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The influence of morphine on the absorption of paracetamol from various formulations in subjects in the supine position, as assessed by TDx measurement of salivary paracetamol concentrations

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Abstract

The aim of this study was to determine the influence of the type of paracetamol formulation on the rate of absorption when subjects are in the supine position, with or without taking concomitant morphine. Two groups of healthy volunteers were used, who were in the fasting state and remained in the supine position during the study. One group took 1500 mg of paracetamol on three occasions as conventional tablets, dispersible tablets or a suspension in a randomized crossover design. Seventeen saliva samples per subject were obtained (time zero to 360 min post-dose), which were then centrifuged and kept at −20 °C prior to analysis. The second group repeated the study following four doses of morphine syrup (10 mg 4 hourly) in the 12 h preceding paracetamol ingestion. In this phase of the study, paracetamol absorption from suspension was not investigated. A TDx assay was used to determine salivary paracetamol concentrations. The t_{max} for conventional tablets when taken concomitantly with morphine was 160 (±81) min compared to 51 (±58) min for subjects not taking morphine. For dispersible tablets the t_{max} in the morphine group was 14 (±9) min compared to 15 (±12) min without morphine. The results suggest that patients who are confined to bed and taking morphine will have an unacceptably long delay between taking conventional paracetamol tablets and the paracetamol reaching therapeutic plasma concentrations. Conversely, there is little effect on the absorption of dispersible paracetamol under the same conditions.

Introduction

Paracetamol is routinely used post-operatively as an adjunct to opioid therapy. However, it is well known that opioid analgesics delay gastric emptying and thus delay the absorption of paracetamol from the small intestine (Nimmo et al 1975; Murphy et al 1997). Posture has also been shown to influence the absorption of a number of drugs, including paracetamol (Nimmo & Prescott 1978; Channer et al 1984; Warren et al 1985). Thus, in the hospital setting where patients may be confined to bed in the supine position and taking opioids along with other drugs, including paracetamol, significant delays in absorption may be expected. However, using a basic knowledge of formulation and pharmacokinetics, these influences may be reduced, and therefore the onset of action of paracetamol enhanced, if dispersible tablets are taken rather than conventional tablets or even suspension. Despite this, at the time of writing, Panadol tablets and Paracare suspension are the only oral paracetamol preparations that are widely used within the New Zealand Health System as these products have lower acquisition costs compared to their competitors and enjoy sole supply status under the Pharmaceutical Management Agency Ltd (Pharmac). No funding whatsoever is available for dispersible paracetamol tablets, thus patient therapy is determined by acquisition costs, regardless of any pharmacokinetic or patient considerations.

In order to assess the potential impact of the choice of formulation on patient therapy, the study presented here was conducted to characterize how the formulation of paracetamol influences its absorption in volunteers who are in the supine position, and the effect of morphine on this. Paracetamol absorption was characterized through

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the use of salivary paracetamol concentrations, which were determined using a fluorescence polarization immunoassay (TDx).

Materials and Methods

Subjects and study design

Ethics approval was obtained from the Otago Ethics Committee and written informed consent was collected prior to the study. Volunteers were excluded based on the following criteria: hypersensitivity to paracetamol, liver disease, pregnancy, breast-feeding, or HIV or hepatitis A, B or C positive. Two groups of healthy volunteers participated in one of two studies investigating the absorption of paracetamol from different formulations when in the supine position: (i) without morphine, (ii) with morphine, as detailed below. Participants were required to be over 18 years of age and of medium height and build. Participants were instructed to avoid all non-essential medications, including caffeine, alcohol and herbal/recreational drugs, for 24 h prior to the study and were required to fast for 8 h prior to the study. The studies were conducted in the Day Surgery Unit of Dunedin Hospital with a washout period of at least one week.

Paracetamol absorption studies

Without morphine protocol

In this study, 12 volunteers (20–24 years) took a different paracetamol formulation on each of three occasions in a randomized crossover design.

