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How close is the dose? Manipulation of 10mg hydrocortisone tablets to provide appropriate doses to children.

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Abstract

This study explores the methodology advised by healthcare professionals and the methods used by parents/carers to identify whether there is a best practice method for manipulation of 10mg hydrocortisone tablets to provide an accurate dose to children. Bespoke surveys were used to identify methods recommended and used in manipulation of tablets. Hydrocortisone tablets were manipulated to provide a specified dose by both naïve participants and parents/carers. The accuracy of manipulation was assessed using HPLC analysis. Competed surveys were received from 159 parent/carers reporting doses that ranged from 0.25-15mg. Parents/carers most commonly reported splitting the tablet and administering the solid fraction; however more than 30% of those reporting physically splitting tablets were preparing doses that were not simply halving or quartering tablets. In a naïve population the dose accuracy, defined as percent of doses within 20% of the theoretical dose ranged from 57-58% depending on the tablet brand and the method of manipulation used. Almost three-quarters (74.1%) of parent/carers (n=27) were able to produce a dose within 20% of the theoretical value and the most accurate method was to split tablets and administer the solid fraction. This study shows that a lack of age-appropriate medicines results in children being at risk of sub-optimal dosing.

Keywords: hydrocortisone, tablet, manipulation, age-appropriate

1. Introduction

The lack of age-appropriate medicines that are specifically designed for children results in the need to manipulate adult medicinal products to provide the required dose to children (Kayitare et al., 2009; Skwierczynski and Conroy, 2008). The manipulation of medicines (e.g. crushing of tablets) renders its use unlicensed. Previous reports state that up to 29% of medicines are manipulated within ward and home settings (Venables et al., 2015). There is limited evidence and a lack of understanding about the range of manipulations that occur in practice (Richey et al., 2017). The risks of error to neonatal and paediatric patients, as a result of manipulation has previously been highlighted (Conroy et al., 2007).

In this study the term manipulation is defined as the physical alteration of a tablet for the purpose of extracting the required proportion of the drug dose. Previously different definitions of "modification" and "manipulation" have been used (EMA, 2013; Ernest et al., 2012). There is currently no standard method(s) for an acceptable and safe way to manipulate tablets, although guidance is available from several sources. Medicines for Children is a partnership between Wellchild; Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group; that provides advice for parents on giving a part dose from a tablet or capsule (http://www.medicinesforchildren.org.uk/part-dose-tablet-or-capsule, accessed 15th November 2017). MODRIC: Manipulation of Drugs Required in Children provides guidance for health care professionals (http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC_Quick_Reference_Guide.pdf, accessed 26th March 2018). The NEWT Guidelines provide advice to healthcare professionals on the administration of medication to patients with enteral feeding tubes or swallowing difficulties and can provide advice on manipulation of solid dosage forms (www.newtguidelines.com, accessed 26th March 2018 (subscription required)).

Although guidelines exist for healthcare professionals, the methods that parents use to manipulate tablets may vary depending upon: the dose required; the advice provided by their consultant or other health care professional; the product(s) they are provided with; and the equipment they have to hand. Inter-individual variability may also occur, where different carers use different techniques for the same patient.

Tablets can be manipulated using different methods; splitting, crushing or dispersing. Verrue et al., compared tablet splitting devices and demonstrated that splitting devices were superior to knives or scissors yet there were still large dose deviations (Verrue et al., 2011). The accuracy of tablet

splitting may vary with different devices, users, and tablet shapes (Abu-Geras et al., 2017; van Riet-Nales et al., 2014). Size, shape, and the presence or absence of tablet score lines can affect the content uniformity and weight variation of split tablets (Ciavarella et al., 2016). European pharmacopoeial guidelines on subdivision of tablets require that the parts meet the following criteria "at least 194 of 200 parts resp. 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical weight of a tablet part" (EDQM, 2013).

Dispersion of tablets into a known volume of liquid then withdrawal of the required volume is also associated with variability in dosing (Abu-Geras et al., 2017). Insoluble drugs can be particularly challenging as the drug needs to be homogeneously dispersed within the liquid as it will not form a solution. Issues with unhomogenous liquids produced by dispersion of insoluble drugs was highlighted by Standing and Tuleu; they suggested that inclusion of a suspending agent would be beneficial rather than mixing directly with water (Standing and Tuleu, 2005). Even dispersible aspirin tablets were not superior to crushing and dispersing a conventional aspirin tablet as inconsistent doses were found when sampled from different depths within the liquid produced following dispersion of the tablet (Broadhurst et al., 2008). It has previously been reported that scored hydrocortisone tablets are harder than an unscored alternative and therefore do not disperse as readily (Saimbi et al., 2016).

