This is a repository copy of *Hydrocortisone granules are bioequivalent when sprinkled onto food or given directly on the tongue*.

Article:

Hydrocortisone Granules are Bioequivalent When Sprinkled onto Food or Given Directly on the Tongue

Eleni Daniel, Dena Digweed, Jo Quirke, Bernard Voet, Richard J Ross, Madhu Davies

Hydrocortisone Granules are Bioequivalent When Sprinkled onto Food or Given Directly on the Tongue

Eleni Daniel[1], Dena Digweed[2], Jo Quirke[2], Bernard Voet[2], Richard J Ross[1], Madhu Davies[2]

1. University of Sheffield Medical School, Department of Oncology and Metabolism, Beech Hill Road, Sheffield, S10 2RX, UK

2. Diurnal Ltd, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ, UK

ORCiD numbers:

0000-0001-9222-9678

Ross

Richard J

0000-0003-4699-420X

Daniel

Eleni

0000-0003-2388-4753

Davies

Madhu

Background: Immediate-release hydrocortisone granules in capsules for opening in paediatric appropriate doses have recently been licensed for children with adrenal insufficiency. This study evaluated the bioavailability of hydrocortisone granules administered as sprinkles onto soft food and yoghurt compared to direct administration to the back of the tongue.

Methods: Randomised, three-period crossover study in 18 dexamethasone-suppressed healthy men. In each period the fasted participants received hydrocortisone granules 5mg either directly to the back of the tongue, or sprinkled onto soft food (applesauce), or yoghurt, followed by 240mL of water. Serum cortisol was measured by LC-MS/MS.

Results: The cortisol geometric mean C_{max} and AUC for direct administration, sprinkles onto yoghurt, and sprinkles onto soft food were: C_{max} 428, 426, 427 nmol/L & AUC_{0-inf} 859, 886, 844 h*nmol/L, & AUC_{0-t} 853, 882, 838 h*nmol/L respectively. The 90% confidence intervals (CI) for the ratios of C_{max}, AUC_{0-inf} & AUC_{0-t} for administration with soft food or yoghurt to direct administration were well within the bioequivalent range, 80-125%. Median T_{max} was similar between methods of administration: 0.63h

administered directly, 0.75h on soft food and 0.75h on yoghurt. No adverse events occurred during the study.

Conclusions: Hydrocortisone granules administered as sprinkles onto soft food or yoghurt but not mixed with are bioequivalent to those administered directly to the back of the tongue. Carers, parents or patients may choose to administer hydrocortisone granules either directly or sprinkled onto soft food or yoghurt.

Introduction

Hydrocortisone is the standard treatment for children with adrenal insufficiency who need life-long glucocorticoid hormone replacement (1,2). Congenital adrenal hyperplasia is the commonest cause of adrenal insufficiency in children and hydrocortisone replacement therapy needs to be initiated at diagnosis in the neonate to avoid death due to an adrenal crisis. Hydrocortisone doses are calculated according to body surface area and require careful adjustment as children grow to prevent under- or over-treatment. The total daily dose is usually 8-15mg/m^2 divided in 3-4 administrations with the highest level in the morning and doses as low as 0.5mg may be needed to appropriately titrate treatment (1-5).

Currently, children are medicated with compounded tablets prepared by pharmacists or carers to achieve paediatric appropriate doses (3). However, studies of compounding hydrocortisone reported that up to 25% of batches from pharmacies and 50% by parents were out of specification leading to clinically evident under- or over- treatment (6-8). Immediate-release hydrocortisone granules in paediatric-appropriate doses of 0.5, 1.0, 2.0 and 5.0mg have been shown to be well tolerated, easy to administer and to provide appropriate cortisol levels in neonates, infants and children with adrenal insufficiency (9). They have been designed for children with taste masking to cover the bitter taste of hydrocortisone. Administration is by opening the capsule and placing the granules onto a spoon or directly onto the child's tongue (4). The granules have been recently approved in the European Union for replacement therapy of adrenal insufficiency in infants, children and adolescents, from birth to < 18 years old.

