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Comparative Plasma and Cerebrospinal Fluid Pharmacokinetics of Paracetamol After Intravenous and Oral Administration

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BACKGROUND: We compared plasma and cerebrospinal fluid (CSF) pharmacokinetics of paracetamol after intravenous (IV) and oral administration to determine dosing regimens that optimize CSF concentrations.
METHODS: Twenty-one adult patients were assigned randomly to 1 g IV, 1 g oral or 1.5 g oral paracetamol. An IV cannula and lumbar intrathecal catheter were used to sample venous blood and CSF, respectively, over 6 hours. The plasma and CSF maximum concentrations (C_{max}), times to maximum concentrations (T_{max}), and area under the plasma and CSF concentration-time curves (AUCs) were calculated using noncompartmental techniques. Significance was defined by $P < .0167$ (Bonferroni correction for 3 comparisons for each parameter). Probability (X < Y) (p'') with Bonferroni corrected 95% confidence intervals (CIs) were calculated (CIs including 0.5 meet the null hypothesis). Results are presented as median (range) or p'' (CI). *P* values are listed as 1 g IV vs 1 g orally, 1 g IV vs 1.5 g orally and 1 g orally vs 1.5 g orally, respectively.
RESULTS: Wide variation in measured paracetamol concentrations was observed, especially in the oral groups. The median plasma C_{max} in the 1 g IV group was significantly greater than the oral groups. In contrast, the median CSF C_{max} was not different between groups. The median plasma T_{max} in the 1 g IV group was 105 and 75 minutes earlier than in the 1 and 1.5 g oral groups. The median CSF T_{max} was not significantly different between groups. The median plasma AUC (total) was not significantly different between groups; however, in the first hour, the median plasma AUC was significantly greater in the IV group than in the oral groups. In the second hour, there was no difference between groups. The median CSF AUC (total) did not significantly differ between groups; however, in the first hour, the median CSF AUC was significantly greater in the IV compared with the orally groups. In the second hour, there was no difference between groups. Our analysis indicated that the median C_{max}, T_{max}, and AUC values lacked precision because of small sample sizes.
CONCLUSIONS: Peak plasma concentrations were greater and reached earlier after IV than oral dosing. Evidence for differences in CSF C_{max} and T_{max} was lacking because of the small size of this study. (Anesth Analg 2016;123:610–15)

Paracetamol frequently is administered intravenously (IV) in the perioperative period. Plasma sampling suggests a more rapid concentration peak with IV than oral paracetamol dosing.[1–3] It is likely, however, that the analgesic effect of paracetamol is mediated centrally[4–8] with little peripheral effect,[9] as the analgesic effect more closely mirrors the cerebrospinal fluid (CSF) concentration than plasma concentration of the drug.[10,11] Four previous studies have sampled plasma and CSF concurrently after paracetamol administration by a single route[5,12–14]: 3 of these studies were in children[12–14] and 1 pediatric study employed repeated sampling.[14] Only Singla et al[15] have compared paracetamol pharmacokinetics after multiple routes of administration using repeated simultaneous plasma and CSF sampling. This study was conducted in 6 adult volunteers who received paracetamol 1 g IV, 1 g orally, and 1.3 g per rectum. In summary, these studies found that CSF paracetamol concentrations peaked later than plasma concentrations and were greater after IV administration than other routes.

To date, no study has compared CSF concentrations of 1 g IV paracetamol with oral doses greater than 1 g. Greater oral doses might obviate the need for IV administration if CSF pharmacokinetics are similar. Therefore, we conducted a randomized clinical trial to compare pharmacokinetics in plasma and CSF after 1 g IV, 1 g oral, and 1.5 g oral paracetamol in adult patients presenting for surgery under spinal anesthesia. We hypothesized that 1 g IV paracetamol

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would result in an earlier and greater peak in CSF concentration than 1 or 1.5 g oral paracetamol.

METHODS

Study Design

This was a parallel-group randomized clinical trial that was conducted in the Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia, between February 2008 and March 2009. The trial was approved by the Human Research Ethics Committee of the Royal Melbourne Hospital (approval number: 2007.233). The trial was registered retrospectively (approval number: ACTRN12615000322538).

