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## ORIGINAL ARTICLE

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# Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen

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Neil K. Singla, MD<sup>\*,†</sup>; Cherri Parulan, BSN, RN<sup>\*</sup>; Roselle Samson, CLS<sup>\*</sup>; Joel Hutchinson, MD<sup>†</sup>; Rick Bushnell, MD<sup>†</sup>; Evelyn G. Beja, CRC<sup>\*</sup>; Robert Ang, MD<sup>‡</sup>; Mike A. Royal, MD, JD, MBA<sup>‡</sup>  
*\*Lotus Clinical Research LLC, Pasadena, California, U.S.A.; †Huntington Memorial Hospital, Pasadena, California, U.S.A.; ‡Cadence Pharmaceuticals, Inc., San Diego, California, U.S.A.*

### ■ Abstract

**Background:** This is the first study to compare plasma and cerebrospinal fluid (CSF) pharmacokinetics of intravenous (IV), oral (PO), or rectal (PR) formulations of acetaminophen. **Methods:** Healthy male subjects ( $N = 6$ ) were randomized to receive a single dose of IV (OFIRMEV<sup>®</sup>; Cadence) 1,000 mg (15 minute infusion), PO (2 Tylenol<sup>®</sup> 500 mg caplets; McNeil Consumer Healthcare), or PR acetaminophen

(2 FEVERALL<sup>®</sup> 650 mg suppositories; Actavis) with a 1-day washout period between doses. The 1,300 mg PR concentrations were standardized to 1,000 mg. Acetaminophen plasma and CSF levels were obtained at T0, 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hours.

**Results:** IV acetaminophen showed earlier and higher plasma and CSF levels compared with PO or PR administration. CSF bioavailability over 6 hours ( $AUC_{0-6}$ ) for IV, PO, and PR 1 g was 24.9, 14.2, and 10.3  $\mu\text{g}\cdot\text{h}/\text{mL}$ , respectively. No treatment-related adverse events were reported. One subject was replaced because of premature failure of his lumbar spinal catheter. The mean CSF level in the IV group was similar to plasma from 3 to 4 hours and higher from 4 hours on. Absorption phase, variability in plasma, and CSF were greater in PO and PR groups than variability with IV administration.

**Conclusions:** These results demonstrate that earlier and greater CSF penetration occurs as a result of the earlier and higher plasma peak with IV administration compared with PO or PR. ■

Address correspondence and reprint requests to: Neil K. Singla, MD, Owner, Managing Member, Lotus Clinical Research, LLC, 100 W California Blvd, Pasadena, CA 91105, U.S.A. E-mail: neil@lotuscr.com.

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## INTRODUCTION

Acetaminophen has been known as an analgesic for more than a century, and its oral (PO) and rectal (PR) formulations have been used for pain relief in the United States (U.S.) for decades. Acetaminophen is thought to act via central mechanisms<sup>1</sup> and therefore must cross into the central nervous system (CNS) to have an effect. As there is no active transport mechanism across the blood–brain barrier, passive diffusion of acetaminophen into the CNS is highly dependent on a concentration gradient with the  $C_{\max}$  being of primary importance.<sup>2</sup> There is a direct correlation between the analgesic (and antipyretic) activity of acetaminophen and its concentration–time curve in the cerebrospinal fluid (CSF), which is consistent with its predominantly central site of action.<sup>3</sup>

In 2002, IV acetaminophen (paracetamol as it is known internationally) was first commercialized in Europe (Perfalgan® or Perfusalgan®; Bristol-Myers Squibb Company, New York, NY, USA). OFIRMEV® (acetaminophen) injection (Cadence Pharmaceuticals, Inc. [Cadence]) is the same formulation as Perfalgan® and was approved by the US FDA in November 2010 for the treatment of acute pain and fever in children (age 2 years and older) and adults.

Many studies have compared various formulations of acetaminophen: IV to oral,<sup>4–7</sup> rectal to oral,<sup>8–14</sup> and IV to rectal.<sup>15–17</sup> However, no study has compared the underlying pharmacokinetic (PK) differences of all 3 routes of acetaminophen administration with specific attention to CSF PK. This study was conducted to compare the plasma and CSF acetaminophen concentration–time curves and PK parameters in healthy adult men after a single dose using each of these routes of administration in a 3-way crossover design.

## METHODS

The objective of this IRB-approved, investigator-initiated, single-site, open-label study was to determine the

plasma and CSF acetaminophen time–concentration profiles over 6 hours and PK parameters after administration of a single-dose of IV, PO, or PR acetaminophen. Each treatment period consisted of acetaminophen administered as IV 1,000 mg (OFIRMEV®) 15 minute infusion, PO 1,000 mg (two 500 mg Tylenol® caplets; McNeil Consumer Healthcare, Fort Washington, PA, USA), or PR 1,300 mg (two 650 mg suppositories Feverall®; Actavis, Zug, Switzerland). The 1,300 mg PR dose was used, as there is no approved 500 mg presentation or higher dose than the 650 mg adult suppository dose currently approved in the United States. Each subject provided written informed consent and served as his own control.