Co-administration or sprinkling of medications onto food is a commonly used practice that provides flexibility and ease of administration for caregivers, particularly of young children or children with difficulty swallowing medication (10-12). Sprinkling medication onto food could alter its pharmacokinetic characteristics and it is not known if co-administration of hydrocortisone granules with food affects its bioavailability. This clinical study was performed in dexamethasone-suppressed healthy men to investigate if hydrocortisone granules administered sprinkled onto soft food or yoghurt are bioequivalent to hydrocortisone granules administered directly to the back of the tongue.

Methods

Study population:

The target sample size was 18 participants. Between June 2017 and July 2017 19 participants were enrolled. All participants signed an informed consent form and satisfied the inclusion and exclusion criteria. One participant withdrew for personal reasons after the second treatment period and was replaced. Serum cortisol concentration values from the 18 participants that completed all three treatment periods were included in the

pharmacokinetic analysis and safety and tolerability data from all 19 participants were collected and analysed (13).

The inclusion criteria were: healthy men aged 18-45 years with no significant medical history and a satisfactory baseline physical examination, body mass index (BMI) 18-30kg/m^2, normal baseline safety tests (biochemistry, haematology, electrocardiography, vital signs, urine analysis), negative urine drug screen, negative viral serology for HIV, Hepatitis B and C and use of effective contraception. The exclusion criteria were: use of concomitant medications other than acetaminophen within 14 days prior to dosing, vaccination within the previous month, any significant medical history including history of any gastrointestinal disorder likely to affect drug absorption, history of infections such as current or past tuberculosis, systemic fungal or viral infection and acute bacterial infection, sensitivity or contraindication to hydrocortisone or dexamethasone and/or any of the ingredients contained in soft food or yoghurt, clinically significant history of drug or alcohol abuse, positive alcohol screen prior to dosing, participation in another clinical trial or blood donation or transfusion ≥450mL within the previous 3 months, smoking within 6 months prior to the study, inability to communicate well with the Investigator and shift work.

Study design
Open label, randomised, single-dose, single-centre, three-period crossover study in dexamethasone-suppressed healthy men to determine the bioavailability of three methods of administration of hydrocortisone granules (Alkindi® Diurnal Ltd, UK): 1. Hydrocortisone granules administered directly to the back of the tongue; 2. Hydrocortisone granules sprinkled onto 5mL soft food (applesauce) and swallowed within 3 minutes of preparation; 3. Hydrocortisone granules sprinkled onto 5mL yoghurt and swallowed within 3 minutes of preparation. All doses were followed by 240 mL of water. *Primary endpoints* were the pharmacokinetic parameters: C_{max} (peak cortisol concentration), AUC_{0-t} (area under the curve from the time of administration to the final time-point of serum cortisol measurement at 12h), AUC_{0-inf} (area under the curve from the time of administration projected to infinity) of hydrocortisone granules 5mg administered as sprinkles onto soft food and yoghurt compared to hydrocortisone granules 5mg administered as dry granules to the back of the tongue. *Secondary endpoints* were T_{max} (time to peak cortisol concentration), safety and tolerability. The study design was based on the European Medicines Agency and the United States Food and Drug Administration guidelines for the design, conduct and evaluation of bioavailability and bioequivalence studies and complied with the ethical standards laid by the Declaration of Helsinki and regulatory bodies (13-17). The study was reviewed and approved by the Wales Research Ethics Committee (reference number: 17/WA/0114). Clinical Trials Authorisation was obtained from the Medicines and Healthcare Regulatory Agency prior to the start of the study in accordance with Part 3, Regulation 12 of the United Kingdom (UK) Statutory Instrument.