Changes in the bioavailability of crushed or split tablets that are designed to be swallowed whole has been well documented (e.g. (Argenti et al., 2001; Cleary et al., 1999; Dodds Ashley et al., 2007; McNeely et al., 2013; Nunn, 2003)). Bioavailability of tablets can be affected by their manipulation in cases where integrity of formulation is essential for controlled release of the drug substance. For immediate release tablets this is less significant yet changes in the overal surface area of the solid dosage form can change the rate of dissolution of medicines. Furthermore maniplations that require crushing or splitting a tablet can affect the overall exposure due to inaccuracies in the dose obtained. Thus, there is a risk of under- or over- dosing due to inprecise measurements within a manipulation and the change in physical dimentions of the resulting product.

Orally administered hydrocortisone is used widely in paediatric endocrinology for the treatment of primary adrenal disorders such as congenital adrenal hyperplasia (CAH), adrenal hypoplasia and Addison's disease and secondary adrenal insufficiency due to hypothalamic and pituitary disorders. Hydrocortisone replacement therapy is essential in children with CAH and adrenal insufficiency to control androgen excess and optimise their growth and development. Hydrocortisone is used to mimic glucocorticoid levels of a healthy child and the best therapy will be one that matches the circadian rhythm of cortisol (Ng and Stepien, 2017). The rapid half-life of hydrocortisone means that

frequent administration of low doses best matches the normal physiological endogenous cortisol levels. Hydrocortisone is administered to children according to body surface area three to five times daily (Bornstein et al., 2016). The dose is carefully titrated and the low doses involved mean that dosing accuracy becomes important in providing optimised glucocorticoid levels for these children. There is currently a wide range of oral hydrocortisone treatment regimens administered to neonates, infants and children with adrenal insufficiency, with the dosages varying from 0.5 to 5mg; the most common being 1 and 2mg per dose (Whitaker et al., 2015). There are long term consequences of poor hydrocortisone therapy in childhood as adult CAH patients who remain short may have been underexposed as children (Han et al., 2014).

During this research project only hydrocortisone tablets were licensed for use in children to treat endocrine disorders (BNF-C, 2017), however, there are "Special" liquid products prepared as a suspension although these have short shelf-lives and can be costly. Many children used manipulated 10mg hydrocortisone tablets to obtain the necessary dose (Richey et al., 2013). The unmet need for a licensed infant preparation of hydrocortisone which allows dosing from 0.5mg up to 2mg has previously been identified based on both dose and poor palatability of the crushed tablets (Kauzor et al., 2014; Orlu-Gul et al., 2013; Whitaker et al., 2015). In December 2017 a novel hydrocortisone formulation was approved 0.5 mg, 1.0 mg, 2.0 mg and 5.0 mg granules in capsules for opening (EMA, 2017).

Many studies that have investigated the accuracy of manipulated tablets have used medical/pharmacy students, nurses, pharmacists as the population yet an experienced person may be better able to prepare an accurate dose from a manipulated tablet (Abu-Geras et al., 2017). This study seeks to explore current methods of manipulation reported and used by parents and carers to identify whether there is a method that is more likely to provide the most accurate dose. A population of naïve adults will be compared to experienced parents/carers to note any differences in results based on population.

2. Aims and Objectives

The aim of this study was to determine whether parents/carers can prepare accurate doses of hydrocortisone for the child in their care from manipulation of 10 mg tablets.

The objectives of this study included; identification of the methods recommended to parents and carers by health care professionals to manipulate hydrocortisone tablets to deliver the appropriate dose for the child in their care; determination of the methods (and tools) used by parents and carers in preparing doses of hydrocortisone for the child in their care; and to quantify the accuracy of doses

obtained by naïve adults and parents/carers of children who require hydrocortisone in the preparation of doses of following manipulation of a 10mg hydrocortisone tablet. The impact of tablet score lines was also explored.

3. Methods

3.1. Survey method

Bespoke surveys were developed based on key questions that were identified by a multidisciplinary team (three paediatric endocrine consultants; one paediatric endocrine specialist nurse, pharmaceutical researcher; parents of children with adrenal insufficiency) to collect information on strategies that health care professionals advise and that parents currently use or have used previously to manipulate hydrocortisone tablets to provide the appropriate dose for children.

Three surveys were developed for: (i) Paediatric endocrinologists; (ii) Endocrine nurses; and (iii) parents/carers of children who require treatment using hydrocortisone. Key areas of interest included: strategies used to manipulate 10mg hydrocortisone tablets; the tools used to manipulate tablets and instructions provided for manipulation. Although the questions were different in each survey there was some overlap allowing comparison of data between the three groups. Draft questionnaires were reviewed by the multidisciplinary team to assess ease of completion and ensure that questions were phrased unambiguously. Bristol Online Survey, (www.onlinesurveys.ac.uk) was deemed most appropriate software as it is specifically designed for academic research and public sector organisations and is fully compliant with UK data protection laws. A non-probability based convenience sampling method was selected and participants were left with a choice to “opt in” to the questionnaire following an invitation. A target sample size was not set as this was a consultation and not research therefore statistical powering is not relevant. The surveys used in this study were approved by South Central – Oxford B Research Ethic Committtee REC reference: 17/SC/0048 (HRA/ IRAS Ref: 217947).The final surveys are included as supplementary files.

