Evaluation of a 12-Hour Sustained-Release Acetaminophen (Paracetamol) Formulation: A Randomized, 3-Way Crossover Pharmacokinetic and Safety Study in Healthy Volunteers

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Abstract

Acetaminophen (paracetamol) is a first-line treatment for mild and moderate pain. A twice-daily sustained-release (SR) formulation may be more convenient for chronic users than standard immediate-release (IR) acetaminophen. This randomized, 3-way crossover study evaluated pharmacokinetics and safety of single-dose 1500- and 2000-mg SR acetaminophen formulations and 2 doses of IR acetaminophen 1000 mg given 6 hours apart in healthy adults (n = 14). Primary outcome was time that plasma acetaminophen concentration was ≥ 4 μg/mL ($T_{C \geq 4\mu g/mL}$). Key secondary outcomes were area under the plasma concentration–time curve (AUC) from time 0 to time t, when plasma acetaminophen was detectable (AUC_{0-t}), AUC from 0 to infinity (AUC_{0-inf}), and maximum plasma acetaminophen concentration (C_{max}). $T_{C \geq 4\mu g/mL}$ from 2000-mg SR acetaminophen was similar to that from 2 doses of IR acetaminophen, whereas $T_{C \geq 4\mu g/mL}$ for 1500-mg SR acetaminophen was significantly shorter than that for IR acetaminophen ($P = .004$). The extent of acetaminophen absorption from 2000-mg SR and 2 doses of the IR formulation was similar and within bioequivalence limits with regard to AUC_{0-12}, AUC_{0-t}, and AUC_{0-inf}. The extent of acetaminophen absorption from 1500-mg SR was significantly lower than that from IR acetaminophen. The 2000-mg SR represents a potential candidate formulation for 12-hour dosing with acetaminophen.

For nearly half a century, acetaminophen (paracetamol) has been one of the most widely used drugs in the world.[1] It has well-established efficacy and is recommended as a first-line treatment for mild to moderate acute pain[2] as well as chronic or persistent pain disorders (eg, osteoarthritis).[3–9] For adults and children older than 12 years of age, immediate-release (IR) acetaminophen is taken at doses of 500 to 1000 mg every 4 to 6 hours. Its analgesic and antipyretic effects last ≈3 to 4 hours.[1] Several modified-release or extended-release (ER) formulations of acetaminophen are already available, including Panadol Extend (GlaxoSmithKline Consumer Health Care, Brentford, UK) and Tylenol 8 HR ER caplets (McNeil Consumer Healthcare, Fort Washington, Pennsylvania). These products are taken 3 times daily (maximum, 6 tablets in 24 hours). Sustained-release (SR) formulations that reduce dosing frequency while prolonging therapeutic effects offer greater convenience and might make it easier for people to adhere to treatment compared with IR formulations that require more frequent dosing.[10,11]

