Paediatric and Perinatal Drug Therapy, 2006; 7 (4)

Palatability of two forms of paracetamol (acetaminophen) suspension: a randomised trial

D W Herd, B Salehi

Emergency Department, Waikato Hospital, Hamilton, New Zealand

Corresponding author

David W Herd, Children's Emergency Department, Starship Children's Hospital, Private Bag 92024, Auckland, New Zealand. Email: david.herd@mac.com

Introduction: **Paracetamol is the most prescribed medicine in New Zealand. In February 2004, the New Zealand Pharmaceutical Management Agency (PHARMAC) changed the sole-supply paracetamol from Paracare TM (Healthcare Manufacturing Group, NZ) to Parapaed TM (Pinewood Healthcare, Ireland). Child health workers noticed the new paracetamol appeared less palatable than the previous suspension.**

Aim: **To determine which of Paracare Double Strength or Parapaed Six Plus suspension is the more palatable to children in the Emergency Department.**

Method: **A randomised double blind cross-over trial was performed in a tertiary teaching hospital emergency department. All children prescribed paracetamol suspension were eligible for the trial. Participants were randomly allocated to receive 15 mg/kg of Paracare Double Strength orange or Parapaed Six Plus orange suspension. Four hours later they were eligible to receive the same dose of the other paracetamol suspension. The primary outcome measure was a Visual Analogue Scale (VAS) from 0 (did not like at all) to 99 mm (liked very much). VAS scores were collected from the parents, nurse and child (if > 6 years) for both suspensions.**

Results: **106 children participated over a four month period. An order effect or 'carry-over' effect was discovered and further analysis was restricted to the first dose given. Wilcoxon / Kruskal-Wallis Tests (Rank Sums) of unpaired VAS scores for Paracare Double Strength were significantly higher than Parapaed Six Plus for parent (Z=2.88, *P*=0.004), nurse (Z=2.61, *P*=0.009) and child (Z=2.83, *P*=0.005). VAS scores for the Paracare Double Strength group were above 50 mm (or palatable) in 75% of all cases. In the Parapaed Six Plus group 47% of VAS scores were above 50 mm.**

Conclusion: **Paracare Double Strength is significantly more palatable than Parapaed Six Plus.**

Paed Perinat Drug Ther 2006; 7: 189–193

Keywords: paracetamol – acetaminophen – palatability – tolerability

Introduction

Paracetamol (acetaminophen) is the most prescribed medication in New Zealand with more than 1.1 million prescriptions written for the year ending June 2004[1]. Paracetamol suspension is the most common childhood medication in New Zealand. In 2004 there was 108,359,444 ml of 120 mg/5 ml suspension and 88,519,679 ml of the 250 mg/5 ml suspension fully subsidised by the New Zealand Pharmaceutical Management Agency (PHARMAC)[1]. Paracetamol is used for the relief of mild pain[2] and is commonly used for fever but this indication is being questioned[3]. Paracetamol is the most common accidentally ingested medicine of childhood although rarely is sufficient ingested to cause morbidity[4]. Chronic overdosing and idiosyncratic responses at normal doses can also cause hepatotoxicity[5]. We still have more to learn about optimal dosing for paracetamol[6].

Since 1997 paracetamol has been provided as a sole-supply medicine in New Zealand, which means only one brand is subsidised. Since 2002 PHARMAC has been purchasing medicines on behalf of District Health Board (DHB) hospitals (Section H of the Pharmaceutical Schedule). DHB hospitals have an obligation to provide the Section H medicine although they have a small discretionary variance. In the community, parents may purchase their brand of choice.

In February 2004 PHARMAC changed sole-supply community and Section H paracetamol suspensions. Paracare TM (Healthcare Manufacturing Group, NZ) suspensions were replaced with equivalent strength Parapaed TM (Pinewood Healthcare, Ireland). Paracare Junior (120 mg/5 ml) strawberry flavour was replaced with Parapaed Junior (120 mg/5 ml) cherry flavour. Paracare Double Strength (250 mg/5 ml) orange flavour was replaced with Parapaed Six Plus (250 mg/5 ml) orange flavour.