Potential parent/carer participants were recruited via distribution of the survey uniform resource identifier (Ocal et al.) via parent groups associated with CLIMB, Addison's Disease Self-Help Group and the child growth foundation (http://www.livingwithcah.com; www.addisons.org.uk; http://www.childgrowthfoundation.org). The inclusion criteria were that the survey participant identifies as caring for a child who has taken oral hydrocortisone and has been required to manipulate tablets to provide a dose (no exclusion criteria).

Questionnaires were distributed to paediatric endocrinologists and endocrine nurses at UK tertiary centres for paediatric endocrinology via personal contacts of the author team.

3.2. Accuracy of manipulated 10mg hydrocortisone tablets

The variability in dose resulting from the manipulation of a 10mg hydrocortisone tablet was quantified. Manipulations were undertaken by naïve study participants as well as parents/carers who routinely manipulate hydrocortisone for their children. The difference between the measured and theoretical dose was calculated and the overall accuracy of dosing assessed. This study was approved by South Central – Oxford B Research Ethic Committtee REC reference: 17/SC/0048 (HRA/ IRAS Ref: 217947).

3.2.1.Naïve study

The participants were given either a 10mg hydrocortisone tablet with score lines marking quarters (brand was Auden McKenzie; batch 16B11/H) or an unscored 10mg tablet (brand was AMDIPHARM; batch 6066492). Images of the tablets are provided in Sumpplementary material 1. The participants then received brief instructions on how to manipulate the 10mg hydrocortisone tablet to obtain a 2.5mg dose. They manipulated their tablet by one of two methods: (i) quartering the tablet, a tablet splitter (PillMate Pill Cutter) was available if they wanted to use this OR (ii) crushing the whole tablet between two spoons, dispersing the powder in 10mL of water and then drawing up a 2.5mg dose. For method (ii) two spoons, a cup, water and a 10mL syringe (Medicina 10mL home oral/enteral syringe, Ref: HE10) were provided. After manipulation the prepared dose was collected and analysed within 7 days of sample collection. The solid fractions were stored in individual airtight universal tubes and refrigerated prior to analysis; the liquid samples were stored in airtight universal tubes and frozen at -20°C prior to analysis. Previous literature suggested that hydrocortisone is stable for up to 14 days at room temperature (Chappe et al., 2015). In this study a dispersionof a single tablet in water was stored for 14 days and measure on 5 occasions; there was no change in the measured hydrocortisone concentration over time.

3.2.2.Parent/carer study

Parents/carers were provided with a 10mg scored Auden McKenzie hydrocortisone tablet (batch 16B11/H) and requested to prepare the smallest dose of hydrocortisone that they would usually give to their child as part of their treatment regimen as they would in a home setting. All participants were provided with tools including: differing sized spoons; medicine spoons; tablet

crushers/splitters; syringes and other items identified in the survey. The samples were anonymised with only the intended dose and the method of preparation recorded. The prepared samples was collected and stored as per the naïve samples prior to quantitative analysis.

3.2.3.Quantitative analysis via HPLC

The hydrocortisone content was analysed according to the current European Pharmacopoeial method. In brief, a stationary phase end-capped octadecylsilyl silica gel column 250 x 4.6mm i.d., 5µm particle size. Elution was established with a mobile phase composition of acetonitrile and water (40:60 v/v) at a flow rate of 1.0ml/min. The chromatographic signal was monitored at 254nm with an injection volume of 20µL.

The drug content of the tablet batches used was assessed to determine their actual content compared to the labelled content of 10mg. Ten individual tablets from each manufacturer (Auden McKenzie and AMDIPHARM) tablets were weighed and then each dissolved in 100mL of mobile phase to ensure complete dissolution of the hydrocortisone.

Hydrocortisone samples prepared by participants within the study required further manipulation prior to analysis. The solid tablet fractions were weighed and then dissolved in 50mL of mobile phase (acetonitrile and water (40:60 v/v)), samples were sonicated for 10 minutes to ensure full dissolution of hydrocortisone. The liquid samples of dispersed tablets were defrosted, weighed then dissolved at a ratio of 1:10 with the mobile phase and sonicated for 10 minutes to ensure complete dissolution of hydrocortisone (to prepare a solution from the suspension) prior to analysis. For HPLC a small volume (20 µL) of this solution was taken for analysis.