Participants and Randomization

Patients aged ≥18 years presenting for elective surgery under spinal anesthesia were approached, and written informed consent was obtained. Patients were excluded if they had inadequate English comprehension, a contraindication to paracetamol, or administration of paracetamol within the previous 12 hours. Patients were assigned randomly by the use of a computer-generated code to 1 of 3 treatment groups: 1 g oral paracetamol, 1.5 g oral paracetamol, or 1 g IV paracetamol. Randomization results were concealed until after consent was obtained. Demographic data including patient age, sex, weight, height, and American Society of Anesthesiologists' physical status were collected at randomization.

Dosing and Anesthesia

For all patients, 2 peripheral IV cannulae (1 for blood sampling and 1 for drug and fluid administration) and a 23-gauge lumbar intrathecal catheter were inserted preoperatively. Patients were then administered their allocated study medication: 1 g oral paracetamol (2 × 500 mg Panamax tablets), 1.5 g oral paracetamol (3 × 500 mg Panamax tablets), or 1 g IV paracetamol (Perfalgan) infused over 10 minutes, starting at time 0. Spinal anesthesia was induced within 30 minutes of paracetamol administration using a standard technique; between 2 and 3.5 mL of 0.5% bupivacaine (hyperbaric or isobaric, with or without 15 μg fentanyl according to the anesthesiologist's preference) was administered through the intrathecal catheter. Patients were either awake or received midazolam (1–3 mg IV) for conscious sedation. No systemic opioid drugs were allowed during the perioperative period.

Plasma and CSF Sampling

Simultaneous plasma and CSF samples were scheduled to be drawn at 0, 15, 30, 45, 60, 90, 120, 180, 240, and 360 minutes after paracetamol administration (thus 10 plasma and 10 CSF samples per patient). Plasma was sampled from the dedicated peripheral IV cannula: 2 mL of blood was discarded, followed by extraction of a 5-mL sample. CSF sampling was performed under full aseptic conditions, with the first 0.3 mL of CSF discarded (catheter dead space <0.15 mL), followed by extraction of a 0.5-mL sample. All samples were stored below −5°C for analysis after all patients had been recruited. After completion of sampling, the intrathecal catheter was removed, and usual postoperative care was continued. Insertion and removal of catheters and all sampling were performed according to a preestablished protocol.

Analytical Methods

The scientist assaying samples was blind to the randomization. Paracetamol concentrations were assessed with a high-performance liquid chromatography method with ultraviolet absorption after liquid–liquid extraction using ether as previously described.[16] Estimations used quality control based on previously published trials from our laboratory.[17] The lower limit of quantification for paracetamol in both plasma and CSF was 0.02 mg/L. The % coefficients of variation—interrun and intrarun—were 3.8% and 4.5%, respectively, at 2 mg/L. Recovery after storage at −18°C for 3 months was mean 101.1% (standard deviation, 4.4%) at 2 mg/L.

Sample Size

The sample size for this trial was based on the primary endpoint of the maximum paracetamol concentration (C_{max}) in CSF after IV or oral administration. Using information published previously,[1,18] we determined a priori that a sample size of 7 patients per group would be sufficient to detect a 2.8-fold difference in CSF C_{max} between the IV and oral treatment groups (ie, 8.2 vs 2.5 mg/L; standard deviation = 3.3 mg/L) with 80% power and a type I error rate of 5%.