Many health care professionals who work with children in hospital noticed that the new paracetamol suspension appeared to be disliked by many children. Some children would spit the medication out and others would refuse it after the first dose. In 2005 PHARMAC called for tenders to re-supply paracetamol suspensions[7].

Aims

This study was conducted to determine which of Paracare Double Strength or Parapaed Six Plus suspension is the more palatable to children in the emergency department and to provide this information to PHARMAC.

Methods

Protocol

The Waikato Hospital Emergency Department sees approximately 10,000 children each year. All children prescribed paracetamol suspension were eligible for the trial. Parents were given an information sheet about the study and signed a consent form. Children > 6 years (yr) gave assent. The study had the approval of the Waikato Hospital Ethics Committee. Once enrolled an opaque sealed envelope was selected containing two paracetamol syringes, consent forms, data recording sheet and instructions. The syringes were marked "First Dose" and "Second Dose". The order of the paracetamol suspension was randomly allocated at the pharmacy from a computer generated number table.

Parapaed Six Plus is a slightly darker orange colour than Paracare Double Strength and we used opaque adhesive covers on the syringes to mask this colour. A measurement scale was placed on the plunger of the syringe to enable 15 mg/kg (0.333 ml/kg of 250 mg/5 ml). An opaque container was used to dispose of the excess paracetamol and nurses were instructed not to try to observe which paracetamol they were giving. It was not possible to blind the nursing staff completely if they saw the paracetamol ingested by the child or it being spat out or vomited. Investigators, parents and children were blind to the intervention.

Primary outcome measure

The primary outcome measure was a Visual Analogue Scale (VAS) from 0 to 99. Parents, nurses and children independently scored the VAS on separate strips of paper, which contained a 10 cm line with two vertical bars at each end. Participants were asked to mark the line at a point between 0 ("Did not like at all") and 99 ("Liked very much"). The more acceptable the taste the higher the VAS score, and a score of 50 mm was presumed to represent ambivalence. VAS scores have been extensively used in studies of pain in children and have been validated for such use by parents, health professionals or children. Previous studies of palatability have used a VAS in conjunction with a facial hedonic scale[8-11]. The parent and nurse observed the child take the paracetamol and estimated the degree of palatability. Children > 6 yr gave a self-reported score. A VAS score was recorded for the first dose and the second dose by the parent, nurse and child giving a maximum of six scores.

Secondary outcome measures

Qualitative comments were recorded by the nurse including whether the child verbalised (e.g. "Yuk") or physically expressed an opinion (e.g. vomited or spat out the suspension).

Statistical analysis

JMP version 5.1 (SAS Institute Inc. Cary, NC, USA) was used. For paired data Wilcoxon Signed-Rank Test was used and for unpaired data Kruskal-Wallis (Rank Sums) Test.

Results

One hundred and thirty one children were enrolled. Ten had no data recorded. Fifteen did not require paracetamol or took tablets. The remaining 106 had at least one dose of paracetamol suspension. The mean age was 6.4 yr (SD 4.2) in the Paracare Double Strength group and 6.2 yr (SD 4.4) in the Parapaed Six Plus group. Pain was the commonest indication in 63 (59%), followed by fever in 28 (26%) and both pain and fever in 7 (7%). Males and females were equally represented (52 vs 50, 4 not recorded).

Parents provided 56 paired observations. Nursing staff provided 46 paired observations. Children > 6 yr provided 31 paired self-reported VAS scores. When Paracare Double Strength was given first Wilcoxon Signed-Rank Test demonstrated that VAS scores were significantly higher (Parent W+ = 404.50, W– = 60.50, n = 30, P <0.001; Nurses W+ = 329.50, W– = 76.50, n = 28, P = 0.004; Child W+ = 110, W– = 26, n = 16, P = 0.029). When Parapaed Six Plus was given first however there was no significant difference between the groups. An order effect or a "carry-over effect" was assumed to be present. Further analysis was therefore confined to the first dose.