4. Results

4.1. Survey data

4.1.1.Healthcare professionals

Completed surveys were received from 32 paediatric endocrinologists and 20 endocrine nurses. Both endocrinologists and endocrine nurses were comfortable in recommending dispersed, cut and crushed hydrocortisone tablets to children. Interestingly, more endocrinologists were comfortable in recommending the use of half a 10mg tablet (90.6%) compared to a quarter of a tablet (46.9%) as a manipulation. When endocrine nurses were asked directly what advise they would provide to

parents/carers to prepare a dose of 2.5mg the results were split evenly between dispersing the tablet in 10mL water and drawing up 2.5mL and quartering the tablet.

4.1.2.Parents/carers

Surveys were received from 159 parents/carers. The age range of children and young people was 3 months to 23 years with a mean age of 8.7 years. The total number of doses reported was 476 ranging from 0.25mg to 15mg. When the doses for those children under six year of age were separated the total number of doses analysed was 191 and the range from 0.25-7.5mg; the percentage of those doses divisible by 2.5mg was 43.2%, meaning >50% of doses could not be prepared from quartering tablets.

Seventy three percent of respondents reported receiving instructions on how to prepare a dose, of which the majority reported receiving instructions from a nurse, only 6.8% received instructions from a pharmacist. Of those who reported receiving instructions, 63.1% reported this being more than a year ago with only 10.6% reporting to have received an update on instructions for manipulation since diagnosis with adrenal insufficiency. Seventy four percent of parents/carers reported that they had trained between one and ten other people on the preparation of hydrocortisone dose from a 10mg tablet.

Seventy percent of parents/carers reported using the method that was recommended to them by their healthcare professional; discrepancies typically related to those advised to disperse the tablet yet choosing to cut the tablet and administer a solid portion. The methods used by parents/carers to prepare doses for the child in their care are shown in Figure 1a. The most common method reported was to cut the tablet and administer the cut portion as a solid.

Figure 1: *Methods of manipulation of a 10mg hydrocortisone tablet (a) reported by parents/carers (n=119) to achieve an appropriate dose for the child in their care and (b) undertaken by parents/carers within this study (n=27).*

More than 60% of parents/carers reported cutting the 10mg tablet and then administering the cut portion as a solid. Of those cutting tablets 19.6% were administering a dose not divisible by 2.5mg. Doses reported to be prepared by cutting included 0.5, 2, 4, 6 and 14mg. Hydrocortisone tablets are available from a wide range of manufacturers. However, in the UK it is only the Auden Mackenzie

brand that have score lines to produce quarters on the tablet. Seventy four percent of those who reported cutting tablets were using the scored tablets.

It was important to determine the tools used by parents/carers to manipulate the tablet so that we could replicate the typical utensils used for the dose preparation aspect of this study. The most popular tool used in manipulation was either a tablet cutter or knife (>40%); followed by a syringe, cup and water (>15%). Many parents/carers reporting splitting the tablets with their hands; due to the small size of hydrocortisone tablets this is more likely to be the scored tablets.

4.2. Accuracy of manipulated 10mg hydrocortisone tablets

A calibration curve was produced which was linear with an R^2 value of 0.99 over the range 0 – 0.20 mg/mL. The tablets both showed uniform content with a mean content of 9.98mg for the Auden Mackenzie brand and 10.01mg for the Amdi brand tablets.

4.2.1.Naïve study

A total of 30 naïve participants were recruited from events held at the University of Birmingham using posters or word of mouth at engagment events. Naïve participants were invited to prepare 2.5mg doses from tablets that were scored or unscored using either tablet splitting or dispersing the tablet in 10mL of water and withdrawing the relevant volume.

The hydrocortisone content from each of the methods was measured and the results are shown in Figure 2. There were no statistically significant differences (ANOVA $p>0.05$) in the dose produced based either on the method or brand of tablet investigated.

The weights of the quartered tablets ranged from 0.0369 – 0.0888g for the scored tablet and 0.0428-0.0781g for the unscored tablets; both data sets were normally distributed. The mean and standard deviations were 0.068±0.015g and 0.065 ±0.009g for the scored and unscored tabelts respectively. There was a linear relationship between the weight of the quarter and the dose that was contained within the tablet fragment. This demonstrates that the weight may be used as a surrogate for content in comparing these hydrocortisone tablet brands.

The total volume used to disperse the tablet was not recorded, this was suggested to be 10mL and the syringe has an accuracy of ±0.5mL. The volume of liquid removed from the ~10mL dispersion was weighed to examine the variability in volumes withdrawn from the dispersion. Assuming a density of 1g/mL the weight should have been close to 2.5g. The weights of the volume withdrawn from the scored tablet dispersion ranged from 1.95-2.94g with a mean and standard deviation of 2.32±0.22g. The weights of the volume withdrawn from the unscored tablet dispersion ranged from

1.44-3.93g with a mean and standard deviation of 2.36±0.42g. The volume withdrawn did not relate to the dose delivered; the liquid prepared was a suspension rather than a solution which can explain this lack of correlation.

Figure 2: Comparison of the dose produced when non-scored and scored tablets were manipulated by naïve adults. The data points show each manipulation (n=30 in each group). The target dose was 2.5mg.