Key inclusion criteria included healthy nonsmoking men 18 to 45 years with a BMI between 19 and 25 lbs/in<sup>2</sup> (weighing at least 50 kg) with negative drug and alcohol screens, and negative antibody tests for hepatitis and human immunodeficiency viruses. Key exclusion criteria included use of medications or supplements during the 7 days prior to the first clinic dose of acetaminophen, history of excessive bleeding, history of recent infection, known lumbar spine deformities, history of elevated intracranial pressure or other neurological conditions, and allergy to acetaminophen.

A 20-gauge spinal catheter was placed on admission to the clinic for CSF sampling. As acetaminophen has a short elimination half-life ( $t_{1/2}$ ) of approximately 2 to 3 hours in adults,<sup>6</sup> a 24-hours washout (6 to 7 half-lives) from 1 acetaminophen dose to the next was deemed reasonable, especially given the desire to minimize the time the spinal catheter was kept in place. Figure 1 presents the study design and study drug dosing timing. Plasma and CSF acetaminophen levels were obtained at T0 (predose), 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hours following administration of each study drug. During the 3-day treatment and assessment period, no other medications were allowed.

Safety assessments included screening and end of study history, vital signs and physical examinations,

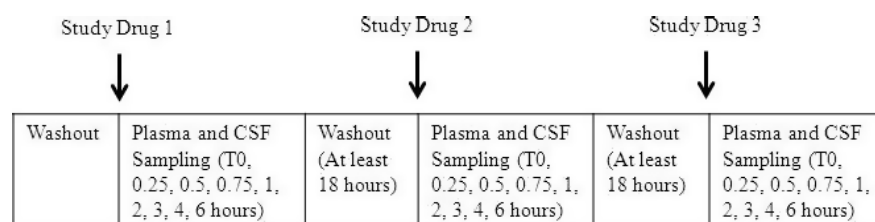


Figure 1. Timing of study drug dosing.

various clinical laboratory tests, and spontaneously-reported adverse events (AEs).

No sample size determination was performed. Individual plasma and CSF concentration-time curves over 6 hours and standard group PK parameters were generated. As acetaminophen plasma and CSF levels are linearly dose proportional,<sup>18,19</sup> individual concentration results from the 1,300 mg PR dose were standardized to 1,000 mg to facilitate comparison with data from IV and PO routes. Mean concentration-time profiles also were generated for each route of administration. The following PK parameters for both plasma and CSF were generated: mean maximum concentration ( $C_{\max}$ /CSF $_{\max}$ ), median time to maximal concentration ( $T_{\max}$ ), mean elimination half-life ( $t_{1/2}$ ), and mean area under the curve from T0 to 6 hours ( $AUC_{0-6}$ ).

MedTox Laboratories, Inc. (St Paul, MN, U.S.A.) performed the plasma acetaminophen assays, and iC42 Integrated Solutions in Systems Biology for Clinical Research & Development (Aurora, CO, U.S.A.) performed the CSF assays. Both companies used validated analytical LC/MS/MS methods to generate acetaminophen concentration values. Pharsight, a Certara™ Company, generated the mean concentration-time curves and conducted the noncompartmental PK analyses. The mean differences in PK parameters from each route of administration were compared using a paired t-test.

## RESULTS

### Baseline Demographics

Five Caucasian and 2 African-American men with a mean (range) age of 29.4 (19 to 44) years were enrolled. All subjects met eligibility criteria with the exception of 2 subjects given a waiver for BMIs of 25.3 and 25.6. Each subject had an unremarkable medical history, was afebrile, and had normal vital signs and physical examinations on clinic admission. One subject was discontinued from study participation and replaced because of premature failure of his spinal catheter on day 2 after post PO PK assessments were completed; however, his results from day 1 PO dosing were included in the final PK results (Table 1). One subject in the PR group had missing CSF samples and was therefore excluded from the analysis (Table 2).

### Pharmacokinetic Parameters

The plasma PK results are presented in Table 1, and the CSF results are presented in Table 2. Note that to standardize the PR dose to 1,000 mg, individual concentration values at each time point were adjusted to create standardized concentration-time curves, and these individual values were used to calculate mean PK parameters.