The paracetamol formulations investigated were:

conventional tablets: 3×500 mg paracetamol caplets (Panadol, SmithKline Beecham) taken with 200 mL of water

suspension: 30 mL of 50 mg mL^{-1} suspension (Paracare, PSM Healthcare Ltd) followed by 170 mL of water, aliquots of which were used to rinse the vessels and swallowed

dispersible tablets: 3×500 mg dispersible tablets (Panadol, SmithKline Beecham) dissolved in 100 mL of water and swallowed. The vessels were then washed with aliquots from a further 100 mL of water, which was also swallowed.

Prior to the collection of saliva samples, the subjects rinsed their mouths out with water, then stimulated saliva production by chewing on a piece of Parafilm (2 cm^2) for 60 s. The samples were spat into plastic bottles and approximately 2 mL was then transferred to microtubes. These were then centrifuged at 5000 *g* for 5 min using a bench centrifuge (Biofuge 15 Heraeus Sepatech) and frozen at $-20\,^{\circ}C$ prior to analysis. Time zero saliva samples (collected as described above) were obtained from all subjects before taking the paracetamol. All subjects lay in the supine position immediately after taking their paracetamol dose. A total of 17 samples were collected at times 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 210, 240, 300 and 360 min.

With morphine protocol

The protocol above was repeated in a different group of volunteers (n = 17, 21–26 years), who received four doses of 10 mg morphine syrup (RA-Morph, 2 mg mL^{-1}) at times 0, 4, 8 and 12 h prior to the ingestion of paracetamol. In this part of the study the effects of morphine on the absorption of paracetamol from suspension were not investigated, and there were some slight differences in sampling times (t = 0, 10, 20, 30, 40, 50, 60, 80, 100, 120, 160, 200, 240 and 300 min).

Analysis of paracetamol in saliva

Paracetamol has been found to pass freely from blood to saliva, producing a good correlation between salivary and serum concentrations (Adithan & Thangam 1982; Kamali et al 1987; Hahn et al 2000). Paracetamol saliva concentrations are usually measured using high pressure liquid chromatography (Kamali et al 1987; Hahn et al 2000). However, serum paracetamol concentrations can be rapidly and accurately determined through the use of the Abbott TDx assay (Edinboro et al 1991), although there is no evidence in the literature (or available from Abbott), to confirm that paracetamol concentrations in saliva can be measured using TDx.

For this reason, the studies described below were conducted to ensure that the TDx assay was suitable for the analysis of salivary paracetamol.

In-vitro spiked saliva vs serum calibrator correlation

In-house saliva standards were prepared and compared to manufacturer's serum calibration standards in order to determine the validity of measuring paracetamol concentrations in saliva. Various concentrations (0, 20, 40, 60, 80 and 100 $\mu g\,mL^{-1}$) of spiked saliva were compared to the equivalent plasma calibration standards (Figure 1). There was a close correlation ($r^2 = 0.996$), and so the following in-vivo study was conducted to confirm that there was a correlation between in-vivo plasma and saliva concentrations, following ingestion of paracetamol, when the samples were analysed using the TDx system.

In-vivo plasma-saliva correlation

Following collection of simultaneous blood and saliva samples at time = 0, a group of volunteers (n = 13, 21–49 years) swallowed three 500 mg conventional paracetamol caplets (Panadol, SmithKline Beecham) with 200 mL of water, and then assumed the supine position. Further blood and saliva samples were collected simultaneously at times 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 210, 240, 300 and 360 min. Blood samples were collected from an indwelling catheter and extension line (BD peripheral IV 20G catheter with injection valve, Baxter 15 cm catheter extension set of 1.0 mL volume, Medex one-way stopcock, locking luer male adapter plug short). These samples (3–4 mL) were collected in a heparinized saline vacutainer and centrifuged using an Eppendorf Centrifuge 5810R at 4000 *g* for 5 min. Plasma was then removed and transferred to a 2 mL microtube (Eppendorf safe lock)