The accuracy was better for the non-scored tablets with 70% and 87% being within the 20% limits (2-3mg) compared to 57% and 67% for the scored tablets for the quartered vs dispersed tablets respectively.

4.3. Parent/carer study

Parent/carers were recruited from paediatric endocrinology clinics held at Birmingham Children's Hospital. A total of 27 parents/carers were recruited to this study. The target doses they prepared ranged from 0.5-7.5mg.

The methods used by the parents/carers within this study were representative of those reported by the 119 parents/carers within the survey. This is shown in Figure 1b. The most common method in both cases was to cut the tablet and administer the cut portion as a solid.

The accuracy of dosing of parent/carers is shown in Figure 3.

Figure 3: The accuracy of methods used by the parents/carers, the dashed red lines show ±20%.

Based on this data and the small sample size the most suitable methods included (i) crushing the tablet prior to dispersion and withdrawing the relevant volume and (ii) cutting the tablet. Dispersing the tablet in water without first crushing gave the widest range of doses with one dose being greater than 250% of the target dose.

4.4. Comparison of the parent/carers vs naïve participants

Table 1 compares the percentage of parents/carers versus the percentage of naïve participants who were able to produce a dose that was within 20% of the required dose.

	Quartered Tablets		Dispersed Tablets	
	Scored	**Unscored**	**Scored**	**Unscored**
Naive participants (n=	30	30	30	30
% within 80-120% target dose	56.7	70	66.7	86.7
Parent/carers (n=	18		7	
% within 80-120% target dose	83.3		42.9	

Table 1. The percentage of participants that prepared a dose within 20% of the target dose based on the population, method and tablet brand used.

When quartering tablets a greater proportion of the parent/carers were able to generate accurate doses for the child in their care. However, when dispersing tablets the parent/carers were less able to generate doses that were within 80-120% of the target dose.

Overall 74.1% of the parents/carers prepared doses that were within 20% of the stated dose of hydrocortisone using the scored (Auden Mackenzie brand of tablets). This suggests that parent/carers are somewhat better at obtaining accurate doses for the child in their care. However, it is important to support parents/carers at diagnosis as they will be naïve when preparing the initial doses for the child in their care.

5. Discussion

This study supports other work ((Orlu-Gul et al., 2013; Whitaker et al., 2015)) which have highlighted the need for age-appropriate hydrocortisone formulations. Parents and carers of children are required to manipulate tablets to provide an appropriate dose for the child in their care. The techniques described in this study reflect common practice across the UK as they are reported by those involved in the manipulation of hydrocortisone tablets. Although new formulations of low dose hydrocortisone are now available in the UK this study has relevance to the many other manipulations that parents undertake. Hydrocortisone, as a poorly soluble drug where dosing accuracy greatly improves therapy is a useful example to consider as it represents a “worse-case” scenario.

The results from the naïve study showed that hydrocortisone tablets without score lines gave more accurate results compared to those with score lines when producing a 2.5mg dose. The reason for this is unknown and in the case of the tablet splitting was unexpected as the presence of score lines was anticipated to generate superior data (Ciavarella et al., 2016). This study was limited to hydrocortisone tablets that were split into quarters either using score lines or using a tablet splitter on a circular tablet. Extrapolation of this data to other products should be undertaken with caution

as the shape and hardness of tablets have previously been demonstrated to affect accuracy following tablet splitting (Abu-Geras et al., 2017; Saimbi et al., 2016; van Riet-Nales et al., 2014).

Dispersion of the tablets to provide an accurate dose relied on participant crushing the tablet adequately prior to mixing with the water then withdrawal of a suspension of the hydrocortisone within the liquid. Greater errors were anticipated in this method due to the number of processing steps involved and the equipment available. The 10mL water volume was withdrawn typically using a 10mL syringe with graduations every 1mL which has an accuracy of ±0.5mL. This water was then combined with the 10mg tablet, typically this had been crushed between two teaspoons and stirred for a period from a few seconds up to 2 minutes. A 2.5mL sample was withdrawn using the same 10mL syringe (with the same error of ±0.5mL) which was used for subsequent analysis. The weight of the liquid volumes was measured to note the variability in volumes withdrawn (assuming equal density in all cases). In the naïve study the mass of the volume withdrawn ranged from 1.3 to 3.0g showing large variability in volume; however when this was correlated to dose there was limited correlation between the mass and the dose provided.