After an IV, PO, or PR 1,000 mg acetaminophen dose, the mean plasma  $C_{\max}$  values were 21.6, 12.3,

**Table 1. Mean (%CV) Acetaminophen Plasma PK Parameters**

| PK Parameter                       | IV (1,000 mg)     | PO (1,000 mg)            | PR (1,300 mg)          | PR (Standardized to 1,000 mg) |
|------------------------------------|-------------------|--------------------------|------------------------|-------------------------------|
| N                                  | 6                 | 7                        | 6                      | 6                             |
| Mean $C_{\max}$ (μg/mL)            | 21.6 (17.9)       | 12.3 (45.2)              | 7.90 (49.0)            | 6.07 (49.0)                   |
| Median $T_{\max}$ (range)* (hours) | 0.25 (0.25, 0.25) | 1.0 (0.50, 2.0)          | 2.5 (2.0, 4.0)         | 2.5 (2.0, 4.0)                |
| Mean $t_{1/2}$ (hours)             | 2.17 (20.0)       | 2.53 (19.3) <sup>†</sup> | 3.00 (NC) <sup>‡</sup> | 3.00 (NC) <sup>‡</sup>        |
| Mean $AUC_{0-6}$ (μg·h/mL)         | 42.5 (16.5)       | 29.4 (52.3)              | 31.9 (29.2)            | 24.5 (29.2)                   |
| Mean $AUC_{0-\infty}$ (μg·h/mL)    | 50.0 (18.7)       | 44.4 (35.4) <sup>†</sup> | 41.3 (NC) <sup>‡</sup> | 31.8 (NC) <sup>‡</sup>        |
| Mean CL/F (L/hours)                | 20.7 (19.8)       | 24.6 (28.9) <sup>†</sup> | 32.5 (NC) <sup>‡</sup> | 32.5 (NC) <sup>‡</sup>        |

\*(Min, Max).

<sup>†</sup>N = 6.

<sup>‡</sup>N = 2 and mean (% CV).

NC, not calculated, % CV, coefficient of variation.

**Table 2. Mean (%CV) Acetaminophen CSF PK Parameters**

| PK Parameter                        | IV (1,000 mg)  | PO (1,000 mg)   | PR (1,300 mg)  | PR (Standardized to 1,000 mg) |
|-------------------------------------|----------------|-----------------|----------------|-------------------------------|
| N                                   | 6              | 7               | 5              | 5                             |
| Mean CSF $_{\max}$ (μg/mL)          | 5.94 (18.4)    | 3.72 (39.1)     | 4.13 (25.6)    | 3.18 (25.6)                   |
| Median $T_{\max}$ * (range) (hours) | 2.0 (1.0, 4.0) | 4.0 (0.75, 6.0) | 6.0 (3.0, 6.0) | 6.0 (3.0, 6.0)                |
| Mean $AUC_{0-6}$ (μg·hours/mL)      | 24.9 (17.4)    | 14.2 (52.1)     | 13.4 (24.6)    | 10.3 (24.5)                   |

\*(Min, Max).

CSF, cerebrospinal fluid; % CV, coefficient of variation; PK, pharmacokinetic.

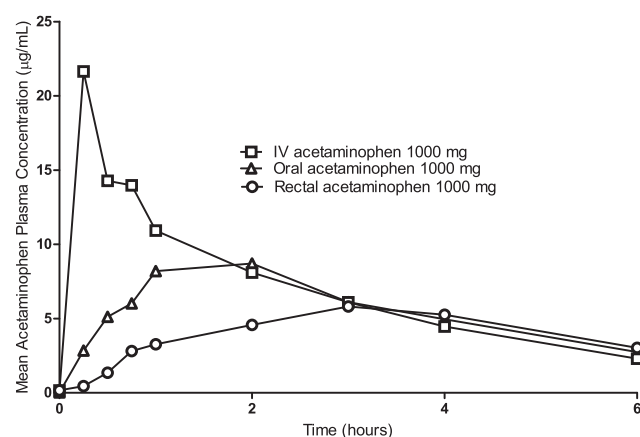
and 6.1  $\mu\text{g/mL}$ , respectively (Table 1). The IV route produced a 76% or 256% higher  $C_{\text{max}}$  than the PO ( $P = 0.0004$ ) or PR ( $P < 0.0001$ ) routes, respectively, and the PO route produced a 103% higher value than PR administration ( $P = 0.0803$ ). Comparing mean  $\text{CSF}_{\text{max}}$  values, the IV route was 60% higher than PO ( $P < 0.0001$ ) and 87% higher than PR ( $P < 0.0001$ ), and PO was 17% higher than PR ( $P = 0.4763$ ) (Table 2). PO or PR routes of administration exhibited higher variability (larger % CV) in concentration-time values during the absorption phase compared with the IV route (Table 1 and Figure 6A–C).

Median plasma  $T_{\text{max}}$  values also were different between the routes of administration; values for IV, PO, and PR were 0.25, 1.0, and 2.5 hours, respectively. The IV group exhibited significantly shorter  $T_{\text{max}}$  values compared with PO ( $P = 0.0018$ ) and PR ( $P = 0.0025$ ) groups, consistent with absorption delays for PO or PR administration. Median CSF  $T_{\text{max}}$  values for IV, PO, and PR were 2.0, 4.0, and 6.0 hours, respectively, again with numerically shorter times for IV compared with PO ( $P = 0.1035$ ) and statistically significantly shorter for IV vs. PR ( $P = 0.0195$ ) routes. As previously stated, the time to reach maximum CNS concentrations, as measured by CSF assessments, correlates well with the peak pharmacodynamic effect.

