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


**Neil K. Singla[a], Cherri Parulan[a], Roselle Samson[a], Joel Hutchinson[b], Rick Bushnell[b], Evelyn G. Beja[a], Mike A. Royal[c]**

[a] Lotus Clinical Research LLC, Pasadena, CA; [b] Huntington Memorial Hospital, Pasadena, CA; [c] Cadence Pharmaceuticals, Inc., San Diego, CA



## ABSTRACT

**Background:** Intravenous (IV) acetaminophen was FDA-approved in November 2010 for the treatment of acute pain and fever in adults and children ≥ 2 years. In an IRB-approved, single site study conducted by Singla, 6 healthy adult males were given IV, oral (PO) or rectal (PR) acetaminophen in a 3-way crossover design. A spinal catheter was placed for cerebrospinal fluid (CSF) sampling. The objective was to show comparative plasma and CSF concentration-time curves in healthy adult males after IV, PO, or PR acetaminophen.

**Methods:** The IV group received Ofirmev® (acetaminophen) injection 1000 mg (Cadence) over 15 min. The PO group received two Tylenol® 500 mg caplets (McNeil). No approved PR suppository dose of acetaminophen higher than 650 mg exists, nor is there a 500 mg dose, therefore two Feverall® 650 mg suppositories (Alpharma) were used for the rectal group. After subjects were admitted to the clinic, a spinal catheter was placed at the lumbar level, and on the next 3 mornings, each subject received a single dose of IV, PO or PR acetaminophen in random order. The short acetaminophen elimination half-life and the desire to reduce the time during which the spinal catheter was kept in place, made a 1 day washout reasonable. Plasma and CSF acetaminophen levels were obtained at T0 (predose), 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hours. Because both plasma and CSF levels are linearly dose proportional (Jensen 2004), individual concentration results from the 1300 mg PR dose were standardized to 1000 mg. Safety assessments included laboratory tests, physical exams and spontaneous adverse events (AE).

**Results:** Five Caucasian and 2 African American males with a mean (range) age of 29.4 (19-44) years were enrolled. One subject was replaced due to premature failure of his spinal catheter. The mean IV Cmax was nearly twice that observed with PO administration and nearly four times that observed with PR. The IV plasma and CSF maximum concentration values were statistically significantly higher vs. PO (p=0.0004 and p<0.0001, respectively) or PR (p<0.0001 and p<0.0001, respectively). The plasma mean $C_{max}$ / median $T_{max}$ for IV, PO and PR was 21.6 µg/mL / 15 minutes, 12.3 µg/mL / 1 hour, and 6.07µg/mL / 2.5 hours, respectively. Maximum mean CSF concentrations for IV (5.94 µg/mL), PO (3.72 µg/mL) and PR (3.18 µg/mL) were observed at a median of 2, 4 and 6 hours, respectively. Plasma (Coefficient of Variation, %CV) / CSF (%CV) $AUC_{0-6}$ values (µg•hr/mL) for IV, PO and PR were 42.5 (16.5) / 24.9 (17.4), 29.4 (52.3) / 14.2 (52.1), 24.5 (29.2) / 10.3 (24.5), respectively. The IV CSF $AUC_{0-6}$ value was 75% higher than PO and 142% higher than PR. No AEs were reported.

**Discussion:** In the current study, the IV group showed consistently earlier and higher peak plasma and CSF values as shown in Figures 1 and 2. The mean CSF level is similar to plasma values from 3 to 4 hours in the IV group, and is higher from 4 hours on. As expected, due to absorption issues, the variability in plasma and CSF results are much higher in the PO and PR groups compared to that observed for the IV route.

**Conclusion:** The results from this study provide a rationale for the superior analgesic results seen in previous investigations that compared IV vs. PO (Petterson 2005), IV vs. PR (Romsing 2002, Pettersson 2006), and PO vs. PR (Anderson 1996) acetaminophen.


### Abbreviations

| | |
|---|---|
| AE | Adverse Events |
| AUC | Area under the curve (bioavailability); µg•h/mL |
| BMI | Body mass index |
| $C_{max}$ | Maximum plasma (CSF) concentration; µg/mL |
| CNS | Central nervous system |
| CSF | Cerebral spinal fluid |
| CV | Coefficient of variation |
| F | Absolute bioavailability comparison; % |
| IRB | Independent review board |
| IV | Intravenous |
| PACU | Postanesthesia care unit |
| PK | Pharmacokinetics |
| PO | Per oram (Oral) |
| PR | Per rectum (rectal) |
| SD | Standard deviation |
| t ½ | Elimination half-life; h |
| $T_{max}$ | Time to maximal concentration; h |

## 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 (US) for years. In 2002, intravenous (IV) acetaminophen (paracetamol) was first commercialized in Europe (Perfalgan® or Perfusalgan®; Bristol-Myers Squibb Company). OFIRMEV® (acetaminophen) injection (Cadence Pharmaceuticals, Inc.) 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.

