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Early bioavailability in day surgery: a comparison between orally, rectally, and intravenously administered paracetamol

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Abstract

Purpose: Compare early bioavailability of rectal, effervescent oral, and i.v. paracetamol.
Scope: Five groups of $N = 7$ patients received 1 or 2 g paracetamol orally or rectally or 1 g i.v. immediately after day surgery. Paracetamol concentrations taken after 20, 40 and 80 min. Median plasma paracetamol concentrations for 1 versus 2 g effervescents were 78 (25–114) versus 108 (95–146) μmol L^{-1} at 80 min and 16 (9–30) versus 17 (10–30) μmol L^{-1} for 1 versus 2 g suppositories. Paracetamol i.v. gave median 97 (77–135) μmol L^{-1} after 40 min.
Conclusion: Only intravenously and 2 g effervescent paracetamol gave therapeutic concentrations during the period studied.

Keywords: Day surgery; Postoperative analgesia; Paracetamol; Suppositories; Effervescent tablets

1. Introduction

Pain is still one of the most common complaints after day surgery [1]. Multi-modal pain management, the gold standard for ambulatory surgery, is based on a combination of local anaesthetics, orally administered paracetamol and non-steroid anti-inflammatory drugs (NSAID), When necessary weak opioids are added with the potent classical opioids reserved as rescue medication [2,3]. The optimal drug form, route of administration and dose for the non-opioid paracetamol has not been adequately determined in day surgery [4]. The optimal drug formulation has been discussed ever since Prescott wrote one of the first articles on paracetamol kinetics [5,6].

The primary aim of the present study was to investigate early bioavailability for two different fixed doses of rectal, oral effervescent and one fixed dose of the recently introduced intravenous paracetamol formulation, Perfalgan®. All drugs were given immediately after day surgery in general anaesthesia.

2. Materials and methods

Thirty-five ASA I–II day surgical patients participated in the study after ethical committee approval and written informed patient consent. The patients were divided into five groups, seven patients in each group. Patients were excluded if they had any liver disease or any contraindication for paracetamol. The patients, 20 women and 15 men, were scheduled for ordinary day surgery and had a median age of 49 (20–72) years and weight 74 (57–105) kg. They were randomly assigned using sealed envelopes to receive paracetamol as either 1 or 2 g suppositories or effervescent tablet or 1 g intravenous paracetamol (Perfalgan®; Bristol-Myer-Squibb AB; Stockholm, Sweden).

All patients were anaesthetised according to standard departmental routines. No premedication was given apart from cyclozine 50 mg orally. Anaesthesia was induced with propo-

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Table 1
Patient characteristics, age, weight and the amount of paracetamol administered (mg kg^{-1})

	1 g rectally	2 g rectally	1 g i.v.	1 g orally	2 g orally
Male/female	1/6	3/4	4/3	4/3	3/4
Age (years)	46 (20–54)	56 (36–68)	46 (25–61)	54 (29–72)	51 (32–64)
Weight (kg)	62 (59–86)	72 (65–90)	75 (57–90)	76 (66–105)	80 (62–104)
Paracetamol (mg kg^{-1})	16 (12–17)	28 (22–31)	13 (11–18)	13 (10–15)	25 (19–32)

All values shown as median (range).

fol and fentanyl (0.1 mg) followed by the placement of a laryngeal mask airway. Anaesthesia was maintained with oxygen in nitrous oxide (1:2), and sevoflurane was titrated to clinical needs. At the end of surgery anaesthetic gases were discontinued and replaced by oxygen 100% until patients regained consciousness.

Patients randomised to rectal paracetamol received the suppository just prior to removal of the laryngeal mask while the patients randomised to the oral or intravenous paracetamol received their medication just after entry in the recovery room. All patients were also given an NSAID orally (lornoxican) and were encouraged to drink and eat as soon as possible.

VAS-values were noted and documented at the same time as the blood samples were taken and rescue analgesia, dextropropoxyphene 100 mg, was given orally whenever VAS > 4. Side effects such as nausea and vomiting were also noted and treated accordingly (metoclopramide).