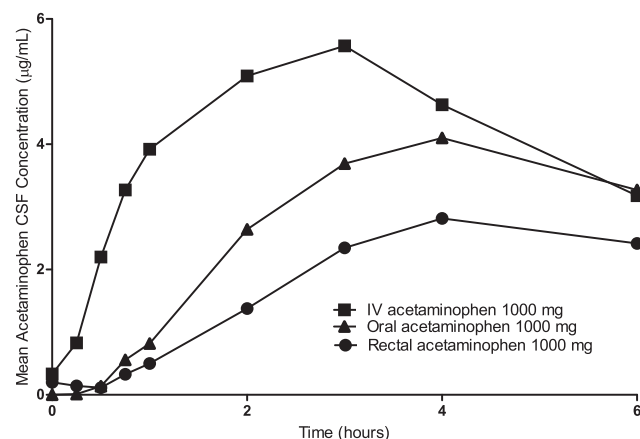
$\text{AUC}_{0-6}$  values for IV, PO, and PR were 42.5, 29.4, and 24.5  $\mu\text{g}\cdot\text{h/mL}$  in plasma, and 24.9, 14.2, and 10.3  $\mu\text{g}\cdot\text{h/mL}$  in CSF, respectively. The IV CSF  $\text{AUC}_{0-6}$  value was 75% higher than PO ( $P = 0.0099$ ) and 142% higher than PR ( $P = 0.0004$ ). The comparison for  $\text{AUC}_{0-6}$  values between the PO and PR routes was not significant ( $P = 0.4268$ ). Note that the CSF/plasma partition coefficients for IV, PO, and PR routes are 0.59, 0.48, and 0.42, respectively, which demonstrates the value of the higher  $C_{\text{max}}$  peak providing the necessary steep concentration gradient to drive acetaminophen into the CNS.

The mean plasma  $t_{1/2}$  was slightly longer after PO or PR administration, but the differences were not statistically significant, and the range of 2 to 3 hours is consistent with previously published data in adults.<sup>6</sup> The systemic clearance (CL) normalized by absolute bioavailability (F) is similar across the routes of administration. Absolute bioavailability comparison values for PO or PR routes, calculated by comparing mean  $\text{AUC}_{0-\infty}$  vs. IV dosing, was 89% and 72%, respectively. These AUC values are consistent with prior published data.

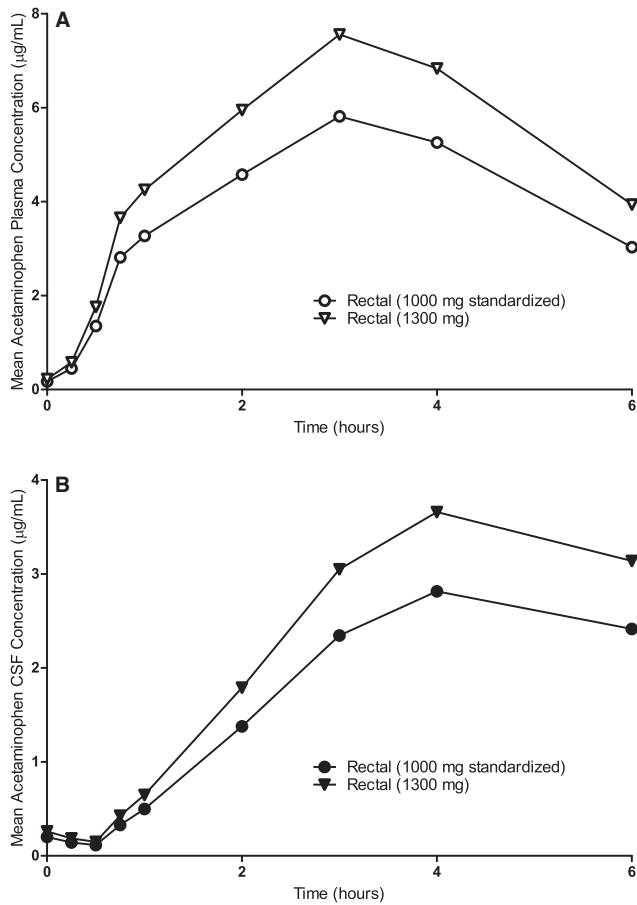
The mean concentration-time curves for plasma are presented in Figure 2, and the curves for CSF are presented in Figure 3. The IV route of administration showed consistently earlier and higher peak plasma or CSF concentration values than PO or PR routes (Figures 2 and 3, respectively). Figures 4A (plasma) and B (CSF) show the effect of standardizing the individual PR concentration-time values after two 650 mg suppositories (1,300 mg) to 1,000 mg. Figure 5A–C display the plasma and CSF concentration-time curves for each route of administration plotted on the same graph (IV, PO, and PR, respectively). Figure 6A–C show the individual subject plasma concentration-time curves for each route of administration (IV, PO, and PR,



**Figure 2.** Mean plasma acetaminophen concentration-time curves after IV, PO, and PR administration of 1,000 mg ( $N = 7$  for PO and 6 for IV/PR).