For the first dose there were 96 parent observations (48 Paracare; 48 Parapaed), 100 nurse observations (51 Paracare; 49 Parapaed) and children > 6 yr provided 49 self-reported VAS scores (28 Paracare; 21 Parapaed).

Median VAS scores for Paracare Double Strength were 79.5, 70 and 83 for parent, nurse and child respectively. Median scores for Parapaed Six Plus were 48, 45 and 40 for parent, nurse and child respectively but with a much wider inter-quartile range (Figure 1). Kruskal-Wallis Tests (Rank Sums) of unpaired VAS scores for Paracare Double Strength were significantly higher than Parapaed Six Plus for parent (Z = 2.88, P = 0.004), nurse (Z = 2.61, P = 0.009) and child (Z = 2.83, P = 0.005).

Qualitative results

In the Parapaed Six Plus group four children spat out the paracetamol, one held the medicine in her mouth and two others vomited. In the Paracare Double Strength group two children spat the paracetamol out. Children > 6 yr were more likely to express their feelings verbally. 25 children commented on one syrup and

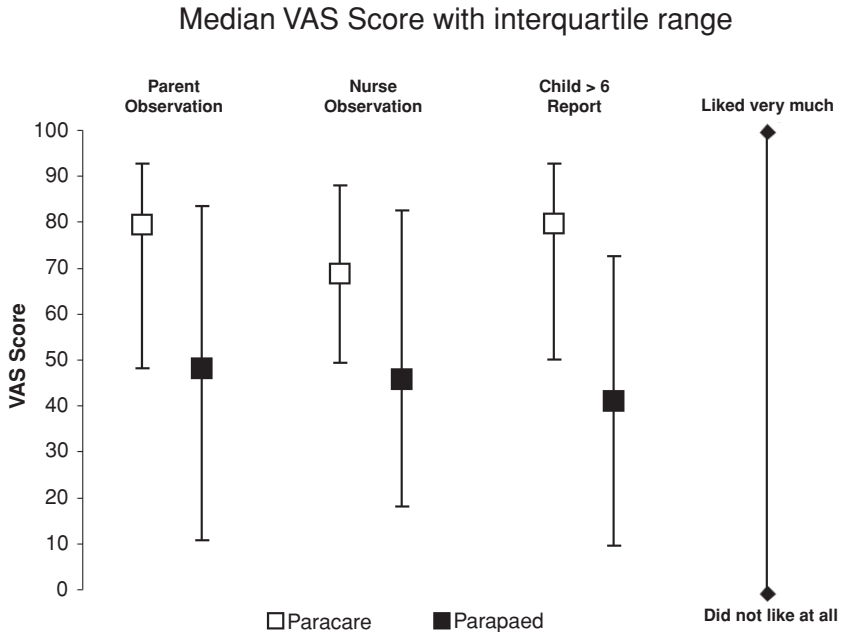

Figure 1 Median VAS scores with interquartile range for parents, nurses and children (> 6 yr). There was a significant difference between Paracare Double Strength and Parapaed Six Plus for parents, nurse and child (P = 0.004, P = 0.009, P = 0.005 respectively).

20 made a comment for both syrups, giving a total of 65 comments. There were 37 comments for Paracare and 28 comments for Parapaed. All the comments children > 6 yr spontaneously made were collated. Key phrases were identified and then ranked in order by one of the authors (DH) from "least palatable" to "most palatable". The frequency of occurrence of these key phrases for each group is shown in Figure 2.

Discussion

Paracare Double Strength paracetamol suspension (250 mg/5 ml) is more palatable than Parapaed Six Plus paracetamol suspension (250 mg/5 ml). Our study suffered from an order-effect or 'carry-over' effect. This can invalidate cross-over design studies and occurs when the intervention being measured (in this case palatability) has an ongoing effect when the comparison intervention is introduced. To avoid this a suitable 'wash-out' period is required. We were limited by the clinical situation to a four hour 'wash-out' period. It is unlikely that the taste of the paracetamol suspension was still present four hours later, however, the memory of the taste would persist. The other reason an order effect could be present is the VAS anchor points used. The distribution of VAS scores were bunched at either end of the scale. Our anchor points may have been better replaced with the more extreme "Hated it" and "Loved it". A weakness of the study was the use of a VAS without the presence of a facial hedonic scale[8-11]. It was reassuring, however, to see that the VAS scores and the verbal comments were in agreement with each other.