This study compared the ability of parents and carers (with experience of manipulating hydrocortisone tablets) to naïve participants in their ability to manipulate tablets to prepare a fixed dose. The results showed that a higher percentage of parents/carers were able to manipulate a tablet to provide a dose that was within 20% of the specified dose when simply cutting tablets. There are more processing steps involved in the dispersion of tablets method, therefore where possible an age appropriate dosage form or dose increment of 2.5mg should be prescribed for children who require hydrocortisone from a 10 mg tablet. One of the parent/carer target doses prepared by dispersion of a tablet was 0.5mg; a small change in the measured dose equates to a large percentage change due to the very low target dose. It is not possible to prepare such a low dose by cutting the solid tablet and this example illustrates the variability and issues in dosing very low doses to children from manipulation of a tablet. Many parent/carers have never received formal training on the use of syringes and are unaware of their limitations in terms of accuracy. It would be prudent to ensure that parent/carers are appropriately trained and have access to a range of syringes if manipulation via dispersion of a poorly soluble drug in a tablet form is their only means of generating the appropriate dose for the child in their care. From the parent/carer data there is insufficient evidence to promote a particular manipulation process yet where possible simply cutting tablets along score lines appeared to give a more accurate dose. Where possible, health care professionals should recommend cutting solid dosage forms rather than dispersing them when extracting a dose.

Provided that parents/carers have access to a tablet splitter there is no need to specify scored tablets on the prescription as the dose accuracy was not compromised in the naïve data set; this may also result in cost savings to the healthcare provider or payer. The NHS indicative price for the scored tablets is £84.45 for 30x10mg tablets whereas the unscored are £41.22 (Committee., 2017). However, this is only applicable to dosing multiples of 2.5mg. For lower doses dispersions are still required yet there should be training provided to all those involved in administration of manipulated medicines to children to ensure that the most suitable tools are being used. This may involve providing several syringes with a range of graduations.

6. Conclusions

More than 25% of children are at risk of receiving doses of hydrocortisone that are not within 25% of the prescribed dose which is likely to have a significant clinical impact. Hydrocortisone is used to mimic typical glucocorticoid levels therefore ideal treatment will match circadian rhythms. Optimizing glucocorticoid therapy during childhood is critical to prevent adrenal crisis, optimise linear growth, body composition, cardiovascular and bone health and ensure normal progression through puberty (Webb and Krone, 2015).

In the absence of 2.5mg age-appropriate hydrocortisone formulations a 10mg hydrocortisone tablet should be cut and the dose administered as a solid as this has shown good dose accuracy and avoids the poor palatability associated with dispersions of crushed tablets.

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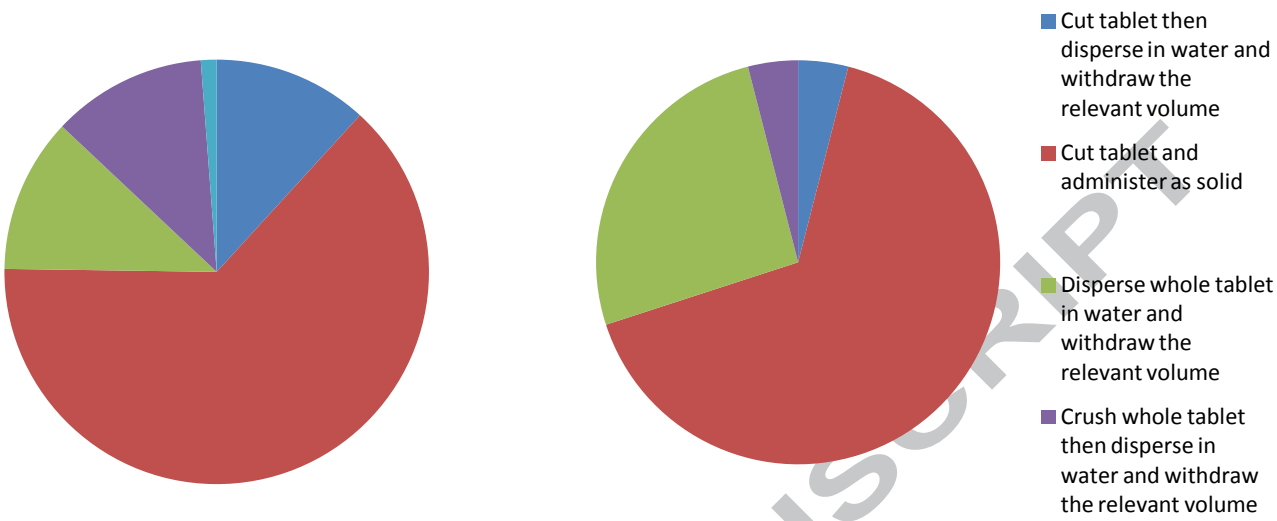

Figure 3: *Methods of manipulation of a 10mg hydrocortisone tablet (a) reported by parents/carers (n=119) to achieve an appropriate dose for the child in their care and (b) undertaken by parents/carers within this study (n=27).*