Acetaminophen is thought to act via central mechanisms (Bertolini 2006), and therefore must cross into the central nervous system (CNS) to have an effect. Many studies have compared various formulations of acetaminophen: IV to oral (Peacock 2011, Pettersson 2005, Schutz 2007, van der Westhuizen 2011), rectal to oral (Anderson 1996, Anderson 1999, Blume 1994, Coulthard 1998, Hahn 2000, Scolnik 2002, van der Marel 2001) and IV to rectal (Breitmeyer 2010, Capici 2008, Pettersson 2006). However, no study has compared the underlying pharmacokinetic differences of all three routes of acetaminophen administration with specific attention to cerebrospinal (CSF) pharmacokinetics. This study was conducted to compare the plasma and CSF acetaminophen concentration-time curves and pharmacokinetic parameters in healthy adult males after a single 1000 mg dose using each of these routes of administration in a three-way cross-over 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 6h and pharmacokinetics (PK) after administration of a single-dose of intravenous (IV), oral (PO) or rectal (PR) acetaminophen. Each treatment period consisted of 1000 mg of acetaminophen administered as IV (OFIRMEV®; Cadence) 15 minute infusion or PO (two 500 mg Tylenol® caplets; McNeil Consumer Healthcare), and for the PR formulations (two 650 mg suppositories Feverall®; Alpharma). A 1300 mg PR dose was used, since there is no approved 500 mg presentation or dose higher than the 650 mg adult suppository dose currently approved in the US.

Key inclusion criteria included healthy non smoking males 18 to 45 years with a BMI between 19 and 25 lbs/in$^2$ (weighing at least 50 kg) with negative drug and alcohol screens, 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 spinal catheter was placed on admission to the clinic for CSF sampling. Since acetaminophen has a short elimination half-life in adults (Schutz 2007), a 24h washout from one acetaminophen dose to the next was felt reasonable especially given the desire to minimize the time the spinal catheter was kept in place. Plasma and CSF acetaminophen levels were obtained at T0 (predose), 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hours. 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, various clinical laboratory tests, and spontaneously-reported adverse events (AEs).

No sample size determination was performed. Plasma and CSF concentration-time curves over 6h and PK parameters were generated for all patients. Since acetaminophen plasma and CSF levels are linearly dose proportional regardless of route of administration (Jensen 2004), individual concentration results from the 1300 mg PR dose were standardized to 1000 mg to facilitate comparison with data from IV and PO routes. Mean concentration-time profiles were generated for each route of administration. The following PK parameters for both plasma and CSF were generated: maximum concentration ($C_{max}$), time to maximal concentration ($T_{max}$), elimination half-life (t ½), and area under the curve from T0 to 6h ($AUC_{0-6}$).

MedTox Laboratories, Inc. (St. Paul, Minnesota) performed the plasma assays and iC42 Integrated Solutions in Systems Biology for Clinical Research & Development (Aurora, Colorado) performed the CSF assays. Both companies used validated analytical methods to generate acetaminophen concentration values. Pharsight, a Certara™ Company, generated the mean concentration-time curves and conducted the non-compartmental PK analyses. The variables were compared by dose group using 2-sided t-tests.

## RESULTS

### Baseline Demographics

Five Caucasian and 2 African American males with a mean (range) age of 29.4 (19-44) years were enrolled. All subjects met eligibility criteria, however 2 subjects with a BMI of 25.3 and 25.6 were given waivers for enrollment. 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 due to premature failure of his spinal catheter on day 2 after PK assessments were completed, however his results from day 1 PO dosing were included in the final PK results (Table 1).

### Pharmacokinetic Parameters

The plasma PK results are presented in Table 1 and the CSF results are presented in Table 2.