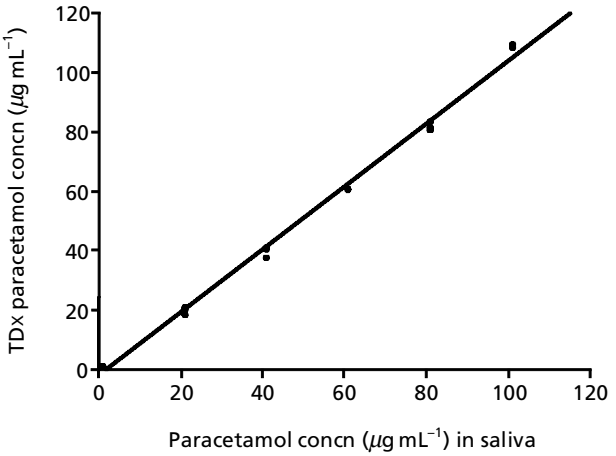

Figure 1 Calibration curve of spiked saliva versus supplied TDx standards (for plasma) ($r^2 = 0.996$).

prior to freezing at −20 °C. Between samples the catheter line and extension were kept patent using heparinised saline (10 IU mL^{-1}) flushes. Saliva was collected as previously outlined. Blood and saliva levels were then analysed and compared as described below.

TDx assay protocol

Samples were thawed, re-centrifuged at 8000 *g* for 5 min, and 70 μL of each sample was analysed according to the standard manufacturer's TDx protocol using the TDx/TDxFLx acetaminophen assay system (Abbott Laboratories, Number 9520-XX). The system was calibrated using standard concentrations (0–200 μg mL^{-1}) of paracetamol in human serum (SYSTEMS Calibrators, Abbott Laboratories). The range of the paracetamol assay was 1–200 μg mL^{-1}. The accuracy and reproducibility of the assay was determined by using three controls (SYSTEMS Controls, Abbott Laboratories). These controls were tested with every other sample batch.

Given the close correlation between the spiked saliva samples and serum calibrators, and the results of the in-vivo plasma/saliva correlation (see results), it was decided that the TDx system could be used as an assay method for the analysis of paracetamol concentrations in the saliva for the paracetamol absorption studies.

Data analysis

The mean (± s.d.) of the C_{max} and t_{max} for paracetamol preparations within each of the studies were compared using a paired Student's *t*-test with $P < 0.05$ being considered significant. Comparison between the different studies was undertaken using unpaired Student's *t*-tests. Identification of the t_{max} following dispersible tablets or suspension was difficult in some cases as there was initially a high peak in a number of samples, which could have been caused by inadequate rinsing of the mouth. However, in the case of the suspension this was often followed by a second (lower) peak some time later, which was taken as the true t_{max}. In the case of dispersible tablets, secondary peaks were not observed and so the initial peak was taken as the t_{max}. In these cases the C_{max} may be higher than the true value.

The complete results for one subject in the non-morphine study were disregarded following a high (30 μg mL^{-1}) salivary paracetamol concentration at t = 0 in one of the studies. The subject later confirmed that they had taken paracetamol prior to the study. Similarly, data for four subjects in the morphine study were disregarded as the subjects withdrew from the study after the first phase, due to experiencing nausea. Samples where the paracetamol concentration was outside the stated range of the assay (1–200 μg mL^{-1}) were also omitted from the analysis (8 samples 200 μg mL^{-1}, 82 samples < 1 μg mL^{-1}). These were mainly the t = 0 or t = 10 min samples, except for samples in a number of subjects taking conventional tablets in the morphine study, as discussed below.