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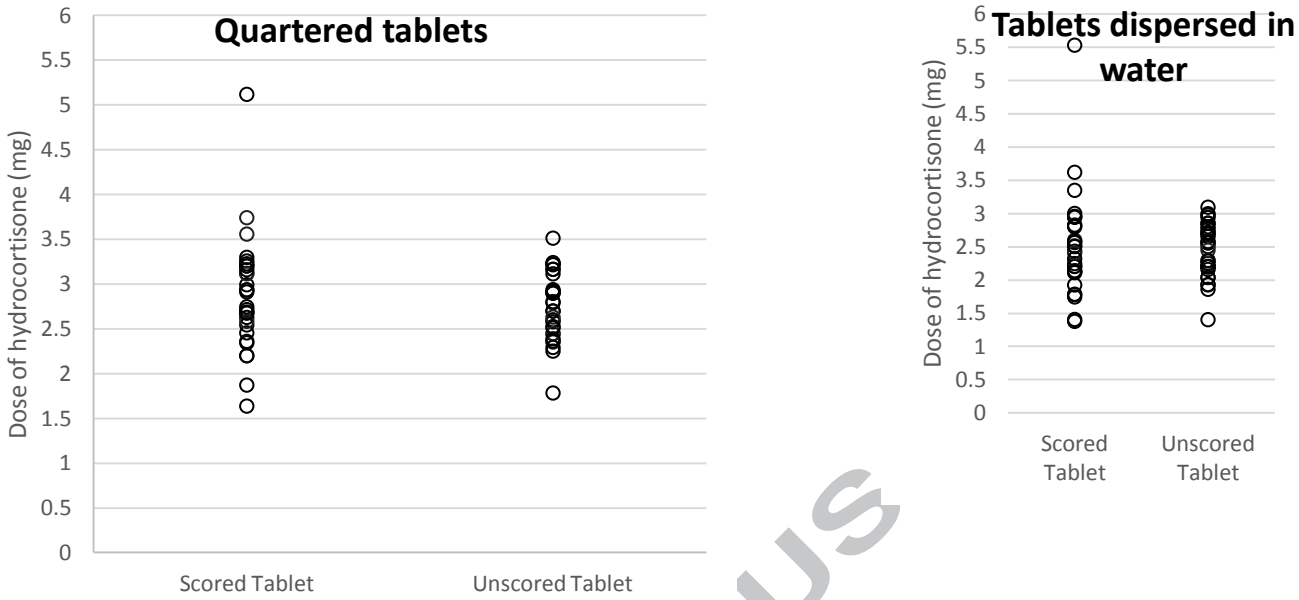


Figure 2: Comparison of the dose produced when non-scored and scored tablets were manipulated by naïve adults. The data points show each manipulation (n=30 in each group). The target dose was 2.5mg.

