for single doses of 1000 or 2000 mg.[18,19] Peak plasma concentration is reached approximately 45 minutes after administration of a single 650-mg oral dose in tablet form.[19] AUC is dose related with single and multiple doses.[20,21] Paracetamol is extensively metabolized, predominantly in the liver, and therefore can cause hepatotoxicity when taken in overdose.[12] Paracetamol and its metabolites are predominantly cleared renally.[12]

The PK profile of ER paracetamol has been compared with that of IR paracetamol largely in studies using supratherapeutic doses (ie, overdose). In such studies, ER paracetamol had a lower AUC and C_{max} and a delayed T_{max} compared with IR paracetamol despite comparable doses.[22,23] Peak concentration was reached within 4 hours for ER paracetamol, after which PK parameters overlapped with those of IR paracetamol.[22,23]

Paracetamol absorption is influenced by food. As such, this study was conducted under fed conditions with a standard food regimen. Previously, we reported that food has a significant effect on the PK parameters of SR paracetamol, specifically in increasing C_{max} and reducing T_{max}.[7] Furthermore, food hastened the decay in the terminal concentration curve (ie, it shortened the half-life).[7] Although food is unlikely to change the dissolution properties of the new SR formulation, it may enhance absorption by prolonging the time the drug resides in the gastrointestinal system.

A total of 12 AEs for elevated levels of ALT and AST were observed (Table 5). Four subjects discontinued the study because their AST/ALT levels were greater than 3× ULN. In all subjects, elevated ALT/AST levels were asymptomatic, and levels returned to normal by the time of the scheduled follow-up visit. Asymptomatic elevations in ALT have been previously observed in healthy adults receiving up to 4000 mg/day of paracetamol.[24,25] Acute liver failure is a known complication of paracetamol taken in overdose[26]; however, systematic reviews have found little quality evidence from prospective studies demonstrating that liver failure occurs with the maximum therapeutic dosage of 4000 mg/day.[27,28] The enzyme elevations observed in the present study are within the range, frequency, and pattern in the published literature and appear to follow a similar time course.[24,28] There were no new paracetamol safety concerns related to the SR formulation.

Conclusions

At steady state, during the last 24-hour period of a 3-day dosing regimen, a new twice-daily SR paracetamol formulation was bioequivalent to both ER three times daily and IR paracetamol four times daily as measured by AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{maxSS}, and C_{avSS}. Mean plasma paracetamol concentrations remained at or above a level of 4 μg/mL for a significantly longer time with the SR formulation than with the IR formulation and for a time comparable to that of the ER formulation. SR paracetamol exhibited SR properties such as longer time to reach maximum paracetamol concentration and longer half-life. Although asymptomatic liver enzyme (ALT/AST) elevations were observed, they resolved within the study period and were in the range and pattern previously observed during treatment with 4000 mg/day paracetamol. There were no new safety concerns related to the SR formulation. Whether the added convenience of twice-daily dosing for patients seeking pain relief from chronic pain will allow for better compliance, therapeutic efficacy, and quality of life warrants further investigation.

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Declaration of Conflicting Interests

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