Statistical Analysis

Noncompartmental pharmacokinetic analysis techniques were used to address the study objectives. The C_{max} and time to C_{max} (T_{max}) in plasma and CSF were identified in each patient. The area under the plasma and CSF concentration-time curves (AUC) was calculated for each patient between 0 and 360 minutes (total time course, 0 and 60 minutes and 60 and 120 minutes) using the trapezoidal rule. The time at which the CSF concentration crossed the threshold of ≥3 mg/L was identified for each patient. This threshold was based on an a priori prediction that the C_{max} in CSF after 1 g of oral paracetamol would be approximately 2.9 mg/L.[1,18] Because of the small number of patients, the Mann-Whitney *U* test with exact *P* values was used to compare the derived parameters in plasma and CSF across the 3 dose groups, with Bonferroni correction for 3 pairwise comparisons for each parameter reducing the *P* value for significance to .0167. Probabilities (X < Y) (p'') with Bonferroni-adjusted confidence intervals (CIs; ie, 100 × [(1 − 0.05)/3] = 98.3%) were calculated using methods described by Divine et al.[19,20] The quantities X and Y are random observations from the 2 groups being compared. If there is no difference between the 2 groups, then p'' will equal 0.5. A statistically significant difference will be a value where the 95% CIs do not include 0.5. We have assigned as X the group with the larger rank sum in each case. Upper CIs >1.00 were coded as 1.00. Analyses were performed with Stata 14.0 (Stata Corporation, College Station, TX).

RESULTS

Recruitment and Patient Characteristics

Fifty patients were approached. Twenty-seven patients declined participation, and 23 patients consented and were assigned randomly. Of these, 2 patients who were assignedrandomly

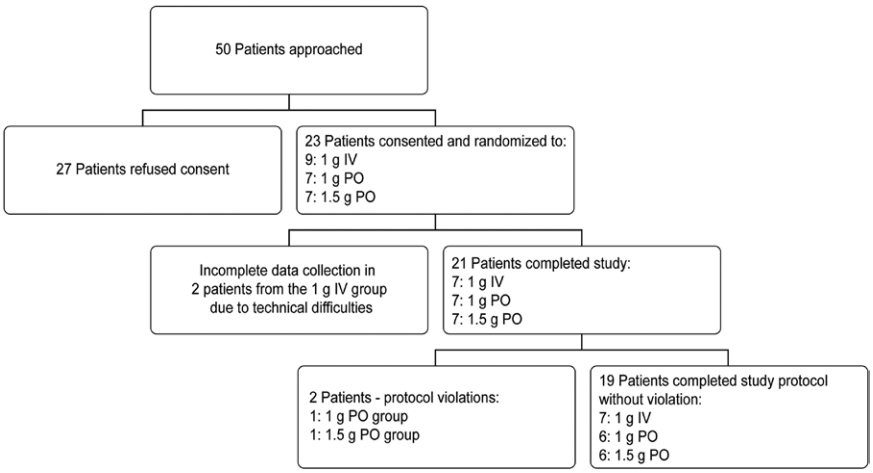

Figure 1. Recruitment flowchart. IV, intravenous; PO, orally.

Table 1. Demographic Data

	1 g Intravenous Paracetamol	1 g Oral Paracetamol	1.5 g Oral Paracetamol
Number	7	7	7
Sex (male:female)	7:0	5:2	5:2
Age (y)	71 (9)	72 (7)	68 (9)
ASA physical status (1:2:3)	0:4:3	0:2:5	1:1:5
Weight (kg)	77 (17)	69.5 (14)	98 (23)
Height (m)	1.73 (0.8)	1.69 (1.2)	172 (1.2)

Data are presented as mean (standard deviation) or counts.
Abbreviation: ASA, American Society of Anesthesiologists.

to the 1-g oral group did not complete the study because of substantial difficulty with CSF sampling, and their data were excluded for analysis. The remaining 21 patients were equally divided among the 3 groups (Figure 1). Six of the 210 required plasma samples and 19 of the 210 required CSF samples could not be obtained because of sampling difficulties.

No adverse events were noted throughout the study period or at 24 hours after intrathecal catheter removal. There were 2 protocol violations: A patient in the 1 g oral group volunteered to the team retrospectively that he or she had taken 1 g oral paracetamol within 12 hours of the start of the study, and, furthermore, this patient was administered 1 mg of IV alfentanil an hour after the study commenced. The other patient, who was in the 1.5 g oral group, required conversion to general anesthesia during the study period because of block failure. Data from these 2 patients were retained in the analysis.