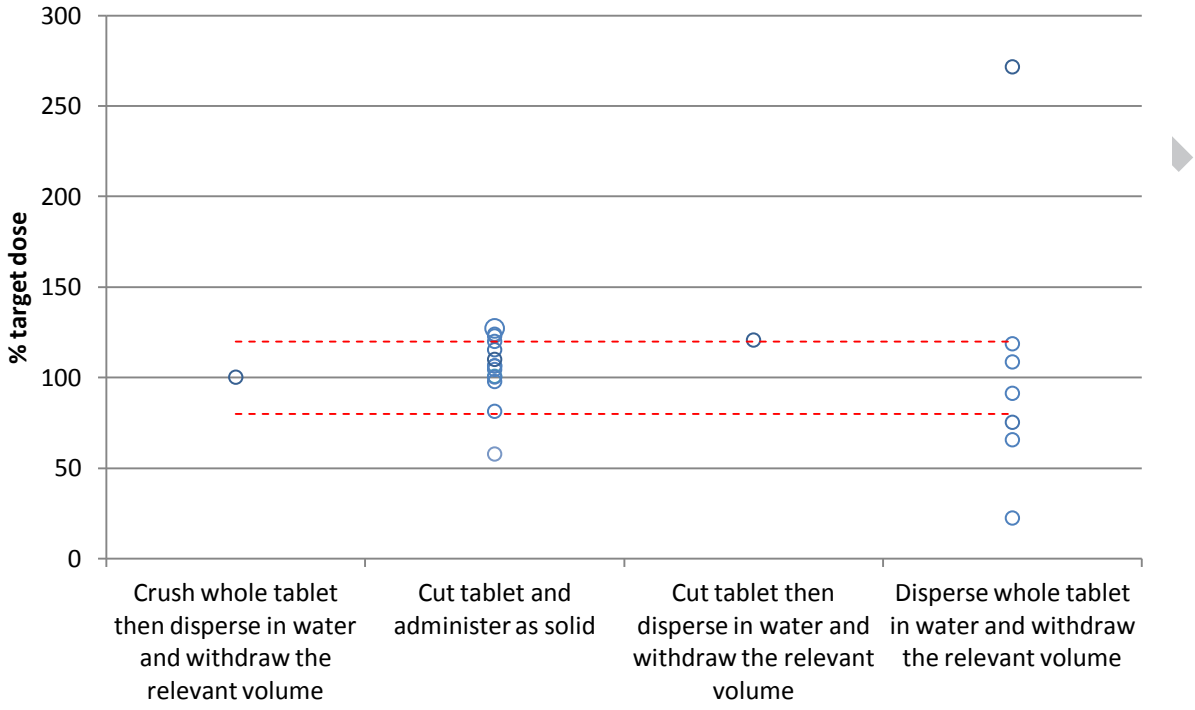
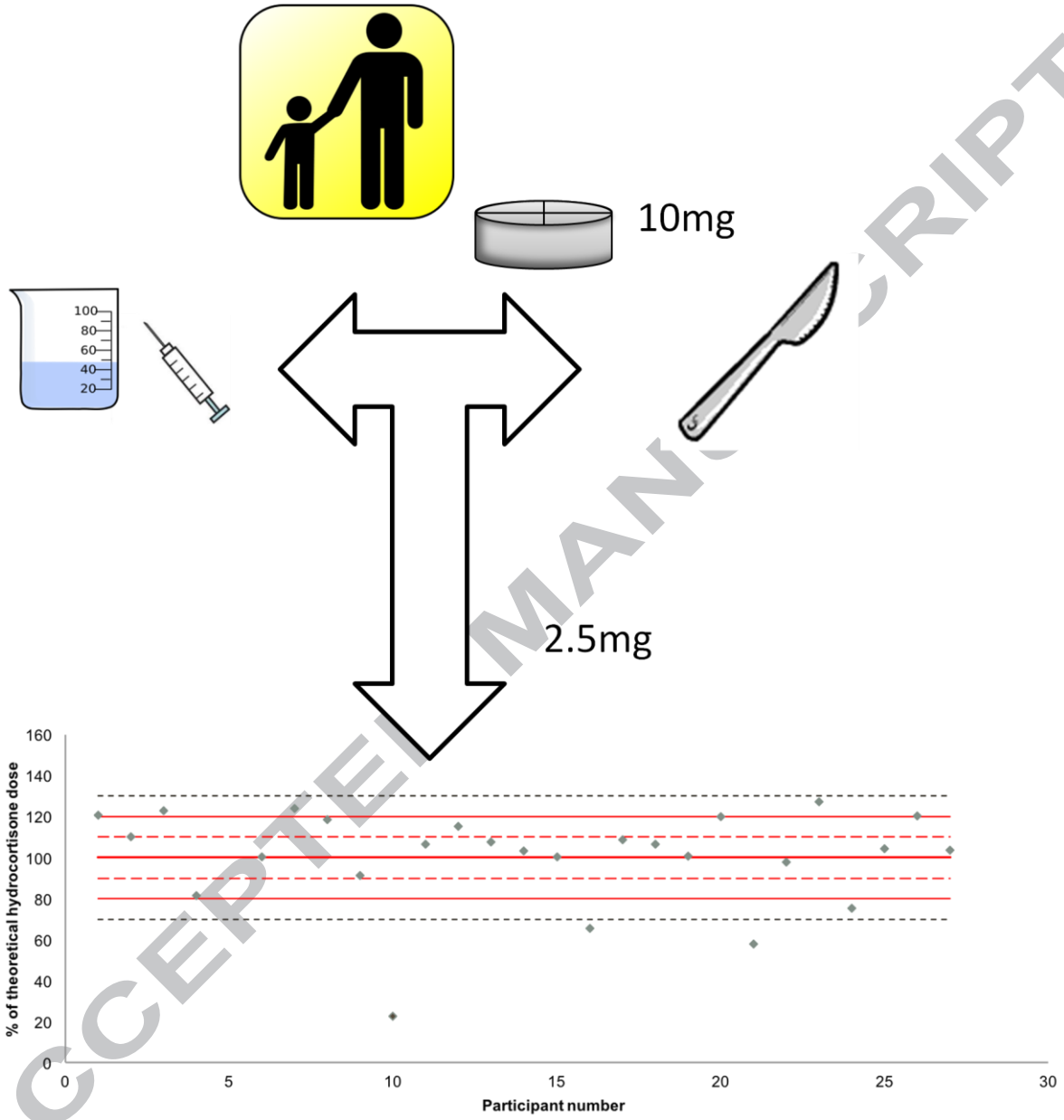


Figure 3: The accuracy of methods used by the parents/carers, the dashed red lines show ±20%.

Graphical abstract



	Quartered Tablets		Dispersed Tablets	
	Scored	**Unscored**	**Scored**	**Unscored**
Naive participants (n=	30	30	30	30
% within 80-120% target dose	56.7	70	66.7	86.7
Parent/carers (n=	18		7	
% within 80-120% target dose	83.3		42.9	

Table 1. The percentage of participants that prepared a dose within 20% of the target dose based on the population, method and tablet brand used.