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│         Screened within 21 days prior to treatment (N=43)          │
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                         │                      ┌──────────────────┐
                         │──────────────────────│  Excluded (n=29) │
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│  Randomized to:                                                    │
│   •  Single 2000-mg dose of SR acetaminophen (2 x 1000 mg)         │
│   •  Single 1500-mg dose of SR acetaminophen (2 x 750 mg)          │
│   •  Two doses of IR acetaminophen 1000 mg (2 x 500 mg) given 6    │
│      hours apart                                                   │
│                           (N=14)                                   │
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                         │        48-h washout period
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│     Crossed over to second treatment in random order (N=14)        │
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│     Crossed over to third treatment in random order (N=14)         │
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│              Completed all 3 treatments (N=14)                     │
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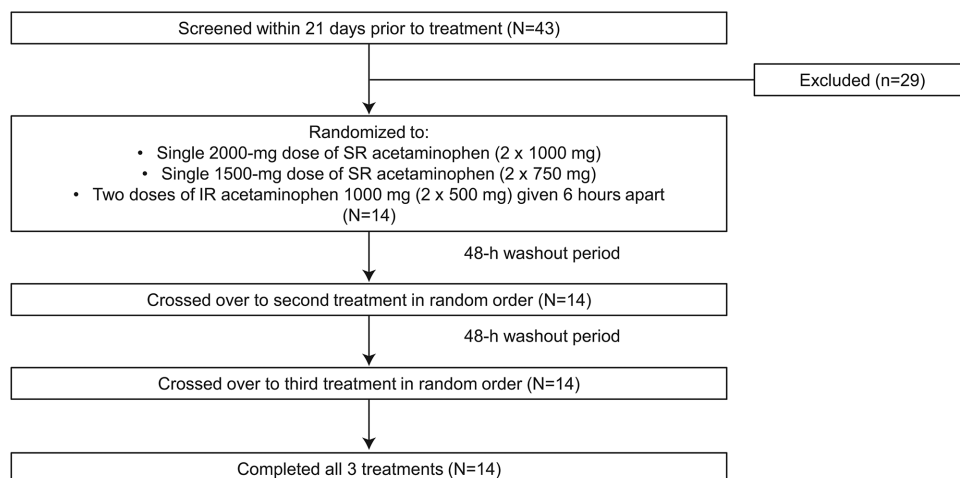
Figure 1. Study design and subject disposition. IR, immediate release; SR, sustained release.

We evaluated the pharmacokinetics (PK) of investigational 750- and 1000-mg SR formulations of acetaminophen developed by LaboPharm, to be taken at doses of 1500 or 2000 mg. These formulations were designed to reduce the dosing frequency to twice daily. The primary objective of this study was to assess the duration of time that plasma acetaminophen concentration was elevated at or above 4 μg/mL following administration of a single 2000- or 1500-mg dose of SR acetaminophen compared with 2 doses of standard IR acetaminophen 1000 mg given 6 hours apart. Secondary objectives were to compare acetaminophen exposure and other PK outcomes, as well as safety profiles, for the SR and IR formulations.

Methods

Study Design

This was a randomized, open-label, single-center, 3-way crossover, proof-of-principle PK study in healthy volunteers. The study was conducted from May 2010 to June 2010 at Charles River Clinical Services, Inc, Tacoma, Washington. The protocol (and any amendments) was reviewed and approved by the ethics committee and institutional review board (Alpha IRB, San Clemente, California) in accordance with local requirements. Study participants provided written informed consent prior to initiation of the study, which was conducted in accordance with the Declaration of Helsinki.[12]

Figure 1 provides an overview of the study design. Each subject received 3 oral acetaminophen regimens in a random sequence based on a computer-generated randomization schedule. The treatment regimens consisted of a single 2000-mg dose of SR acetaminophen (2 × 1000 mg; LaboPharm, Attard, Malta), a single 1500-mg dose of SR acetaminophen (2 × 750 mg; LaboPharm, Attard, Malta), and 2 doses of IR parac-

etamol (acetaminophen) 1000 mg (2 × 500 mg/dose) given 6 hours apart (Panadol; GlaxoSmithKline, Brentford, UK).

Treatments were administered with 150 mL of water in a semifed state (approximately 2 hours after a standardized meal) during a 6-day confinement period at the study site. A semifed state was used to mimic real-world use. IR acetaminophen is dosed every 4 to 6 hours, and the stomach returns to a "fasting state" approximately 4 hours after eating. Therefore, in real-world use, administration is likely to take place while the stomach is transitioning between fed and fasted states, so the study was designed to mimic these conditions. Treatment regimens were separated by a 48-hour washout period, so dosing occurred on days 1, 3, and 5. The content and timing of all meals were standardized during the confinement period, fluids were restricted within ±2 hours of dosing, and strenuous activity and consumption of alcohol and caffeine were prohibited during the trial.

Study Population

Subjects were recruited from the greater metropolitan area around the study site using IRB-approved advertising and from a large database of potential volunteers. It was estimated that ≈30 subjects would need to be screened to meet the target of randomizing ≈14 subjects and having at least 12 complete all 3 arms of the study.