**Figure 3.** Mean cerebrospinal fluid acetaminophen concentration-time curves after IV, PO, and PR administration of 1,000 mg.



**Figure 4.** Standardization of plasma (A) and cerebrospinal fluid (B) acetaminophen concentration-time values to 1,000 mg after PR administration of 1,300 mg.

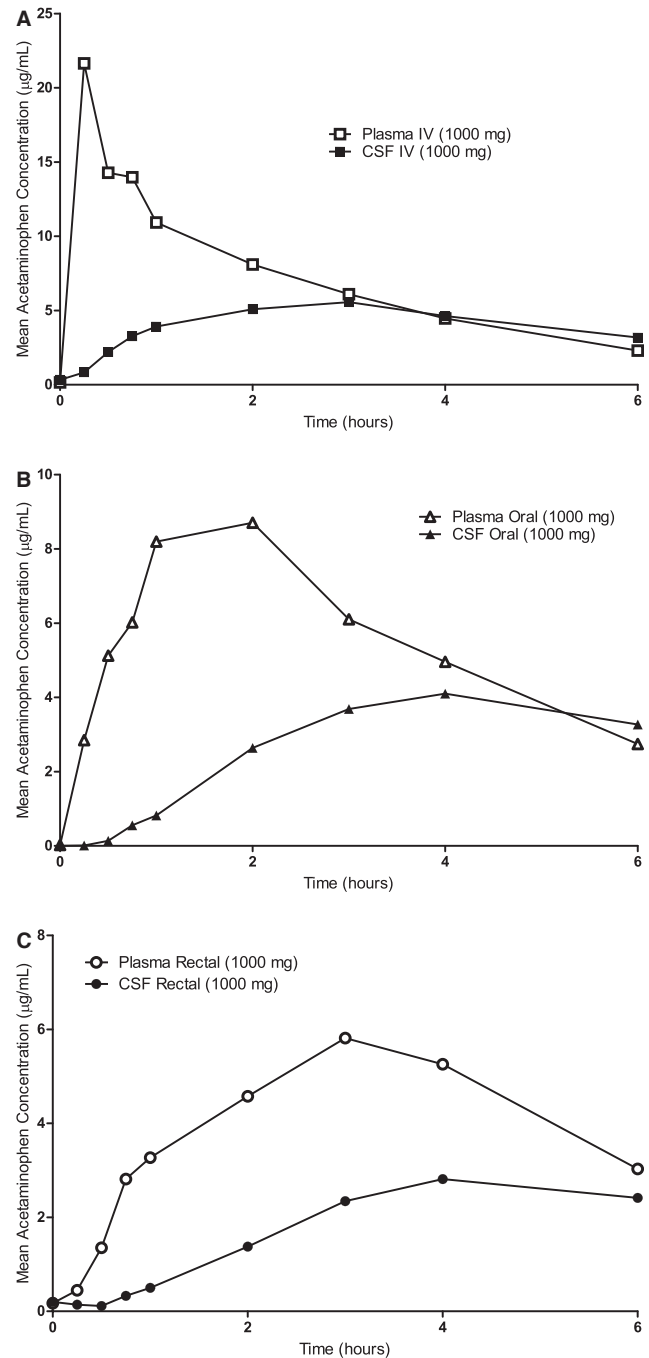
respectively). For all 3 groups, mean CSF levels were similar to plasma values from 3.5, 5, and 6 hours, respectively.

### Safety

All acetaminophen doses were well tolerated. Three subjects experienced 12 AEs with headache, particularly postdural puncture headache, being the most common event (Table 3). None of the events were deemed to be treatment-related AEs (TEAEs). All AEs were mild to moderate in severity, nonserious and deemed not related to study drug. No complications were reported with the spinal catheter placement.

