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Methods of administering oral formulations and child acceptability

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ABSTRACT

Introduction: Children may be unable or unwilling to swallow medicines. In order to avoid or accommodate any such problems, parents may decide to administer medicines other than intended. The aim of this study was to investigate how parents administered four oral placebo formulations to infants and preschool children and how the applied methods correlated with child acceptability.
Methods: Parents were asked to administer a 4 mm mini-tablet, powder, suspension and syrup to their child twice on one day and to report the child characteristics and administration details in a participant diary.
Results: A 151 children were included. The tablet, syrup and suspension were mostly given on their own, whereas the powder was commonly given with food or drink. Generally, the higher the child acceptability (VAS-score) of the first administration of a specific formulation, the less frequently its method of administration was changed. A change in the method of administration of the same formulation involving (a larger quantity of) food or drink generally resulted in a higher VAS-score.
Conclusions: The joint administration of medicines with food or drink is an effective strategy to ensure swallowing. This study supports earlier findings that 4 mm mini-tablets are a suitable dosage form from infant age.

1. Introduction

In young children, the correct use of medicines poses specific challenges to parents, caregivers and health care professionals that are usually not encountered in adults (Matsui, 2007; Breitkreutz and Boos, 2007; Polaha et al., 2008; Bain-Brickley et al., 2011; Terry and Sinclair, 2012). For example, the medicine may not be commercially available in the required strength (a 2 mg tablet needs breaking or splitting to administer a 1 mg dose), the medicine may not be available in a dosage form that the child is able to take (babies cannot swallow large tablets), or the medicine may not be available in a dosage form that the child is willing to take (bad taste; adequate taste, but child does not like it; recalcitrance) (Balakrishnan et al., 2007; Balakrishnan et al., 2006; van Riet-Nales et al., 2011; Walsh et al., 2014).

Clear instructions on how to overcome any administration challenges are hardly available (Ernest et al., 2012). As a consequence, parents, caregivers and health care professionals may handle medicines in ways that they consider best in a particular situation, such as breaking, crumbling or crushing tablets, mixing medicines with food or drink, or even refraining from administering them (Ernest et al., 2012; Richey et al., 2013; Milani et al., 2010). All these strategies may reduce clinical efficacy and/or increase the risk of adverse drug reactions when the dosing accuracy, chemical stability, physical stability and/or bio-availability of a formulation is affected (Choonara and Conroy, 2002; Cuzzolin et al., 2006; Bellis et al., 2013).

In a previous study amongst infants and preschool children in the domiciliary setting, we showed that the child and parent acceptability were related to the type of an oral formulation, e.g., tablet or syrup, and that there is no reason to question the

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acceptability of 4-mm tablets in children from one year old (van Riet-Nales et al., 2013). In this study, we investigated how parents administer different types of oral formulations to infants and preschool children at home, and whether the applied methods correlate with child acceptability.

2. Materials and methods

2.1. Study design and setting

The analysis is based on data collected for a randomized cross-over trial (RCT) that investigated the child and parent acceptability of four oral placebo formulations in infants and preschool children in the Netherlands and that has been described in detail elsewhere (van Riet-Nales et al., 2013). The current analysis had already been planned in the RCT protocol (ISRCTN63138435). In brief, 151 children were recruited through six preschool preventive health care clinics in the Netherlands. Children were eligible for inclusion if they were 1–4 years old and excluded if they suffered from a condition that might negatively affect swallowability. They were also excluded if they were (potentially) hypersensitive to any of the excipients in the formulations.

Parents were instructed verbally and in writing to offer the formulations to their child at home in the same way as they would administer a prescribed medicine, but without any mental or physical pressure. Each formulation had to be administered twice on the same day and in a randomized order for the type of formulation i.e., at eight occasions. Parents did not receive any additional instruction on how to administer the formulations to their child other than that the suspension had to be shaken prior to use. This implies that tablet chewing was neither recommended nor forbidden. The placebo character of the formulations was known to the parents and, when appropriate, explained to the child.

Acknowledging that participant adherence to the study protocol and the correct recording of data cannot be fully controlled in a domiciliary setting, particular attention was paid to assuring that parents well understood the aim of the study; why it was so important to behave similarly as if they needed to administer a prescribed medicine with the only instruction “twice daily”; and how the diary had to be filled in.