The study was performed at Simbec Research Ltd. All participants underwent successful screening and eligibility checks. They were admitted to the research facility on the afternoon of the first day (Day -1) and were discharged on the evening of the second day (Day 0) of each of the three treatment periods. Participants fasted from 22:00h on Day -1 to 12:00h on Day 0 and received three doses of dexamethasone 1mg with 240mL water at 22:00h on Day -1, 06:00h and 12:00h on Day 0 for suppression of their

endogenous cortisol production. On Day 0 of each treatment period 5mg hydrocortisone granules were administered at 08:00h by one of the three administration methods. The sequence of administration methods for each participant was determined by a randomisation code generated by SAS® software version 9.3 (SAS Institute Inc., Cary, NC, USA). For each dosing one 5mg capsule was opened, the contents either poured out onto a spoon or sprinkled onto soft food or yoghurt, and the capsule inspected for residual granules. Participants remained seated upright for 4h after dosing. There was a 7 day washout between treatment periods which is longer than 5 elimination half-lives (the half-life of hydrocortisone is approximately 100min) (13). Post-study assessments were performed 7 days after the last dose of hydrocortisone granules. Safety and tolerability assessments (adverse events, laboratory safety, vital signs and 12-lead electrocardiography) were recorded throughout the study.

Sample collection and analysis
Three blood samples were taken 5 minutes apart starting at 0.5h pre-dose to monitor cortisol suppression. Further blood was collected pre-dose and up to 12h post dosing on Day 0 for quantification of serum cortisol concentration (a total of 20 samples for each individual and treatment period with post-dose samples at 0 (-2mins), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 11, 12 hours). The blood samples were processed and kept at -20°C and analysed for serum cortisol concentration by liquid chromatography tandem mass spectrometry (LC-MS/MS) at Seirian Laboratories, Simbec Research Ltd, Cardiff, UK with assay performance data as previously reported (4).

Pharmacokinetic parameters
All participants received dexamethasone for suppression of endogenous cortisol levels to <1.8µg/dL (<50nmol/L). The mean of three samples taken 5 minutes apart 30 minutes pre-dose confirmed suppression and this mean determined the individual endogenous baseline serum cortisol. All serum cortisol concentrations thereafter were corrected for endogenous baseline levels by subtraction. Any negative baseline adjusted values or original concentrations below the limit of quantification were set to zero. The pharmacokinetic parameters were calculated following baseline cortisol correction and therefore reflect the concentrations achieved by the administration of hydrocortisone granules and not endogenous cortisol production (13). The pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, λ_z (elimination rate constant), $t_{1/2}$ (terminal half-life), CL/F (clearance), and V_z/F (apparent volume of distribution), were determined from the individual baseline adjusted serum cortisol concentration-time curve using WinNonlin Phoenix 6.3 (Certara L.P., St Louis, USA). The actual time of blood sampling was used in the calculation of the derived pharmacokinetic parameters.

Statistical analysis
Statistical analysis was performed using SAS® software version 9.3 (SAS Institute Inc., Cary, NC, USA). For the comparative pharmacokinetic analysis the reference administration method was hydrocortisone granules placed directly to the back of the tongue and the test administration methods were hydrocortisone granules sprinkled onto soft food or yoghurt. Following logarithmic transformation C_{max}, AUC_{0-t} and AUC_{0-inf} values were subjected to an analysis of variance (ANOVA) including fixed effects for sequence, period, treatment and subject nested within sequence. Point estimates and 90% two-sided confidence intervals (CI) for the difference between administration methods

were obtained using the residual mean square error obtained from the ANOVA model and back-transformed to give the CI for the ratio on the original scale (13). The administration methods were confirmed to be bioequivalent if the 90% CI of the ratio of the test to the reference administration method was within the 80 to 125% range (13). T_{max} was compared between treatments using separate Wilcoxon Signed-Rank tests at the two-sided 5% significance level to test the differences and Hodges-Lehmann estimates of the median difference between treatments and corresponding 95% CIs were calculated.

Results

Participants and demographics

Nineteen male participants were randomised and received at least one dose of hydrocortisone granules and were eligible for the safety population. Of these, one participant withdrew from the study for personal reasons and was replaced. Eighteen participants completed the three sequences of this study and were eligible for the pharmacokinetic analysis population.