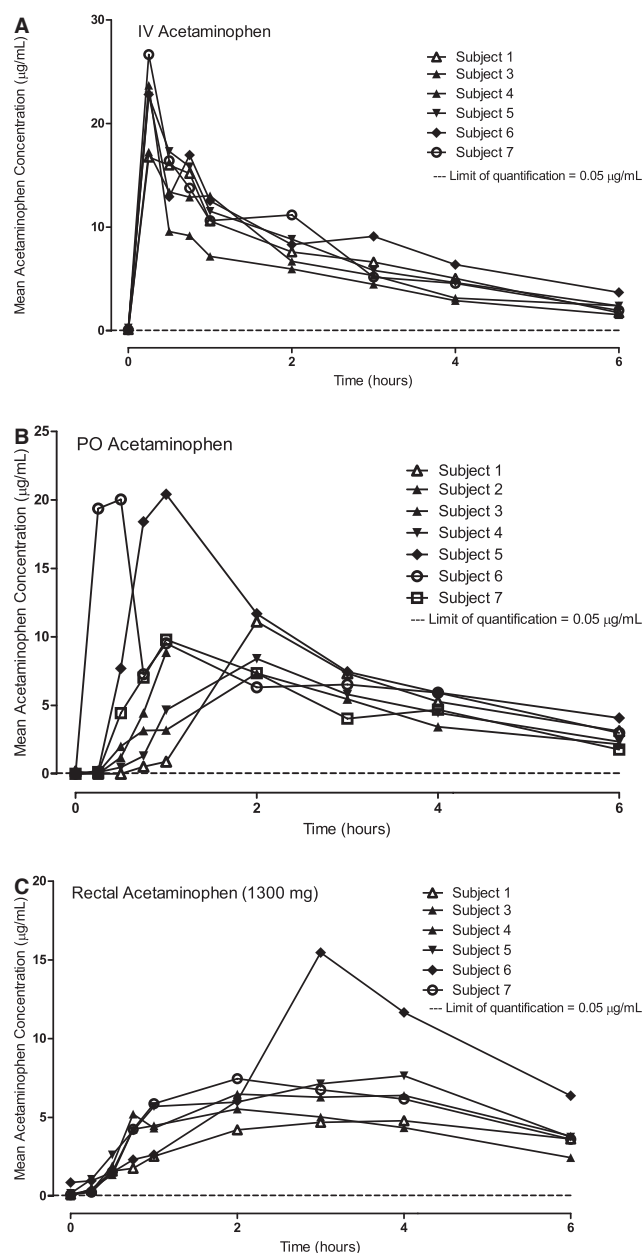
### Limitations

This was a single-dose study in a small number of patients. In a repeated dose PK study,<sup>6</sup> the PK differ-



**Figure 5.** Mean plasma and cerebrospinal fluid acetaminophen concentration-time curves for IV (A), PO (B), and PR (C) routes of administration.

ences between IV and PO dosed at 1,000 mg q6 hours were consistently maintained at steady state, which would predict that acetaminophen CSF levels would similarly be consistently maintained (Figure 7). Although individual variation was typical for PK studies, the small sample size is certainly an important



**Figure 6.** Individual plasma acetaminophen concentration-time curves for IV (A), PO (B), and PR (C) routes of administration.

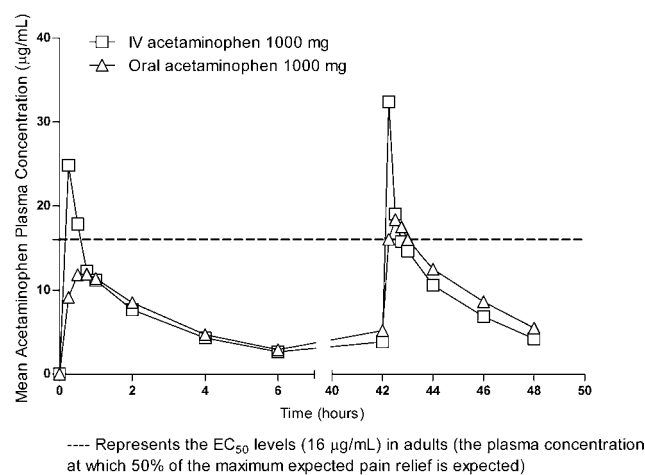
limitation of this study; however statistical significance was reached in many of the PK endpoints for the IV vs. PO or PR comparisons.

Because of concern about keeping the spinal catheter in place for the shortest time possible, a 24-hours washout period was used after each dose. As a result, there was a small but measurable residual predose acetaminophen level (mean < 0.25 µg/mL or < 0.34 µg/mL across dosing days for plasma or CSF, respectively), which was slightly higher for PO or PR

**Table 3. Listing of All Adverse Events**

| Subject # | Treatment Period | Event Description                             | Event Severity |
|-----------|------------------|-----------------------------------------------|----------------|
| 004       | N/A              | Headache                                      | Mild           |
|           | PO               | Torticollis                                   | Mild           |
|           |                  | Vasovagal episode with nausea and diaphoresis | Moderate       |
|           |                  | Headache                                      | Moderate       |
|           | IV               | Nausea                                        | Mild           |
|           | PR               | Postdural puncture headache                   | Mild           |
|           | N/A              | Viral upper respiratory infection             | Mild           |
| 005       | IV               | Headache                                      | Mild           |
|           |                  | Abdominal wall ache                           | Moderate       |
| 006       | PR               | Postdural puncture headache                   | Mild           |
|           | PR               | Postdural puncture headache                   | Moderate       |
|           | N/A              | Postdural puncture headache                   | Mild           |

IV, intravenous; N/A, not applicable; PO, oral; PR, rectal.