Participants were healthy men and women aged 18–50 years with a body mass index of 19–28 kg/m^2 who were willing to comply with all study procedures. Women of childbearing potential had to be using reliable contraception. Exclusion criteria included pregnancy, breastfeeding, allergy or intolerance to any ingredient in the study materials or related compounds, current or recurrent physical or mental conditions that

could interfere with study participation, infection with human immunodeficiency virus or hepatitis, recent use (≤30 days prior to study treatment) of any medication or product known to affect hepatic drug metabolism, recent history (≤5 years) of substance or alcohol abuse, recent use (≤3 months) of nicotine-containing products, vegan/vegetarian diet, participation in another study or receipt of an investigational drug within 30 days of screening, hemoglobin ≤12 g/dL, and donation or significant loss of blood within 1 week of study treatment.

Study End Points

Pharmacokinetic analyses and parameters. Blood samples (2 mL) were taken via venipuncture or indwelling cannula pretreatment and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 14, 15, 16, and 18 hours after dosing for each of the treatment regimens. Samples were centrifuged at ≈3000 revolutions per minute at ≈4°C for ≈15 minutes. Approximately 0.6 mL of plasma was separated from each sample and split into 2 equal aliquots, which were placed into labeled 5-mL polypropylene screw-top tubes. The tubes were frozen at approximately −20°C within 1 hour of sampling and sent to the clinical laboratory (Celerion, Lincoln, Nebraska) for processing and analysis. Plasma samples were analyzed by validated methods, as described in the accompanying work by Yue et al.[13]

The primary PK outcome was the duration of time for which plasma acetaminophen concentration was at or above 4 μg/mL ($T_{C\geq4\mu g/mL}$) during the 18-hour blood sampling period. Previous studies, primarily conducted in febrile children, have indirectly suggested that the minimum acetaminophen concentration for a therapeutic effect lies between 3 and 5 μg/mL,[14,15] and the United Kingdom Over-the-Counter monograph for acetaminophen recognizes a threshold of 3 to 5 μg as the minimal concentration for provision of analgesia.[16] Here, this threshold was chosen as a point of comparison for the SR properties of the new formulation.

Secondary PK outcomes included the area under the plasma concentration–time curve from zero to 6 hours (AUC_{0-6}) and zero to 12 hours (AUC_{0-12}), AUC from time zero to the last time at which acetaminophen remained detectable (AUC_{0-t}), and AUC from time zero extrapolated to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), elimination rate (K_{el}), time to C_{max} (T_{max}), and half-life of elimination ($t_{1/2}$).

Safety. Safety and tolerability of the study treatments were assessed by reporting of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) from the start of the first treatment until posttreatment day 14. Biochemistry laboratory testing, including liver function testing, was performed at

Table 1. Demographic Characteristics of the Study Population

Demographics	Participants (N = 14)
Race, n (%)	
White	7 (50.0)
Black/African American	3 (21.4)
Asian	1 (7.1)
Native Hawaiian/Pacific Islander	1 (7.1)
Multiple	2 (14.3)
Sex, n (%)	
Female	10 (71.4)
Male	4 (28.6)
Age, mean (range), years	29.7 (19–44)
Weight, mean (range), kg	66.9 (50.4–84.9)
Height, mean (range), cm	167.6 (151.0–184.0)
BMI, mean (range), kg/m^2	23.7 (20.0–27.2)

BMI, body mass index.

screening and on days 3, 6, 9, and 14; the assessment on day 3 occurred postdose. Hematology testing was performed at screening and on day 14, and urinalysis and virology testing were performed at screening only.