Mean age (standard deviation sd, range) for the 19 participants who enrolled into the study was 31.4 years (8.71, 21 - 44) and mean BMI (sd, range) was 25.96 (2.75, 20.7 - 29.7). All participants had adequate baseline cortisol suppression with mean pre-dose serum cortisol concentrations <1.8μg/dL (<50nmol/L) at each of the three treatment days (Day 0) prior to administration of hydrocortisone granules. Overall median baseline cortisol for each administration method (direct/ yoghurt/ soft food) (range) was 15.3 (10.6, 72.4)/ 15.9 (12.5-26.6)/ 14.6 (9.85-81.8).

Pharmacokinetic analysis

Following a single 5mg dose of hydrocortisone granules the mean serum cortisol concentration over time curve was plotted for each of the three administration methods, to assess the rate and extent of absorption. Figure 1 shows the mean and the SD of the serum cortisol concentration-time curves adjusted for baseline cortisol for administration as dry granules, sprinkles onto soft food, and sprinkles onto yoghurt. The curves were very similar between the 3 treatments; there was an initial rapid increase in cortisol concentration as expected for an immediate release formulation followed by a gradual decline.

Pharmacokinetic parameters were calculated from the baseline adjusted serum cortisol concentration for each administration method and are shown in Table 1. For direct administration, administration onto yoghurt, administration onto soft food the maximum cortisol concentration C_{max} nmol/L (geometric mean) was 428, 426, 427; AUC_{0-t} (nmol*h/L) was 853, 882, 838; AUC_{0-inf} (nmol*h/L) was 859, 886, 844. There was no statistical difference in C_{max} or AUC between methods of administration. T_{max} (median h, range) for dry granules was (0.625, 0.5-1.25), sprinkles onto soft food (0.75, 0.25-1.25), sprinkles onto yoghurt (0.75, 0.25-1.5) with no relevant difference between methods of administration.

Comparative bioavailability

The ratios of the geometric least square means of the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} for the test (soft food or yoghurt) to the reference (dry granules) administration methods were calculated to compare the bioavailability between the administration methods. The 90% CI of the ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} were well within the 80-125% limits which confirmed that 5mg hydrocortisone granules

administered as sprinkles onto soft food or yoghurt is bioequivalent to 5mg administered directly as dry granules (Table 2). Soft food to direct administration ratios and 90% CI were: C_{max} 99.68 (93.98-105.72), AUC0-t 98.24 (94.42-102.21), AUC_{0-inf} 98.21 (94.24-102.36). Yoghurt to direct administration ratios and 90% CI were: C_{max} 99.43 (94.33-104.80), AUC_{0-t} 103.33 (94.80-112.62), AUC_{0-inf} 103.07 (94.55-112.35).

Safety and tolerability

Hydrocortisone granules were safe and well tolerated. There were no adverse events and no tolerability issues. Safety laboratory tests (biochemistry, haematology, urine analysis), vital signs, and 12-lead electrocardiography parameters were satisfactory at baseline and showed no relevant changes over time. There were no relevant physical examination findings during the study. All treatment periods exhibited similar safety profile and drug tolerability.

Discussion

These data show that hydrocortisone granules sprinkled onto soft food and yoghurt are bioequivalent to granules administered directly to the back of the tongue in dexamethasone-suppressed healthy men. Test-to-reference ratios of the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} were well within the 80-125% limits required to confirm bioequivalence. The peak and total cortisol exposure from hydrocortisone granules measured as C_{max} and AUC was the same for the three administration methods and there was no relevant difference in the rate of absorption measured by T_{max}. In this short study, hydrocortisone granules were safe and well tolerated, which confirms previous findings (4,9).