Patient demographics were similar across the 3 groups (Table 1). Patients underwent urological (12), orthopedic (7), and general surgical (2) procedures. Three patients received intrathecal fentanyl (all in the 1.5 g oral group).

Pharmacokinetic Analysis

Wide variation in measured paracetamol concentrations was observed, especially in the oral groups (Figure 2). The median plasma C_{max} in the 1 g IV group was significantly greater than the median plasma C_{max} in the 1.5 g oral group but not the 1 g oral group. The median CSF C_{max} was not significantly different across the 3 groups (Table 2).

The median plasma T_{max} in the 1 g IV group was significantly greater than in the 1 g and 1.5 g oral groups. The median CSF T_{max} was not significantly different across the 3 groups (Table 2).

The median plasma AUC (total) was not significantly different across the 3 groups. The median plasma AUC up to the first hour in the 1 g IV group was significantly greater than in the 1 g and 1.5 g oral groups. The median plasma AUC in the second hour was not significantly different across the 3 groups (Table 2).

The median CSF AUC (total) was not significantly different across the 3 groups. The median CSF AUC up to the first hour in the 1 g IV group was significantly greater than in the 1 g oral group. The median CSF AUC in the second hour was not significantly different across the 3 groups (Table 2).

The median time to a CSF concentration of ≥3 mg/L was not significantly different across the 3 groups (Table 2). The p'' values indicated that the median C_{max}, T_{max}, and AUC values lacked precision because of small sample sizes

DISCUSSION

In this study, we collected repeated simultaneous plasma and CSF samples after oral and IV dosing of paracetamol in adult surgical patients. There was evidence that peak plasma concentrations were greater and were achieved more rapidly after IV than oral administration. These results do not provide sufficient evidence that greater oral doses obviate the need for IV administration but do provide motivation for larger integrated pharmacokinetic/pharmacodynamics studies to investigate 1 g IV paracetamol and >1 g oral paracetamol.

Our results are consistent with the previous studies reporting greater peak plasma concentrations after IV