Results

Analysis of paracetamol in saliva

The relationship between plasma and saliva paracetamol concentrations following ingestion of paracetamol tablets is shown in Figures 2 and 3. The average peak time (t_{max}) for saliva occurred at 55 ± 27 min and the plasma peak was seen at 61 ± 28 min. This difference was not statistically significant. The C_{max} values for saliva and plasma were 26.6 ± 11.1 μg mL^{-1} and 19.8 ± 9.4 μg mL^{-1} respectively ($P < 0.05$). For most of the distribution phase (30−150 min) the saliva concentrations were significantly higher than the plasma concentrations. However, during the elimination phase there was very little difference between saliva and plasma concentrations (Figure 2).

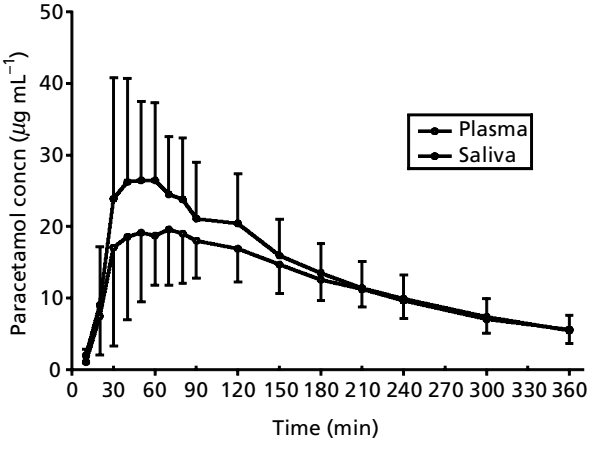

Figure 2 Plasma and saliva concentrations (mean ± s.d.) of paracetamol following ingestion of 1.5 g conventional paracetamol tablets in healthy volunteers (n = 13).

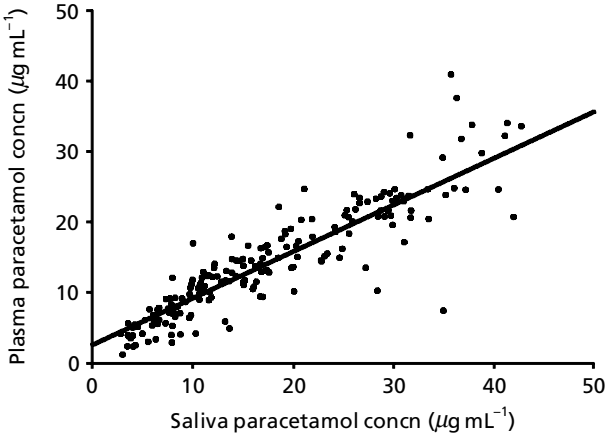

Figure 3 Correlation between saliva paracetamol concentrations and plasma paracetamol concentrations ($r^2 = 0.817$) after ingestion of paracetamol 1.5 g as conventional tablets.

Despite the differences in plasma and saliva concentrations in the early stages following oral ingestion, there was, overall, a close correlation ($r^2 = 0.817$) between saliva and plasma concentrations (Figure 3). Within this scatter plot, 31 pairs of data have been omitted due to one or both of the samples being below the detectable limit of the assay. The data that deviates most from the regression line tend to be those that represent higher paracetamol concentrations, i.e. those occurring around C_{max}.

Paracetamol absorption studies

The results comparing the effects of morphine on absorption from various formulations are summarized in Figure 4.

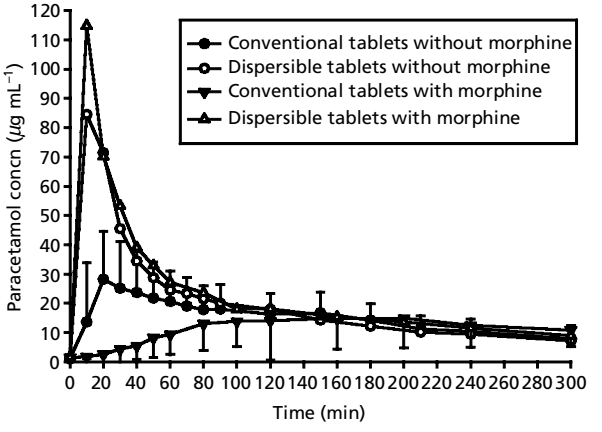

Figure 4 Mean (±s.d.) saliva paracetamol concentrations ($\mu g\,mL^{-1}$) after paracetamol (1.5 g) ingestion, either as dispersible or conventional tablets, taken with (n = 13) or without (n = 11) concomitant morphine. Error bars have been omitted from the dispersible tablet data for reasons of clarity.