The four tested formulations (Fig. 1) were aimed at a neutral taste by choosing a composition that was simple, applying excipients that are commonly used in (pharmacy compounded) paediatric medicines and by omitting the use of flavouring substances and/or taste maskers:

- White to off-white, round, biconvex, uncoated tablet (also referred to as mini-tablet), diameter 4 mm, height 3.05/2.50 mm (top/edge), weight 43.0 mg. Composition: lactose monohydrate 34.69 mg; maydis amylum 6.46 mg; maydis amylum pregelificatum 1.42 mg; magnesium stearate 0.43 mg. The tablets were packed in a PVC/Al blister.
- White, freely flowing powder (granules), 250 mg per single dose. The composition of the powder is proportionally identical to the tablet with exception of the lack of magnesium stearate i.e., lactose monohydrate 203.7 mg; maydis amylum 38.0 mg; maydis amylum pregelificatum 8.3 mg. The powder was packed in a white sachet.
- White, opaque suspension; 2.5 ml per single dose. Composition: methylparahydroxybenzoate 46.0 mg; aluminium magnesium silicate 484.4 mg; carboxymethylcellulose 484.5 mg; citric acid 36.3 mg; sucrose 12.74 g; purified water 37.95 g; microcrystalline cellulosis 2.50 g; purified water ad 50 ml. The suspension was packed in a 50-ml brown glass container with white, syringe adapter that could be connected to a 3-ml oral syringe.
- Clear, colourless syrup (solution); 2.5 ml per single dose. Composition: methylparahydroxybenzoate 63.1 mg; propylparahydroxybenzoate 10.0 mg; citric acid monohydrate 37.5 mg; saccharose 8.28 g; purified water ad 50 ml. The container closure system and dosing device were identical to those used for the suspension.

In order to avoid that parents would accidentally mix up the suspension and syrup upon administration and/or data recording, a red sticker was put on the cap of the suspension and a blue sticker on the cap of the syrup. In the participant diary, the colour of the sticker was repeated where appropriate. Also, parents were asked to confirm that they had used “the bottle with the correct colour of the sticker” when starting the data recording of the suspension and syrup.

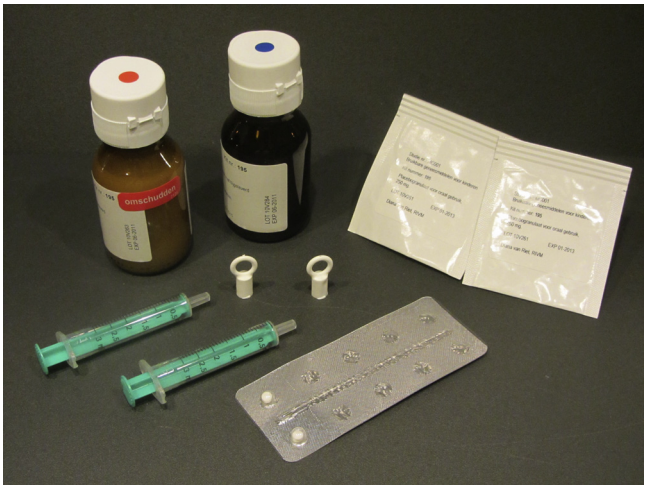

Fig. 1. Oral placebo formulations in this study (4-mm tablet, powder, suspension, syrup).

2.2. Data collection

After each of the eight administrations, parents were asked to provide information in a participant diary on: (1) whether the formulation was offered to the child (yes, no) and, if not, why not; (2) by whom the formulation was offered to the child (father, mother, other); (3) whether the tablets were broken, crumbled or crushed prior to administration; (4) whether the oral liquids (suspension and syrup) were administered with the co-dispensed oral syringe or otherwise; (5) whether the formulations were given with food or drink and, if so, which type and quantity; (6) child acceptability according to the parents’ observation as measured on a 0–10 cm Visual Analogue Scale (VAS-score); (7) child acceptability as measured by the result of each intake (fully swallowed, partly swallowed; not swallowed); (8) other aspects of the administration (optional).

The majority of the information could be provided by ticking box outcomes that were based on the results of an earlier questionnaire study in the Netherlands on the problems encountered by parents when administering medicines to children (van Riet-Nales et al., 2010). Where appropriate, parents were given the possibility to provide an open answer. Other questions in the participant diary related to child and family characteristics and child and parent formulation preferences.