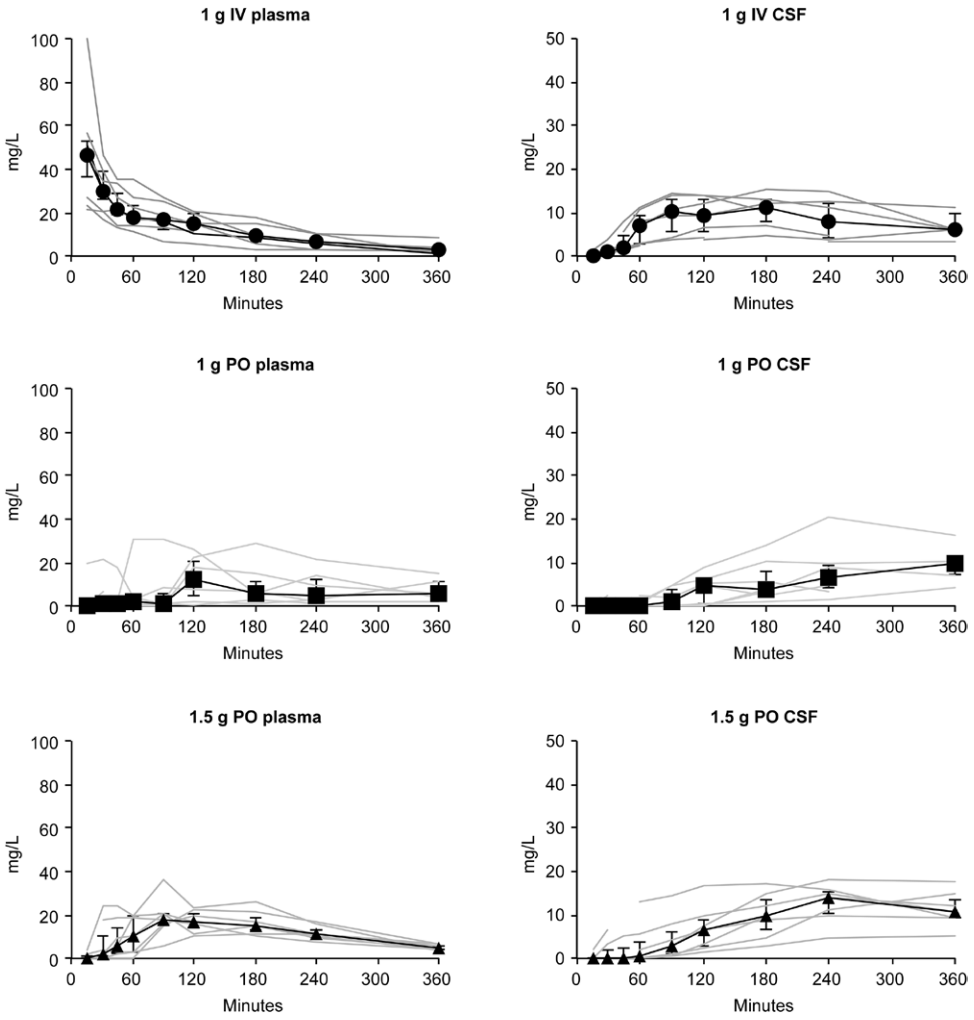

Figure 2. Plasma and cerebrospinal fluid (CSF) paracetamol concentrations over time for each group. Group data (bold line and error bars) are presented as median and interquartile range. Individual patient concentration profiles (gray lines) are measured values. 1 g IV, 1 g intravenous paracetamol; 1 g PO, 1 g oral paracetamol; 1.5 g PO, 1.5 g oral paracetamol.

administration compared with oral administration and after greater oral paracetamol doses.[1] Variation in plasma concentrations after oral dosing has also been reported previously.[1] Paracetamol is absorbed primarily from the small intestine and so is dependent on the rate of gastric emptying. In the perioperative period, gastric emptying can be affected by the type and quantity of food and drink, posture, anxiety, pain, and opioid administration.[21] This variation in absorption likely not only affected our study but also affects patients taking oral paracetamol in the perioperative period.

Our results also are consistent with noncompartmental pharmacokinetic comparisons of plasma and CSF paracetamol concentrations in adults who reported peak CSF concentrations that occurred substantially later than peak plasma concentrations. Bannwarth et al[5] sampled plasma and CSF in 43 adults after 2 g of IV propacetamol. CSF paracetamol concentration peaked at 4 hours (compared with the first hour for plasma), and CSF concentrations exceeded plasma concentrations over the ensuing 8 hours. Singla et al[15] sampled plasma and CSF in 6 volunteers after 1 g oral or 1 g IV paracetamol. Times to peak plasma and CSF concentrations were similar to our results although the measured peak plasma concentrations that they reported were lower after both IV and oral dosing (5.94 and 3.72 mg/L, respectively). Our results are not consistent with those reported in children. Kumpulainen et al[13] took single CSF samples from 32 children after 15 mg/kg IV paracetamol and reported mean peak CSF concentrations of 18 mg/L at 1 hour, suggesting rapid CSF penetration.

We chose to study a 1.5-g oral dose to determine whether its pharmacokinetic profile was similar to the 1 g IV group. This is a novel aspect of our work. We found that 1.5 g oral paracetamol was not equivalent to 1 g IV paracetamol in terms of peak plasma concentration nor time to peak plasma concentration. Previous studies using a 2-g oral dose found no toxic plasma concentrations,[1,22] and hence, this dose could be considered for future studies.

Strengths and Limitations

Our study is the first to sample plasma and CSF simultaneously over an extended period in adult surgical patients after IV and oral doses of paracetamol ≥1 g. Our analyses