Within the non-morphine pharmacokinetic study, the t_{max} obtained with dispersible tablets (15 ± 12 min) was lower than that obtained with either conventional tablets (51 ± 58 min) or suspension (73 ± 62 min). In the case of the suspension, this difference was statistically significant. The corresponding C_{max} values were $87 \pm 52\,\mu g\,mL^{-1}$ for dispersible tablets, $35 \pm 15\,\mu g\,mL^{-1}$ for conventional tablets and $47 \pm 41\,\mu g\,mL^{-1}$ for suspension. The values for the dispersible tablets were significantly higher than those for the conventional tablets.

Due to the similarity of the results between the suspension and the conventional tablets in the non-morphine study, and the problems with oral contamination, no investigation of the suspension was included in the morphine study.

In subjects taking morphine there were no significant changes in the parameters obtained for dispersible tablets, with $t_{max} = 14 \pm 9$ min and $C_{max} = 103 \pm 49\,\mu g\,mL^{-1}$ when compared to the morphine study. However, for conventional tablets the t_{max} increased to 160 ± 81 min and the C_{max} was $21 \pm 12\,\mu g\,mL^{-1}$. These values (for the conventional tablets) were significantly different from those obtained for the dispersible tablets in this study and from the conventional tablets in the non-morphine study. This delay in absorption of paracetamol from conventional tablets is highlighted by the fact that three of the subjects had no detectable salivary paracetamol concentrations for at least 2 h post-dose (120, 160 and 200 min).

Discussion

Paracetamol is often used as an opioid-sparing analgesic in the clinical setting either alone as an alternative to, or together with, NSAIDs (Montgomery et al 1996; Cobby et al 1999).

The route of administration used may vary depending on the individual situation. Suppositories are an option, but there have been questions raised with regard to reduced or erratic absorption from this route (Feldman 1975; Seideman et al 1980), and there may also be issues around patient acceptability. However, within this study it has been demonstrated that the oral route may not be ideal either, as the combined effects of the supine position and morphine administration (which can occur frequently post-operatively) can cause significant delays in paracetamol absorption from conventional tablets, as reflected in the extended t_{max} and reduced C_{max} seen in Figure 4. These changes in pharmacokinetic parameters in themselves would not be critical as long as sufficient paracetamol concentrations were reached to achieve a therapeutic effect. The therapeutic range for the analgesic effects of paracetamol has not been clearly defined, but a plasma concentration of 10–20 $\mu g\,mL^{-1}$ is generally considered acceptable. Whether or not this range would be applicable when multiple synergistic/additive analgesics are used is debatable, as lower plasma concentrations may still be efficacious. However, within the morphine study three of the participants had no detectable paracetamol in the saliva for at least 2 h post-dose when taking conventional

tablets. Furthermore, three other subjects had paracetamol concentrations below 5 μg mL^{-1} throughout this time period. It is the authors' belief that these subjects, representing half of the study population, would not have received any benefit from the paracetamol in the clinical situation during these 2 h. It may be anticipated that the effects on paracetamol absorption will be even more exaggerated if pain and/or food were to cause further delays in gastric emptying.

In contrast to the results obtained using conventional tablets, morphine had no effect on the salivary concentrations of paracetamol following ingestion of dispersible tablets. Thus, it follows that the use of dispersible tablets should produce more reliable analgesia in situations where reduced gastric motility occurs. Whether or not these effects are more critical for a first or 'prn' (when required) dose than during a regular dosing schedule needs to be determined. Further studies within the clinical setting, perhaps accompanied by the use of a pain analogue score to measure clinical efficacy, would help to clarify such issues.