**Figure 7.** First dose and steady-state comparison of IV vs. PO administration (N = 38).

compared with IV. Therefore, results for bioavailability may represent a slight overestimate given the carry-over effects.

Lastly, this PK study was conducted in healthy adult men given no concomitant medications, and results in surgical inpatients may well be different because of the factors such gastric stasis, volume of distribution, and blood-brain barrier considerations.

## DISCUSSION

In this current study, single-dose IV acetaminophen showed consistently earlier and higher peak plasma levels than PO acetaminophen. These results are consistent with previous studies comparing IV and PO administration<sup>6,7</sup> and PO vs. PR administration.<sup>8</sup> The Harriet Lane Handbook<sup>20</sup> suggests a PR loading dose

of 40 to 45 mg/kg in children may be considered to overcome the reduced and erratic rectal mucosal absorption. Arguably, a similar weight-based dose may be necessary in adults as well resulting in a PR dose exceeding 3 g (5 of the 650 mg suppositories). While this may be successful in achieving therapeutic levels, the  $T_{\max}$  will still be about 3 to 4 hours, and many will fail to achieve therapeutic levels. The variability with the PR route of administration is considerable<sup>17,21</sup> and has caused the American Academy of Pediatrics Committee on Drugs<sup>22</sup> to discourage its use in children.

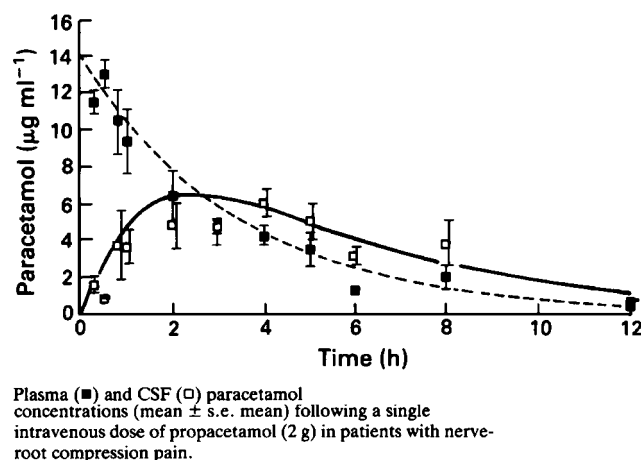
There are no active transport mechanisms for acetaminophen to cross into the CNS. In part because of its negligible protein binding and reasonable lipid solubility, acetaminophen is capable of rapid passive diffusion through an intact blood–brain barrier into the CNS. However, for this passive process to occur, a sufficiently high plasma to CSF concentration gradient is required.<sup>23</sup> As the primary site of action for acetaminophen is within the CNS, Bannwarth et al.<sup>3</sup> have suggested that its pharmacodynamic effect is dependent on achieving a sufficient CSF level.

There is limited published data on CSF penetration after IV acetaminophen administration. The CSF results observed in the current study are similar to those of Bannwarth et al.<sup>3</sup> and Moreau et al.<sup>18</sup> following IV propacetamol 2 g (the acetaminophen prodrug that is converted immediately to approximately 1 g acetaminophen and diethylglycine by plasma esterases) in adults (Figure 8). In Bannwarth et al., 43 adult patients (mean age 52 years and weight 72 kg, M24/F19) with lumbosacral radiculopathy received a single

dose of IV propacetamol over 3 minutes. A single paired blood/CSF sample was obtained per patient at various time points from 20 minutes to 12 hours. In Moreau et al., 12 elderly patients (mean age 77 years and weight 66 kg; 9 M/3 F) who had lower extremity vascular surgery under continuous spinal anesthesia received IV propacetamol 2 g over 15 minutes.<sup>18</sup> In each patient, paired blood and CSF samples were obtained at the end of the propacetamol infusion (15 minutes), 30 minutes, then every 30 minutes to 2 hours, every 15 minutes from 2 to 3 hours, and every 30 minutes from 3 to 6 hours. In both studies, acetaminophen was detected in the earliest CSF samples and increased to a maximum mean value at approximately 3 hours. CSF acetaminophen levels were higher than plasma levels from approximately 3 hours through the end of the study. Results in children<sup>2</sup> dosed with IV acetaminophen 15 mg/kg were similar to adult data after IV propacetamol.