To avoid the carry-over effect we looked at only the first dose given because in our study children were randomly allocated to either Paracare Double Strength or Parapaed Six Plus for the first dose. These observations would not be paired but our study had both large numbers (106 children) and the palatability difference between the suspensions was large making it easy to demonstrate a statistical difference. To quantify the clinical significance we can look at the distribution of the data. If one assumes 50 mm represents ambivalence, then scores above 50 are 'palatable' and scores below 50 are 'unpalatable'. For parent observations 66% of all observations (32 out of 48) were palatable for Paracare Double Strength, whereas 45% of observations (21 out of 49) were palatable for Parapaed Six Plus. Paracare Double Strength to Parapaed Six Plus relative palatability ratio (32/48 divided by 21/49) for parents observation is 1.6. The absolute palatability difference is 0.22 and the number needed to treat to avoid an unpalatable experience is 4.59.

Multiple formulations of paracetamol are available over the counter and parents may purchase the paracetamol suspension of their choice if they are financially able to. Only one other study has compared paracetamol suspensions[12].

In 2004 PHARMAC spent $735,000 for nearly 200,000 litres of paracetamol suspension. The 2004 pharmaceutical listing price for Parapaed is NZD$7.29 for one litre of 120 mg/5 ml suspension and NZD$7.70 for one litre of 250 mg/5 ml solution. The listed Pharmaceutical Schedule price for Paracare in 2003 was $11.20

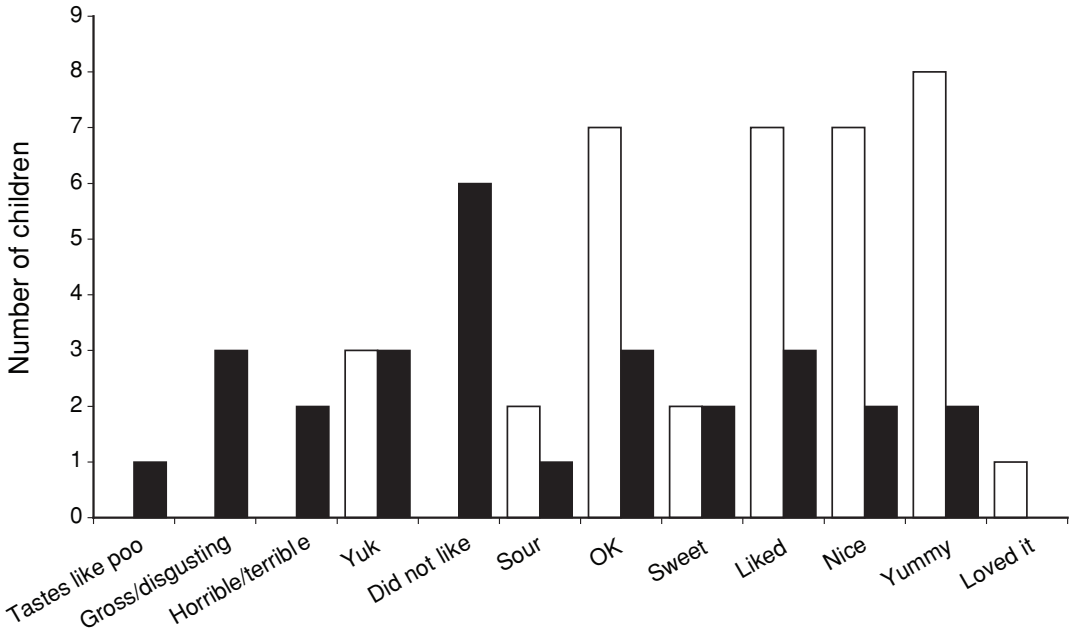

Figure 2 Frequency of key phrases (sorted in order from "least palatable" to "most palatable") from children > 6 yr (first and second dose combined) for Paracare (□) and Parapaed (■)