Statistical Methods

$T_{C\geq4\mu g/mL}$ was analyzed nonparametrically using the Wilcoxon signed rank test based on the median of differences between treatments across subjects and a significance level of 5% ($P = .05$). PK outcomes AUC_{0-12}, AUC_{0-t}, and AUC_{0-inf} were log-transformed (natural log) and analyzed based on a linear mixed model using Proc Mixed of SAS (SAS version 9.2; SAS Institute, Cary, North Carolina). Treatment and period were included in the model as fixed effects, with subjects included as a random effect. The residual variance from the model was used to construct 90% confidence intervals (CIs) for least-squares (LS) mean differences between treatments. These differences were then back-transformed to obtain point estimates (ratios) of geometric means and corresponding 90%CIs. All PK outcomes were summarized by descriptive statistics.

Results

Study Subjects

Of 43 subjects screened, 14 were randomized; all 14 completed the study and were included in the PK and safety analyses (Figure 1). The majority of participants (71%) were female, half were white, and they ranged in age from 19 to 44 years (Table 1).

Pharmacokinetics

Mean plasma acetaminophen concentration over time is shown for each treatment in Figure 2. Single-dose 2000-mg SR acetaminophen showed a pattern of controlled release compared with the 2 doses of IR ac-
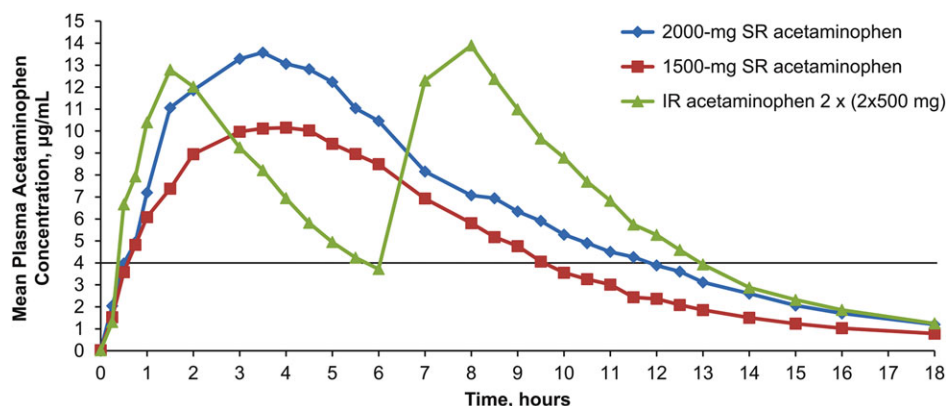
Figure 2. Mean plasma acetaminophen concentration over time by treatment. IR, immediate release; SR, sustained release.

etaminophen 1000 mg given 6 hours apart. A similar release pattern was observed for the single 1500-mg dose of SR acetaminophen, but at a lower concentration than with the single 2000-mg dose.

Time at or above 4 μg/mL plasma acetaminophen concentration from 1 dose of 2000-mg SR acetaminophen was similar to that from 2 doses of IR acetaminophen. Median $T_{C\geq4\mu g/mL}$ for the 2000-mg SR acetaminophen formulation was 10.5 hours compared with 9.8 hours for 2 consecutive doses of IR acetaminophen 1000 mg, and there were no significant differences between the 2 formulations ($P = .7222$; Table 2). In contrast, the median $T_{C\geq4\mu g/mL}$ for 1500-mg SR acetaminophen of 8.1 hours was significantly shorter than the median $T_{C\geq4\mu g/mL}$ of 9.8 hours for the 2 consecutive doses of IR acetaminophen 1000 mg ($P = .0044$; Table 2).

The extent of acetaminophen absorption from the 2000-mg SR formulation was similar to that of 2 consecutive doses of the 1000-mg IR formulation. The 90%CIs for the ratios of geometric means were within bioequivalence limits (0.80–1.25)[17,18] with regard to AUC_{0-12} (ratio, 0.99; 90%CI, 0.94–1.04), AUC_{0-t} (ratio, 0.98; 90%CI, 0.93–1.02), and AUC_{0-inf} (ratio, 0.98; 90%CI, 0.94–1.03); see Table 3. The extent of acetaminophen absorption from 1500-mg SR was significantly smaller than that of 2 consecutive 1000-mg doses of the IR formulation. The ratio of LS means of these 2 products for AUC_{0-12}, AUC_{0-t}, and AUC_{0-inf} was below 80% (<0.8), and the 90%CIs were outside the 0.80–1.25 bioequivalence interval (Table 3).