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

| PK Parameter | IV (1000 mg) | PO (1000 mg) | PR (1300 mg) | PR (Standardized to 1000 mg) |
|---|---|---|---|---|
| N | 6 | 7 | 6 | 6 |
| Mean $C_{max}$ (µg/mL) | 21.6 (17.9) | 12.3 (45.2) | 7.9 (49.0) | 6.07 (49.0) |
| Median $T_{max}$ (range)[a] (h) | 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 ½ (h) | 2.17 (20.0) | 2.53 (19.3)[b] | 3.00 (NC)[c] | 3.00 (NC)[c] |
| Mean $AUC_{0-6h}$ (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)[b] | 41.3 (NC)[c] | 31.8 (NC)[c] |
| Mean CL/F (L/h) | 20.7 (19.8) | 24.6 (28.9)[b] | 32.5 (NC)[c] | 32.5 (NC)[c] |

[a](Min, Max), [b]N=6, [c]N=2 and mean (%CV)
Note: NC = Not Calculated, CV = coefficient of variation

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

| PK Parameter | IV (1000 mg) | PO (1000 mg) | PR (1300 mg) | PR (Standardized to 1000 mg) |
|---|---|---|---|---|
| N | 6 | 7 | 5 | 5 |
| Mean $C_{max}$ (µg/mL) | 5.94 (18.4) | 3.72 (39.1) | 4.13 (25.6) | 3.18 (25.6) |
| Median $T_{max}$ [a](range) (h) | 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 $AUC_{0-6h}$ (µg-h/mL) | 24.9 (17.4) | 14.2 (52.1) | 13.4 (24.6) | 10.3 (24.5) |

[a](Min, Max)
Note: CV = coefficient of variation

After an IV, PO or PR 1000 mg acetaminophen dose, the mean plasma $C_{max}$ values were 21.6, 12.3 and 6.1 µg/mL, respectively (Table 1). The IV route produced a 75.6% (p=0.0004) or 254.1% (p<0.0001) higher mean plasma $C_{max}$ than PO or PR, respectively, and the PO route produced a 101.6% (NS, p=0.0803) higher value than PR. Comparing CSF $C_{max}$ values, IV vs. PO, IV vs. PR, and PO vs. PR comparisons were 59.7% (p<0.0001), 86.8% (p<0.0001), and 17.0% (NS, p=0.4763) higher, respectively (Table 2).

Similarly, median plasma $T_{max}$ values were different between groups: values for IV, PO and PR were 0.25, 1.0 and 2.5h, respectively. Note that the IV group exhibited significantly shorter values compared to PO (p=0.0018) and PR (p=0.0025) groups, consistent with relative delays for PO or PR administration due to dependence on gastrointestinal or mucosal absorption. Median CSF $T_{max}$ values for IV, PO and PR were 2.0, 4.0 and 6.0h, respectively, again with significantly shorter values for IV compared to PO (p=0.1035) and PR (p=0.0195) groups. PO or PR routes of administration exhibited higher variability in plasma and CSF $C_{max}$ results (observed standard deviation values) compared to that observed for the IV route.

The mean plasma elimination half-life (t ½) was slightly longer after PO or PR administration, but the differences were not statistically significantly different and the range of 2 to 3h is consistent with previously published data in adults (Schutz 2007). 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 $AUC_{0-\infty}$ vs. IV, was 88.5 and 72.4%, respectively.

The mean concentration-time curves for plasma are presented in Figure 1, and the curves for CSF are presented in Figure 2. The IV route of administration showed consistently earlier and higher peak plasma or CSF concentration values than PO or PR routes (Figures 1 and 2, respectively). The mean plasma IV $C_{max}$ value was nearly twice that observed with PO and nearly four times that observed with PR administration. For all three groups, mean CSF levels were similar to plasma values from 3.5, 5, and 6h respectively. The IV CSF $AUC_{0-6}$ value was 75% higher than PO and 142% higher than PR. The comparison for $AUC_{0-6}$ values between the PO and PR routes was not significant (p=0.9850). 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 $C_{max}$ peak with IV vs. PO or PR as a steep concentration gradient is necessary to drive acetaminophen into the CNS.

**Figure 1.** Mean (SD) Plasma Acetaminophen Concentration-Time curves after IV, PO and PR Administration of 1000 mg (N=6)

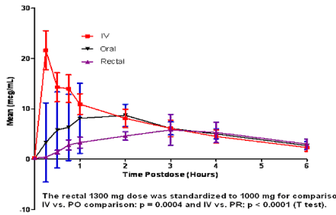
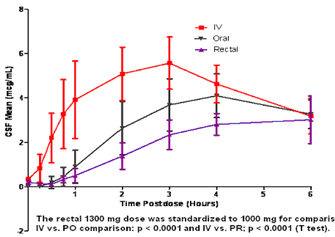