per litre for 120 mg/5 ml and $14.48 per litre for the 250mg/5 ml suspension. Assuming a relative cost of $11.20/$7.29 for 120 mg/5 ml suspension and $14.48/$7.70 for the 250 mg/5 ml suspension and the same volume cost as outlined in the 2005 tender document, then the potential additional cost to PHARMAC would be NZD$511,923 per annum. The results of the study were made available to PHARMAC.

In our study seven children in the Parapaed Six Plus group compared to two in the Paracare Double Strength group vomited, spat or refused the medicine. This difference was not statistically significant and could be due to the study not having enough power or our short follow-up period.

A considerable amount of time and effort goes into reducing the traumatic experience for children that require a hospital visit. Providing an unpalatable medicine runs the risk of alienating that child from health care workers and this effect would be compounded by repeated exposures. Palatability of medicines is thought to be important and there have been efforts to improve the palatability of medicines for children[13]. Unpalatable excipients are used to reduce volume ingested during unintentional overdose. Palatability has been shown to have an effect on adherence to treatment for other medications[11,14,15]. We have demonstrated a significant palatability difference and this was important to many children in the study and we think it should be considered when selecting medicines for children.

Conflicts of interest

This study received no input from the manufacturers of either medication.

Acknowledgments

The Emergency Department and Pharmacy at Health Waikato provided funding for this study.

References

1. PHARMAC. Pharmaceutical Management Agency Media Release 16 November 2004.
2. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. N Engl J Med 2002;347: 1094-1103.
3. Russell FM, Shann F, Curtis N, Mulholland K. Evidence on the use of paracetamol in febrile children. Bull World Health Organ 2003;81: 367-372.
4. Riordan M, Rylance G, Berry K. Poisoning in children 2: painkillers. Arch Dis Child 2002;87: 397-399.
5. Sztajnkrycer MJ, Bond GR. Chronic acetaminophen overdosing in children: risk assessment and management. Curr Opin Pediatr 2001;13:177-182.
6. Anderson BJ. What we don't know about paracetamol in children. Paediatr Anaesth 1998;8:451-460.
7. PHARMAC. Invitation to Tender – Supply of Pharmaceuticals to DHB Hospitals and/or to Community Pharmacies, p46. http://www.pharmac.co.nz/pdf/231204a.pdf [last checked 27 April 2005].
8. Angelilli ML, Toscani M, Matsui DM, Rieder MJ. Palatability of oral antibiotics among children in an urban primary care center. Arch Pediatr Adolesc Med 2000;154:267-270.
9. Dagnone D, Matsui D, Rieder MJ. Assessment of the palatability of vehicles for activated charcoal in pediatric volunteers. Pediatr Emerg Care 2002;18:19-21.
10. Matsui D, Barron A, Rieder MJ. Assessment of the palatability of antistaphylococcal antibiotics in pediatric volunteers. Ann Pharmacother 1996;30:586-588.
11. Matsui DM. Drug compliance in pediatrics. Clinical and research issues. Pediatr Clin North Am 1997;44:1-14.
12. Villarroya J, Segovia C, Aznar A, Garcia J. Assessment of the taste of three paracetamol drop preparations. Aten Primaria 2001;28:210-212.
13. Nunn AJ. Making medicines that children can take. Arch Dis Child 2003;88:369-371.
14. El-Chaar GM, Mardy G, Wehlou K, Rubin LG. Randomized, double blind comparison of brand and generic antibiotic suspensions: II. A study of taste and compliance in children. Pediatr Infect Dis J 1996;15:18-22.
15. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. Pediatr Infect Dis J 2001;20:1-5.

CrossRefs are available in the online published version of this paper:
http://www.librapharm.com
Paper PPDT-0174_3, *Accepted for publication:* 19 December 2006
Published Online: 12 January 2007
doi:10.1185/146300906X167737