Summary statistics for secondary PK end points are given in Table 4. The maximum plasma acetaminophen concentration (C_{max}) of 15.0 μg/mL for 2000-mg SR acetaminophen was about 80% of the C_{max} of 1000-mg IR acetaminophen, whereas the C_{max} for 1500-mg SR acetaminophen was noticeably lower at 11.5 μg/mL (only 61% of the C_{max} for standard IR acetaminophen). A distinct difference was observed in median T_{max} of 3.5 hours for each of the 2 SR formulations compared

with a median T_{max} of 2.0 hours for IR acetaminophen. Both SR formulations demonstrated longer mean half-life values—3.4 and 3.8 hours for the 2000-mg and 1500-mg SR formulations, respectively—compared with the IR formulation half-life of 2.9 hours. However, it must be noted that the half-life values observed for the SR formulations in this study were not dependent on elimination alone. Slower absorption rates from these controlled-release acetaminophen formulations may have caused an overlap with the elimination phase and, as a result, a bias in half-life estimation.

Safety
Ten subjects experienced a total of 27 TEAEs (Table 5). Of these, only 1 (mild dyspepsia), observed after use of 1500-mg SR acetaminophen, was considered treatment related. Eleven TEAEs were observed in 36% of subjects during treatment with 2000-mg SR acetaminophen, 12 were observed in 36% of subjects after 1500-mg SR acetaminophen, and 4 were observed in 21% of subjects after 2 doses of IR acetaminophen 1000 mg given 6 hours apart. Of the 27 TEAEs, 21 were mild, 5 were moderate, and 1 was severe. The severe TEAE consisted of an increase in blood creatine phosphokinase during IR acetaminophen use. No serious TEAEs occurred during the study.

Discussion

In this proof-of-principle PK study, the extent of acetaminophen absorption from a single dose of 2000-mg SR acetaminophen (2 × 1000 mg) was found to be similar to that of 2 doses of IR acetaminophen 1000 mg (2 × 500 mg per dose) given 6 hours apart. Treatment with 1 dose of the 2000-mg SR formulation maintained the plasma acetaminophen concentration at or above the minimum threshold of 4 μg/mL for an amount of time comparable to that of 2 doses of the 1000-mg IR formulation. Median $T_{C\geq4\mu g/mL}$ was 10.5 hours for 2000-mg SR acetaminophen and 9.75 hours for IR

Table 2. Time at or Above 4 μg/mL (T$_{C \geq 4\mu g/mL}$) Plasma Acetaminophen Concentration From Single Doses of 2000- and 1500-mg SR and 2 doses of 1000-mg IR Acetaminophen

End Point	2000-mg SR Acetaminophen 2 × 1000 mg	1500-mg SR Acetaminophen 2 × 750 mg	IR Acetaminophen 2 × (2 × 500 mg)
T$_{C \geq 4\mu g/mL}$, median (hours)	10.50	8.12	9.75
Treatment comparison SR vs IR, median of differences[a] (P)[b]	−0.13 (.7222)	−1.50 (.0044)	—

IR, immediate release; SR, sustained release.
[a]Median of differences represents the median of individual differences between the 2 treatments across all subjects, and not the difference between the medians of 2 treatments.
[b]Probability associated with Wilcoxon signed rank test.

