Serum paracetamol concentrations in adult volunteers following rectal administration

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Paracetamol is usually given in adults at a dose of 10–20 mg kg\textsuperscript{-1} orally or rectally. Work in children suggests that doses of 40 mg kg\textsuperscript{-1} are needed to provide therapeutic concentrations when this drug is used by the rectal route. We have investigated the dose of rectal paracetamol needed to achieve serum concentrations within the accepted therapeutic range of 10–20 µg ml\textsuperscript{-1} in adults. Ten healthy adult volunteers received increasing doses of rectal paracetamol (15, 25, 35, and 45 mg kg\textsuperscript{-1}). Following suppository administration, serum paracetamol concentrations were measured half hourly to 4 h then hourly to 8 h. Sustained concentrations within our therapeutic range were achieved with 35 and 45 mg kg\textsuperscript{-1}. Maximum measured concentrations were 12.5 (10–16), 16.5 (14–20), and 20 (17.5–23) µg ml\textsuperscript{-1}, median (inter-quartile range) after 25, 35, and 45 mg kg\textsuperscript{-1}, respectively. We conclude that doses of 35–45 mg kg\textsuperscript{-1} of rectal paracetamol are needed to achieve sustained therapeutic plasma concentrations in healthy adult volunteers.

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Oral paracetamol doses of 10–20 mg kg\textsuperscript{-1} are used in adults and children and provide plasma concentrations within the accepted therapeutic range. However, when given rectally, these doses may be insufficient. Work in children has shown that doses of up to 40 mg kg\textsuperscript{-1} are needed to achieve these target plasma concentrations.\textsuperscript{2–4} Similar doses may be needed in adults.
The aim of our study was to ascertain what dose of rectal paracetamol is needed, in adult volunteers, to achieve plasma paracetamol concentrations of 10–20 μg ml⁻¹.

**Methods and results**

Following ethics committee approval, 10 ASA I or II adult volunteers were recruited from our anaesthetic departmental colleagues. Exclusion criteria included body mass index greater than 35, pregnancy, regular usage of paracetamol containing medication, intolerance or allergy to paracetamol and abnormal renal or hepatic function. Urea and electrolytes and liver function tests were checked prior to enrolling a volunteer in the study.

Each volunteer took part in the study on four occasions separated by at least 48 h. No paracetamol containing medication was taken for 24 h prior to any of the study days. Volunteers received increasing doses of rectal paracetamol starting with 15 mg kg⁻¹, rising by 10 mg kg⁻¹ to a maximum of 45 mg kg⁻¹.

Paracetamol is not evenly distributed within standard suppositories. Hence, it was not possible to provide exact paracetamol doses by shaving portions off these suppositories. Each volunteer was weighed and suppositories were specifically manufactured to achieve exact doses. Witepsol was used as the base for these suppositories. Multiple numbers of suppositories were used to avoid any single suppository being used as the base for these suppositories. Multiple suppositories are used in order to achieve the most appropriate patient dose. This is important, as it is known that rectal absorption of paracetamol varies with suppository size.

On each day of the study, an i.v. cannula was inserted and a baseline blood sample taken. The suppository was then self administered and serial blood samples taken every 30 min for 4 h and then hourly for a further 4 h. Samples were refrigerated and dispatched to the laboratory as a batch at the end of each day. If any plasma paracetamol concentration had been recorded as greater than 30 μg ml⁻¹ that volunteer would not have received further doses.

The assay used to measure plasma paracetamol concentrations was a Cambridge Life Sciences enzymatic assay using a Roche Hitachi multichannel analyser (inter-assay CV 1.1–1.4%, concentration range 0–300 μg ml⁻¹, intra-assay CV 0.5–1%, concentration range 0–130 μg ml⁻¹, dynamic range of the assay 0–378 g ml⁻¹, sample size per assay is 20). The lower limit of detection in our laboratory was 10 μg ml⁻¹.

Concentration vs time curves were plotted for all 10 volunteers for each dose of paracetamol received. The median values for each time period at each dose are shown in Figure 1.

Values are not shown for doses of 15 mg kg⁻¹ as this failed to achieve median concentrations greater than 10 μg ml⁻¹ at any time period and 25 mg kg⁻¹ produced concentrations at the lower end of the therapeutic range for a brief period. However, 35 and 45 mg kg⁻¹ achieved sustained concentrations within our assumed therapeutic range. These doses resulted in plasma concentrations above 10 μg ml⁻¹ for median time periods of 5.5 h (35 mg kg⁻¹) and 6 h (45 mg kg⁻¹). The graphs also show that there is a 1 h time delay after rectal administration before therapeutic concentrations are recorded. Median (inter-quartile range) maximum measured concentrations (Cmax) and time to maximum concentration (Tmax) are shown in Table 1. The difference between Cmax at all three doses was found to be statistically significant (ANOVA). Based on previous work²–⁵ the sample size was determined to provide a difference in Cmax at the 5% significance level.

**Comment**

In common with previous work in this area, we have assumed analgesic and antipyretic plasma paracetamol concentrations to be similar.²–⁵ Our work has shown that in a population of healthy adult volunteers 15 mg kg⁻¹ of rectal paracetamol is probably inadequate. Doses of 35–45 mg kg⁻¹, administered 2 h prior to any desired effect, are needed to achieve sustained concentrations within the accepted therapeutic range of 10–20 μg ml⁻¹. This confirms recent work suggesting 40 mg kg⁻¹ of rectal paracetamol is needed to achieve therapeutic serum concentrations.⁵ However, this dose was not associated with improved analgesia, leading the authors to conclude that higher plasma concentrations may be needed to provide analgesia than those associated with antipyresis. This contrasts with earlier work showing that rectal doses of 20 mg kg⁻¹ of paracetamol do appear to have a clinical useful morphine

![Serum paracetamol concentrations following rectal administration](image-url)
sparing effect despite probably not providing concentrations within the accepted therapeutic range.\textsuperscript{6}

Concern that these higher doses of paracetamol may cause toxicity appears unfounded, the highest serum concentration we measured was 25 $\mu$g ml\textsuperscript{-1}, this is well below the accepted toxic concentration of 120 $\mu$g ml\textsuperscript{-1}.

The limitation of our assay (lower limit of detection 10 g ml\textsuperscript{-1}) has restricted our ability to perform pharmacokinetic analysis. However, the aim of the study was to ascertain what dose of paracetamol was needed to achieve plasma concentrations of 10–20 g ml\textsuperscript{-1} and our assay was adequate for the purpose of answering this question.

We conclude that doses of 35–45 mg kg\textsuperscript{-1} of paracetamol are needed in adult volunteers to achieve serum concentrations of 10–20 $\mu$g ml\textsuperscript{-1}. This is in agreement with data from paediatric studies. However, more work is needed to establish whether this is in fact the target serum plasma for analgesia.

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**References**