Table 2. Pharmacokinetic Data for Each Paracetamol Group

	1 g IV	1 g PO	1.5 g PO	*P* Value (Exact)* *p″* (95% CI)[a] 1 g IV vs 1 g PO	1 g IV vs 1.5 g PO	1 g PO vs 1.5 g PO
Plasma						
C_{max} (mg/L)	46.1 (21.7–99.7)	18.0 (2.8–30.8)	20.8 (11.6–36.0)	.0175 .88 (0.49–1.00)	.0070* .92 (0.54–1.00)	.4557 .63 (0.25–1.00)
T_{max} (min)	15 (15–15)	120 (30–360)	90 (45–240)	.0006* 1.00 (0.67–1.00)	.0006* 1.00 (0.72–1.00)	.6066 .59 (0.22–0.96)
AUC (total) (mg min/L)	3924 (2937–7323)	2659 (527–5616)	3878 (2823–6582)	.0973 .78 (0.39–1.00)	1.0 .51 (0.13–0.89)	.1649 .73 (0.35–1.00)
AUC (first hour) (mg min/L)	1688 (880–2992)	87 (0–907)	253 (3–928)	.0012* .98 (0.60–1.00)	.0012* .98 (0.60–1.00)	.3829 .65 (0.27–1.00)
AUC (second hour) (mg min/L)	973 (437–1647)	283 (53–1775)	954 (353–1731)	.0262 .86 (0.47–1.00)	.9015 .53 (0.15–0.91)	.0530 .82 (0.43–1.00)
CSF						
C_{max} (mg/L)	12.6 (4.2–15.5)	8.8 (4.1–20.2)	14.8 (5.2–18.1)	.4557 .63 (0.25–1.00)	.2593 .69 (0.31–1.00)	.1649 .73 (0.35–1.00)
T_{max} (min)	180 (90–360)	240 (120–360)	240 (180–360)	.1241 .76 (0.39–1.00)	.0417 .80 (0.44–1.00)	1.0 .56 (0.18–0.94)
AUC (total) (mg min/L)	3488 (1083–3724)	1417 (474–4205)	2715 (962–4761)	.3829 .65 (0.27–1.00)	.7104 .57 (0.19–0.95)	.1649 .50 (0.13–0.87)
AUC (first hour) (mg min/L)	110 (45–275)	11 (0–52)	7 (0–371)	.0012* .98 (0.60–1.00)	.1265 .76 (0.37–1.00)	.7290 .73 (0.35–1.00)
AUC (second hour) (mg min/L)	547 (183–806)	175 (0–321)	203 (33–872)	.0379 .84 (0.45–1.00)	.1649 .73 (0.25–1.00)	.3829 .65 (0.27–1.00)
Time to ≥3 mg/L (min)	56 (25–65)	97 (60–305)	90 (17.5–187.5)	.0242 .93 (0.48–1.00)	.4767 .75 (0.30–1.00)	.2121 .62 (0.24–1.00)

Data are presented as median (range). p'' = Probability (X < Y).[19,20]

Abbreviations: AUC, area under the plasma and CSF concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; CSF, cerebrospinal fluid; T_{max}, time to C_{max}; 1 g IV, 1 g intravenous paracetamol; 1 g PO, 1 g oral paracetamol; 1.5 g PO, 1.5 g oral paracetamol.

[a]CIs are Bonferroni corrected (ie, 100 × [(1 − 0.05)/3] = 98.3%) and 95% CIs including 0.5 meet the null hypothesis. Upper CIs >1.00 were coded as 1.00.

*Significant at $P < .0167$ (Bonferroni correction for 3 comparisons for each parameter).

were limited by the small number of patients in each group and large variability across the observed individual pharmacokinetic profiles, especially in the oral groups. This was reflected in the wide CIs for p'' values. We also presented the results of noncompartmental pharmacokinetic modeling only. Robust population pharmacokinetic modeling would require a larger sample size, samples taken over a longer time, and more covariates describing each patient. We did not measure pain scores or analgesic responses during our study because of the focus on pharmacokinetics, the diverse nature of surgeries performed, and the varied duration of spinal anesthesia, and so cannot integrate the time course of analgesic action with plasma and CSF concentrations of paracetamol.

In conclusion, peak plasma concentrations were greater and reached earlier after IV than oral dosing of paracetamol in adult surgical patients. Our results provide motivation for future studies to investigate the utility of 1 g IV paracetamol versus oral doses >1 g in terms of rapidly achieving CSF concentrations associated with analgesia.

DISCLOSURES

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