Table 3. Extent of Acetaminophen Absorption From Single Doses of 2000- and 1500-mg SR Acetaminophen and 2 Doses of 1000-mg IR Acetaminophen

| PK End Point | LS Mean | | | Ratio of LS Means[a] (90%CI[b]) | |
	2000-mg SR Acetaminophen 2 × 1000 mg	1500-mg SR Acetaminophen 2 × 750 mg	IR Acetaminophen 2 × (2 × 500 mg)	2000-mg SR vs IR Acetaminophen	1500-mg SR vs IR Acetaminophen
AUC$_{0–6}$, μg·h/mL	61.3	47.4	45.3	1.36 (1.27–1.45)[c]	1.05 (0.98–1.12)
AUC$_{0–12}$, μg·h/mL	99.4	76.0	100.4	0.99 (0.94–1.04)	0.76 (0.72–0.80)[d]
AUC$_{0–t}$, μg·h/mL	113.0	83.8	115.7	0.98 (0.93–1.02)	0.72 (0.69–0.76)[d]
AUC$_{0–inf}$, μg·h/mL	118.9	88.0	120.8	0.98 (0.94–1.03)	0.73 (0.70–0.76)[d]

AUC, area under the plasma concentration–time curve; AUC$_{0–12}$, AUC from 0 to 12 hours; AUC$_{0–t}$, AUC from time 0 to the last time when acetaminophen remained detectable; AUC$_{0–inf}$, AUC from time 0 extrapolated to infinity; CI, confidence interval; IR, immediate release; LS, least squares; SR, sustained release.
[a]Ratio of LS means of log-transformed data back-transformed to original data.
[b]90%CI of the ratio of LS means of log-transformed data back-transformed to original data.
[c]$P < .0001$ for 2000-mg SR vs IR acetaminophen. Difference between 1500-mg SR and IR acetaminophen was not statistically significant.
[d]$P < .0001$ for 1500-mg SR vs IR acetaminophen. Difference between 2000-mg SR and IR acetaminophen was not statistically significant.

Table 4. PK Outcome Parameters From Single Doses of 2000- and 1500-mg SR Acetaminophen Formulations and 2 Doses of IR Acetaminophen

Pharmacokinetic End Point	2000-mg SR Acetaminophen 2 × 1000 mg	1500-mg SR Acetaminophen 2 × 750 mg	IR Acetaminophen 2 × (2 × 500 mg)
AUC$_{0–12}$, mean (SD), μg·h/mL	102.5 (26.5)	78.4 (19.3)	103.1 (26.8)
AUC$_{0–t}$, mean (SD), μg·h/mL	116.0 (27.6)	86.4 (22.1)	118.9 (31.1)
AUC$_{0–inf}$, mean (SD), μg·h/mL	122.0 (28.4)	90.9 (24.0)	124.1 (32.9)
C$_{max}$, mean (SD), μg/mL	15.0 (6.3)	11.5 (3.1)	18.8 (6.2)
T$_{max}$, median (range), h	3.5 (0.50–5.0)	3.5 (0.25–5.5)	2.0 (0.27–8.0)
t$_{1/2}$, mean (SD), h	3.4 (0.5)	3.8 (0.7)	2.9 (0.4)
K$_{el}$, mean (SD), 1/h	0.21 (0.03)	0.19 (0.03)	0.25 (0.04)

C$_{max}$, maximum plasma concentration; IR, immediate release; K$_{el}$, elimination rate; PK, pharmacokinetics; SD, standard deviation; SR, sustained release; T$_{max}$, time to maximum plasma concentration; t$_{1/2}$, half-life of elimination.
[a]T$_{max}$, t$_{1/2}$, and K$_{el}$ were calculated for only the first dose of IR acetaminophen.

acetaminophen, with no significant differences between the 2 formulations. In addition, bioequivalence of the 2 formulations was demonstrated for the PK parameters evaluating extent of acetaminophen absorption. Ratios of geometric means between 2000-mg SR acetaminophen and 2 × 1000 mg IR acetaminophen and their respective 90%CIs were within the interval of bioequivalence for AUC$_{0–12}$, AUC$_{0–t}$, and AUC$_{0–inf}$. Maximum plasma concentration from 1 dose of 2000-mg SR acetaminophen (15.0 μg/mL) was comparable to that from 1000-mg IR acetaminophen (18.8 μg/mL). This provides evidence that a single dose of the 2000-mg