Blood samples (5 ml) for analysis of plasma paracetamol concentrations were taken prior to paracetamol administration (baseline) and at 20, 40 and 80 min after administration. Serum was separated by centrifugation and stored at −20 °C plasma paracetamol concentration determination using fluorescent polarisation immunoassay (AxSym from Abbott Scandinavia AB; Stockholm, Sweden). The assay dynamic range is 6.6–1320 μmol L^{-1}. The lower limit of detection is 6.6 μmol L^{-1} and the coefficient of variation is 6% at 100 μmol L^{-1}.

2.1. Statistics

Data are shown as median and range. For differences within groups Friedman ANOVA was used.

3. Results

Patient characteristics and the amount of paracetamol per kilogram given are shown in Table 1. Surgery and postoperative course was uneventful and all patients were discharged after fulfilling departmental routines criteria.

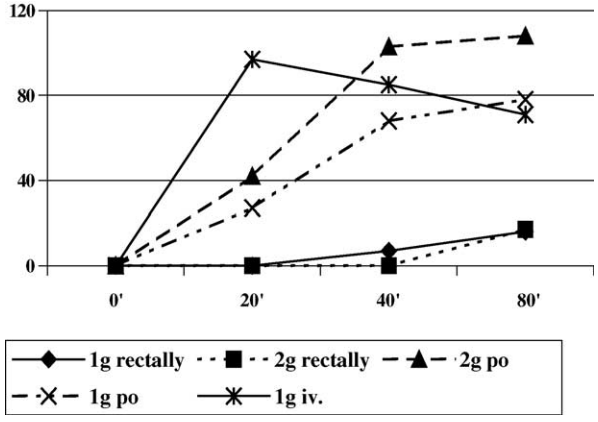

Fig. 1. Maximal plasma paracetamol concentration μmol L^{-1} (median) at any of the three time points (20, 40 and 80 min) after 1 and 2 g of rectally administered paracetamol, 1 g as intravenous paracetamol and 2 g of paracetamol administered orally as an effervescent tablet after minor surgery.

One and 2 g effervescent paracetamol plasma concentrations increased during the 80-min study period to a median value in the same range as intravenous paracetamol at 20 min. Rectally administered paracetamol plasma concentrations increased slowly with time but without any obvious dose effect. The overall plasma concentrations reached after rectal administration remained low during the entire study period. Plasma concentrations after intravenous paracetamol peaked within 40 min. The patients given i.v. or effervescent tablets had higher plasma concentrations at all time points compared to the patients receiving paracetamol rectally (Table 2, Fig. 1).

There were no differences in pain ratings. Six patients needed rescue analgesia, one each in the i.v., one and 2 g effervescent groups and three in the 2 g rectal group. One patient in each of the 1 and 2 g effervescent paracetamol groups as well as the rectal groups and three patients in the i.v. group

Table 2
Plasma concentrations of paracetamol (μmol L^{-1} median and range) when administered after ambulatory surgery as 1 g or 2 g rectally, 1 g intravenously (i.v.) or 2 g effervescent tablets (orally) and the number of patients who reached the therapeutic paracetamol concentration

	1 g rectally	2 g rectally	1 g i.v.	1 g orally	2 g orally
Baseline	0	0	0	0	0
20 min	0 (0–13)	0 (0–8)	97 (77–135)	27 (20–82)	42 (0–150)
40 min	7 (0–17)	0 (0–14)	85 (61–107)	68 (21–102)	103 (10–121)
80 min	16 (9–30)	17 (10–30)	71 (53–81)	78 (25–114)	108 (95–146)
No. of patients (>66 μmol L^{-1})	0	0	7	4	7

experienced a short period of nausea that responded to metoclopramide.

All patients given 2 g effervescent tablets and intravenous paracetamol and 4/7 patients given 1 g effervescent reached a plasma concentration >66 μmol L^{-1}. No patient given a suppository showed a plasma concentration greater than 66 μmol L^{-1} at any time point studied (Table 2). Doubling the suppository dose did not significantly improve measured concentrations.

4. Discussion

The main finding of the present study was a pronounced difference in early plasma concentrations for the different routes of postoperatively administered paracetamol. The newly introduced i.v. paracetamol gave rise to a fast and predictable plasma concentration similar to that seen with a 2 g effervescent dose after 80 min. Rectally administered paracetamol did not create seemingly adequate concentrations and a doubling of suppository dose gave no significant improvement.