**Figure 2.** Mean (SD) CSF Acetaminophen Concentration-Time curves after IV, PO and PR Administration of 1000 mg (N=6)




### Safety

All acetaminophen doses were well tolerated. No treatment-emergent AEs were reported. 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 (Schutz 2007), the PK differences between IV and PO were consistently maintained at steady state which would predict that acetaminophen CSF levels would similarly be consistently maintained. Although individual variation was typical for PK studies, the small sample size is certainly an important limitation of this study, however statistical significance was reached in many of the PK endpoints for the IV vs. PO or PR comparisons. Additionally, because of concern about keeping the spinal catheter in place for the shortest time possible resulting in a 24h washout post dose, there was a small but measurable residual pre-dose acetaminophen level (mean < 0.25 µg/mL or < 0.34 µg/mL across dosing days for plasma or CSF, respectively) which was higher for PO or PR compared to IV. Therefore, results for bioavailability may represent a slight overestimate given the carryover effects.

## DISCUSSION

In this current study, single dose IV acetaminophen showed consistently earlier and higher peak plasma than PO acetaminophen. These results are consistent with previous studies comparing IV and PO administration (Schutz 2007, van der Westhuizen 2011). While a PR loading dose of 40 to 45 mg/kg (Harriet Lane Handbook 2009) may help to overcome absorption limitations, therapeutic levels of acetaminophen may still not be achieved. Romsing and colleagues (2002) noted in their meta-analysis that doses below 40 mg/kg are not likely to achieve significant pain relief. Even if one uses such a loading dose, Montgomery and colleagues (1995) demonstrated that with a 45 mg/kg PR acetaminophen dose, the mean $C_{max}$ was 13 µg/mL (range, 7 to 19), which resulted in nearly a third of the children failing to achieve effective acetaminophen levels. Note that a loading dose of 40-45 mg/kg in a 70 kg adult would equate to a PR dose exceeding 3 g.

Since there are no active transport mechanisms to drive acetaminophen into the CNS, it is dependent on a sufficient concentration gradient to achieve efficacious levels. 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 when "pushed" by a concentration gradient. In children dosed with IV acetaminophen (Kumpulainen 2007) and adults dosed with IV propacetamol (Bannwarth 1992), acetaminophen was detectable in the CSF within minutes once the infusion has started. The CSF results observed in Bannwarth et al. (1992) following IV infusion of propacetamol (2 g) were similar to what was observed in the current study with IV acetaminophen. Since the primary site of action for acetaminophen appears to be within the CNS, Bannwarth and colleagues have suggested that its pharmacodynamic effect is dependent on achieving a sufficient CSF level. A literature review of CSF penetration of acetaminophen by Breitmeyer et al (2009) suggests that rapid CSF penetration and earlier and higher Cmax appear to be responsible for the earlier onset and peak efficacy of IV acetaminophen compared with PO or PR.

While no study has yet to correlate CSF acetaminophen levels with pain response, Anderson and colleagues (1996) 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 µg/mL (0.066 to 0.132 mmol/L, Rumack 1976) are essential in order 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 mmol/L (7.6, 10.6 and 13.6 µg/mL) 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 µg/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 3-4 hours.

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. In a recent UK study (van der Westhuizen 2011) comparing preoperative IV or PO acetaminophen 1000 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. In Schuitmaker et al. (1999), a 2000 mg PO (via nasogastric tube) acetaminophen dose given postoperatively failed to achieve a sufficient plasma level to produce a pain effect, where the mean Cmax was just over 6 µg/mL with a 2000 mg dose. This is compared to a mean value of 12.3 µg/mL using 1000 mg PO in this current study, approximately a 4-fold difference after dose adjustment, demonstrating the effect of postoperative gastric stasis and its effects on absorption of oral medications.

## CONCLUSIONS

Since IV acetaminophen may be reserved for patients who cannot reliably take PO intake (e.g., 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. The results from this study provide a rationale for the results seen in previous investigations that compared IV vs. PO (Pettersen 2005, Schutz 2007, van der Westhuizen 2011), IV vs. PR (Romsing 2002, Petterson 2006), and PO vs. PR (Anderson 1996) acetaminophen. The results from the current study provide pharmacokinetic evidence for the rapid and potent analgesic properties of acetaminophen when administered intravenously.

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### Acknowledgements

We wish to thank the Reporting and Analysis Services of Pharsight – a Certara™ Company (particularly Martin Beliveau and J.F. Marier) for help with the pharmacokinetic analyses, iC42 Integrated Solutions for plasma concentration analyses, MedTox Laboratories for CSF concentration analyses, Brian Kenney and John Arthur from Cadence Pharmaceuticals for clinical and analytical support, and Donna Simcoe from Cadence Pharmaceuticals for medical writing assistance.

FUNDING: Cadence Pharmaceuticals, Inc.