Table 5. Summary of Adverse Events

Adverse Event	2000-mg SR Acetaminophen		1500-mg SR Acetaminophen		IR Acetaminophen 2 × (2 × 500 mg)	
	n (%)[a]	Total TEAEs, n	n (%)[a]	Total TEAEs, n	n (%)[a]	Total TEAEs, n
TEAEs	5 (36)	11	5 (36)	12	3 (21)	4
Headache	3 (21)	3	0	0	1 (7)	1
Ecchymosis	1 (7)	1	2 (14)	2	0	0
Nausea	1 (7)	1	2 (14)	2	0	0
Vomiting	1 (7)	1	1 (7)	1	0	0
Fatigue	1 (7)	1	0	0	1 (7)	1
Thrombophlebitis	0	0	2 (14)	2	0	0
Increased blood creatine phosphokinase	0	0	1 (7)	1	1 (7)[b]	1[b]
Diarrhea	0	0	1 (7)	1	0	0
Dyspepsia	0	0	1 (7)	1	0	0
Erythematous rash	1 (7)	1	0	0	0	0
Skin hyperpigmentation	0	0	0	0	1 (7)	1
Increased AST	0	0	1 (7)	1	0	0
Pharyngitis	1 (7)	1	0	0	0	0
Back pain	1 (7)	1	0	0	0	0
Distractibility	1 (7)	1	0	0	0	0
Dysmenorrhea	0	0	1 (7)	1	0	0

AST, aspartate aminotransferase; IR, immediate release; SR, sustained release; TEAEs, treatment-emergent adverse events.
[a]Number of subjects (%) with at least 1 TEAE.
[b]The case of increased blood creatine phosphokinase in the IR acetaminophen group was the only severe TEAE.

SR formulation achieved bioequivalence with 2 doses of the 1000-mg IR formulation, not because of higher plasma concentration, but because of its controlled-release properties. In this study, longer T_{max} and $t_{1/2}$ were observed for the 2000-mg SR formulation, providing further evidence of its controlled-release properties.

In contrast, the lower 1500-mg dose of SR acetaminophen was found to be significantly inferior to the 2 doses of IR acetaminophen 1000 mg given 6 hours apart. Time of plasma acetaminophen concentration at the level of 4 μg/mL from 1 dose of 1500-mg SR acetaminophen was significantly shorter than that from 2 doses of 1000-mg IR acetaminophen. Also, the extent of absorption from 1 dose of 1500-mg SR acetaminophen was significantly lower than that of 2 doses of 1000-mg IR acetaminophen, as measured by AUC_{0-12}, AUC_{0-t}, and AUC_{0-inf}. Ratios of geometric means and 90%CIs for each of these parameters were below the minimum bioequivalence level.

Results from this study and prior studies[19] support further investigation of modified-release acetaminophen formulations designed for 12-hour dosing intervals. From the 2 doses of the SR formulation studied, only the 2000-mg dose was equivalent with 2 doses of 1000-mg IR acetaminophen. Thus, the 2000-mg SR formulation appears to be a potential substitute for the IR formulation, with a more convenient dosing regimen; properly powered PK bioequivalence studies between the 2 formulations are required to confirm these results.

In the current study, there were no serious safety findings reported with single 2000- or 1500-mg doses of SR acetaminophen. Adverse events from a single 2000- or 1500-mg dose of SR acetaminophen were similar to those from the 2 doses of IR acetaminophen at 1000 mg.

Conclusions

This randomized, open-label crossover PK study in healthy volunteers demonstrated that the extent of acetaminophen absorption from a single 2000-mg dose of SR acetaminophen (2 × 1000 mg) was bioequivalent to 2 doses of IR acetaminophen 1000 mg (2 × 500 mg) given 6 hours apart. The 2000-mg SR acetaminophen formulation was well tolerated. Thus, this SR formulation at a dose of 2 × 1000 mg represents a potential candidate for 12-hour acetaminophen dosing.

Acknowledgments

Declaration of Conflicting Interests

Funding

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