The therapeutic antipyretic plasma concentration for paracetamol is considered to be 66–132 μmol L^{-1} or 10–20 mg L^{-1} [4]. The minimum plasma concentration for paracetamol's analgesic effect is not well described, but it is not likely to be lower than the concentration for the antipyretic effect [7,8]. Both lower and higher concentrations have been suggested for paracetamol's analgesic effect [9–11].

Patients receiving intravenous paracetamol showed sufficient (i.e. what is considered therapeutic) plasma concentrations after only 20 min in all seven patients studied. It is not possible from the present study to state whether the peak concentration after i.v. administration was reached even earlier.

The orally treated group was given paracetamol as an effervescent formulation as they are known to be absorbed significantly faster than ordinary commercial paracetamol tablets [12,13]. We found that the effervescent formulation had a quite rapid onset and the majority of patients reached "therapeutic" plasma levels in all patients within 80 min. This favourable bioavailability for the effervescent formula has also been shown by others [14,15]. It is, however, of importance to notice that three out of seven patients did not reach the desired plasma concentration within 80 min among the 1 g group.

Orally administered analgesics may not always be an option in post-surgical patients, especially not after more extensive surgery and or in patients at risk for PONV. The rectal route for administration in adults is slower and more erratic than the oral route and the usefulness of rectally administered paracetamol has been discussed for several years [4,6,16]. The rectal route is, however, still frequently used in many institutions as it is considered safer than early oral administration in the perioperative period [4,10]. The subtherapeutic concentrations achieved here with the 1-g rectal dose are in good agreement with a recent study by Kvalsvik et al. [17]. Higher rectal doses have been suggested based on kinetic simulations [11]. Doubling the rectally administered paracetamol dose did not increase the maximal plasma paracetamol concentrations at any time point studied. Overall plasma concentrations following rectal administration were low and never approached those considered therapeutic during the 80 min studied, a finding similar to that found by others [9,18].

It is important to consider the limitations of the present study. Registered nurses familiar with the use of the rectal route gave all suppositories. Nevertheless a full guarantee for optimal placement cannot be given. We did not intend to perform a full classical pharmacokinetic study of paracetamol uptake but merely to study the early plasma concentrations following postoperative administration in the clinical setting. We are therefore not able to say anything about peak plasma concentrations following rectally administered paracetamol, only those within the early postoperative period. Both Hahn and Stocker followed paracetamol plasma concentrations for up to 4 h after rectal administration without being able to detect therapeutic plasma concentrations from doses lower than 35 mg kg^{-1} [9,18]. We consider it important to reach a therapeutic concentration within about an hour if the clinical strategy is to have pharmacological impact during the early phase of postoperative pain management. Rectal administration of paracetamol is not an optimal route.

None of our patients had eaten within at least 6 h prior to anaesthesia and had had nothing to drink for at least 2 h prior to anaesthetic induction. No patient received muscle relaxants and all remained normothermic. Patients were encouraged to drink within 30 min after surgery and to eat a sandwich when adequately awake. Intake of food has been shown to potentially delay absorption of oral paracetamol [12], but all patients receiving the oral effervescent paracetamol reached levels above 66 μmol L^{-1} in less than 80 min.

We studied a relatively small number of patients, but the groups' results in terms of plasma concentrations differed distinctly with potentially significant clinical relevance. The number of patients studied in combination with the fact that different surgical procedures were included precludes making any concentration–effect relations.

When given postoperatively, maximal plasma paracetamol concentrations were achieved within 40 min after intravenous administration, and similar concentrations were reached within 80 min after a 2 g effervescent paracetamol while 1 g still may not guarantee adequate plasma concentrations within 80 min. Paracetamol plasma concentrations achieved after rectal paracetamol administration were low and did not improve significantly by doubling the dose. The current comparison clearly demonstrates that the intravenous route is superior by far in terms of speed and predictability followed by the effervescent formulation and that these two formulations are a far better choice with respect to the plasma concentrations than the rectal route regardless of dose. Paracetamol suppositories appear to be a poor choice for early postoperative pain treatment in day surgery.

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