Within this study, salivary paracetamol concentrations, as measured by the Abbott TDx system, were used to give an indication of paracetamol absorption. Drug concentrations in saliva are usually proportional to the concentrations in plasma and this has led to the suggestion that saliva may be substituted for plasma in therapeutic drug monitoring and in pharmacokinetic studies (Danhof & Breimer 1978; Adithan & Thangam 1982). The potential advantages and disadvantages of using saliva for this purpose are discussed in some depth by Miles et al (1990).

Correlations between salivary and plasma concentrations have been characterized for a number of drugs, including phenytoin (Lifshitz et al 1990; Cai et al 1993), digoxin, theophylline, antipyrine (Danhof & Breimer 1978) and paracetamol (Adithan & Thangam 1982; Kamali et al 1987; Hahn et al 2000). A close correlation between saliva and plasma was also found in this study following ingestion of conventional tablets, although the saliva concentrations did peak earlier and higher than the plasma concentrations. In a study by Kamali et al (1987) to investigate this particular effect with paracetamol, it was found that the elevated saliva/plasma ratio was not due to the loss of paracetamol from plasma during sample preparation, nor due to binding to plasma proteins or adsorption to the buccal mucosa. An anatomical–physiological model was developed by Posti (1982) to explain the finding of higher saliva drug concentrations relative to plasma drug concentrations following the oral ingestion of a drug. In this model it is hypothesised that during absorption the concentration of drug in arterial blood is higher than that in venous blood, this concentration difference being at any moment directly proportional to the rate of absorption, and that the concentration of drug in saliva is in equilibrium with that in arterial blood. The appropriateness of this model was tested by Kamali et al (1987) and a significant correlation ($r = 0.72$, $P < 0.05$) was found. It is therefore suggested that the elevated saliva to (venous) plasma concentration ratio for paracetamol immediately following oral ingestion is a reflection of higher arterial than venous concentrations. This suggestion is further supported by the data presented here where the salivary and plasma levels are almost superimposable during the elimination phase when arterial and venous concentrations would be expected to be the same.

In the pharmacokinetic studies presented here, initial high and variable salivary paracetamol concentrations were observed when the subjects ingested paracetamol in dispersible or suspension form. It is known that contamination from chewable and liquid formulations can remain in the mouth for some time, unless the mouth is adequately rinsed (Miles et al 1990). Thus, prior to sample collection, the mouth was washed three consecutive times with water, each followed by gargling and discharge of the mouthwash contents. Also, saliva samples collected in the first 5 min following ingestion of paracetamol were discarded in order to reduce contamination in the later samples. This technique was found to be effective in removing paracetamol from the mouth during preliminary studies. Despite this, it is suspected that oral and pharyngeal contamination from the dose contributed towards these very high initial values, possibly owing to variations in the application of the mouth-washing technique amongst the participants. This potential source of uncertainty may limit the usefulness of saliva sampling in future studies.

In this study, the saliva samples were frozen for a period of time before the analysis using TDx. It is considered by a number of researchers (personal communications) that the process of freezing and thawing saliva changes some of its properties, such as viscosity, making it more manageable when trying to analyse its contents. If this is the case, then TDx analysis of fresh saliva may not be feasible. Although snap freezing using liquid nitrogen is possible, this may limit the potential of using saliva to measure paracetamol concentrations in emergency situations, such as following a paracetamol overdose.

Conclusions

The results from this study suggest that patients who are confined to bed and taking morphine will have an unacceptably long delay between taking conventional paracetamol tablets and the paracetamol reaching therapeutic plasma concentrations. This will certainly be the case when taking an initial or single dose as used in this study. Conversely, there is little effect on the absorption of dispersible paracetamol under the same conditions. Therefore the extra expense involved in obtaining dispersible tablets for hospital or domestic use is justified in terms of increased patient care.

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