While no study has yet to correlate CSF acetaminophen levels with pain response, Anderson et al.<sup>8</sup> were the first to correlate plasma acetaminophen levels with pain response using a post-tonsillectomy pain model. In 100 children aged 3 to 15 years undergoing elective tonsillectomy given either 40 mg/kg PO or PR acetaminophen 40 minutes prior to the procedure with no other pre- or intraoperative analgesics administered until the PACU (IV morphine as needed), the authors demonstrated that acetaminophen plasma levels of 10 to 20  $\mu\text{g/mL}$  (0.066 to 0.132 mM)<sup>24</sup> are essential to achieve effective pain relief in the PACU. As acetaminophen plasma levels increased, the incidence of successful analgesia (defined as pain score < 6/10) increased: at 0.05, 0.07, and 0.09 mM (7.6, 10.6, and 13.6  $\mu\text{g/mL}$ ), and success rates progressively increased: 68.5%, 74.2%, and 79.6%. More than half of the PR 40 mg/kg group had pain scores over 6/10, which matched acetaminophen levels below 10  $\mu\text{g/mL}$ . The poor response for the PR group was likely due to both absorption variability and timing of dose: even administration 40 minutes prior to surgery is too close to effectively treat postoperative pain given the PR  $T_{\max}$  of 3 to 4 hours.

In addition, several investigators have studied the half maximal effective concentration ( $\text{EC}_{50}$ ) of acetaminophen plasma levels and analgesia. Hutcheson et al.<sup>25</sup> used a population PK-PD model involving 114 patients undergoing surgical extraction of impacted third molar teeth who received a single PO dose of acetaminophen 1,000 mg (either caplet or effervescent



**Figure 8.** Mean plasma and cerebrospinal fluid acetaminophen concentration-time curves after IV propacetamol 2 g (approximately equivalent to acetaminophen 1 g).<sup>3</sup>

solution) or placebo at the onset of significant pain. Similarly, Gelotte et al.<sup>26</sup> studied male subjects receiving either 2 doses PO of 650 mg immediate-release acetaminophen 4 hours apart or 1 dose PO of 1,300 mg extended-release acetaminophen. These studies resulted in EC<sub>50</sub> plasma concentration estimates for acetaminophen of 15.2 and 16.6 µg/mL, respectively. In the current study, 28% of subjects receiving PO acetaminophen and none of subjects receiving PR acetaminophen had C<sub>max</sub> values at or above 15 µg/mL, compared with 100% of subjects receiving IV acetaminophen.

While perioperative PO dosing is often used, absorption may not be as good as published PK data in healthy subjects due primarily to delayed gastric emptying. Delayed emptying and resultant poor oral drug bioavailability has been shown following cardiac surgery,<sup>27</sup> and even in minimally invasive laparoscopic cholecystectomies<sup>28</sup> and gynecological surgeries.<sup>29</sup> This phenomenon can result in major PK shifts; for instance, Goldhill et al.<sup>27</sup> showed that cardiac surgery results in a 4-fold decrease in C<sub>max</sub> and more than 6-fold decrease in AUC<sub>0–60 min</sub> compared with preoperative controls. Normalization of absorption occurs over 1<sup>28</sup> to 3 days<sup>27</sup> after surgery.

Nasogastric delivery is not an effective way to deliver PO medications if gastrointestinal function has not returned to normal. Elfant et al.<sup>30</sup> demonstrated that delivery of acetaminophen via nasogastric tube (NGT) results in significantly lower levels compared with preoperative dosing. Similarly, Schuitmaker et al.<sup>31</sup> showed a 2,000 mg PO dose of acetaminophen delivered via NGT given postoperatively failed to achieve a sufficient plasma level to produce a pain effect. In this study, the mean C<sub>max</sub> was just over 6 µg/mL after a 2,000 mg dose, which is approximately 25% of what is expected in healthy subjects given the same dose. The T<sub>max</sub> was considerably delayed as well.

While surgical intervention itself is well understood to cause decreased gastrointestinal motility and delayed gastric emptying, it has been shown that opioid analgesics,<sup>32–34</sup> the fasting state,<sup>35</sup> and supine positioning<sup>36</sup> all independently contribute to delayed gastric emptying. In a recent United Kingdom study<sup>7</sup> comparing preoperative IV or PO acetaminophen 1,000 mg given preoperatively to patients undergoing surgery produced significantly different postoperative PK results, where the PO group experienced inadequate plasma levels for producing an effective pain response as compared to the therapeutic levels seen in

the IV group. Thus while NPO limitations may not necessarily be in effect in the immediate preoperative period, a 1,000 mg dose of PO acetaminophen will likely result in subtherapeutic levels.

As IV acetaminophen may be reserved for patients who cannot reliably take PO intake (eg, NPO status) or to avoid absorption variability, it is important to understand differences in PK of these different routes of administration, particularly with regard to CNS penetration. This is the first study evaluating the plasma and CSF PK of comparable doses of IV, PO, and PR acetaminophen. IV acetaminophen shows significantly better CNS penetration compared with PO or PR routes, and these results, in conjunction with the typical gastric stasis and poor oral absorption that occurs perioperatively because of fasting or opioid administration, may justify use of IV acetaminophen preoperatively through the immediate postoperative period.

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