Administration of a medication mixed with food is a drug manipulation and could affect the absorption of the active ingredient; for example, due to exposure to different pH (18). The medicines regulatory agencies in the US and Europe, the FDA and EMA respectively, recommend that any such manipulation of drug administration should be studied and verified 'with respect to its potential impact on efficacy and safety' which may include bioavailability studies to confirm if medications sprinkled onto food have the same bioavailability as direct administration (18,19). In accordance with this advice several studies have assessed the bioequivalence of sprinkles versus the intact form of the medication in children and adults (20-25). This study was designed to compare the bioavailability of sprinkling the hydrocortisone granules onto food compared to the approved use as dry granules to the back of the tongue and confirmed that sprinkling hydrocortisone granules onto food does not change its pharmacokinetics. Mixing or stirring of hydrocortisone granules with food is not recommended and was not assessed due to hydrocortisone granules having a taste-masking layer added to neutralise the bitter taste of hydrocortisone which could dissolve if granules are stirred into food. The results on direct administration of dry granules in this study mirror previous findings by Whitaker et al who tested the pharmacokinetics of single administration of hydrocortisone granules in varying doses (0.5, 2.0, 5.0 and 10mg) in 16 dexamethasone-suppressed healthy adult men (4). The dose tested in our study (5mg) is part of the dose range used to treat adrenal insufficiency both in paediatric and adult patients (4,26). In the paediatric population the pharmacokinetics of hydrocortisone granules have been studied in twenty-four young children with adrenal insufficiency (1month to 6 years old) with results comparable to the healthy adult men (9). The palatability of hydrocortisone

granules was assessed in healthy men who found that the taste was neutral (neither good nor bad) [4].

Administering medications to children can be challenging and many children report problems swallowing solid and liquid medicines in the absence of underlying neurological disease (27). Compounding of medications to administer as powder and mixing medication with food, juice, and sweeteners is a common approach that parents and paediatric nurses take to improve compliance especially when there are problems swallowing or bitter tasting medications (10,12,28,29) and joint administration of medicines with food or drink is an effective strategy to ensure swallowing in children (11). Liquid formulations are favoured by young children and contain sweeteners to mask any bitter taste. However, such hydrocortisone suspensions are not licensed, the hydrocortisone content may be inconsistent leading to treatment failures (30) and may contain sucrose that can have adverse effects on teeth with long-term use (31). Food is chewed to <2mm (32) therefore sprinkling beads of smaller size onto food should not cause problems swallowing. Furthermore, sprinkling of medication may have advantages in improving adherence and facilitate caregiving of patients with swallowing difficulties and this approach has been explored in children and elderly patients with potential swallowing and adherence difficulties such as in Alzheimer's disease, attention-deficit hyperactivity disorder, and epilepsy (21,22,24,25).

Dosing errors are common in young children and cause 20% of all medication errors in acute neonatal care (33). This is due to the lack of paediatric-appropriate dosage and the common use of unlicensed, 'off-label' and/or compounded medicines that don't have appropriate labelling, safety or dosing data (33,34). In children adverse drug reactions are more common with unlicensed medications (35) and international initiatives have tried to address these issues and proposed approaches to improve availability of paediatric-appropriate formulations and treatment outcomes (29,36). For children with adrenal insufficiency compounding hydrocortisone from adult tablets and splitting of adult tablets provides much needed flexibility in dosing however recent studies show significant inaccuracy in the content of active ingredient leading to clinically significant consequences including Cushing's syndrome (6-8).

The FDA defines yoghurt products as having a pH of up to 4.6 (37) . The pH of fresh plain yoghurt is around 4.3-4.6 and this decreases rapidly with storage time to 4.0-4.2 (38-40). The pH of different yoghurt products vary within these ranges and is affected by the time since production, the initial dairy culture used, addition of fruit or fruit puree and the type of fruit added (38). The addition of sweeteners only slightly reduces pH (41) (range of pH 3.94-3.98 vs 4.09-3.94). For comparison, the pH of applesauce is lower than yoghurt and is between 3.1-3.6. Since the pharmacokinetic analysis in our study showed bioequivalence between sprinkles on yoghurt and applesauce we believe that any commercial yoghurt product with a pH in the above ranges could be used as a vehicle for the sprinkling of hydrocortisone granules.

The strengths of the study lie in the 3-period crossover design that ensures same within-participant control and thus less variability of the data obtained. A double- blind design was not required as the primary objective of the study was to compare the bioavailability of hydrocortisone granules administered via 3 different methods. The pharmacokinetic parameters investigated were objective, and the sequence of administration methods was randomly allocated for each individual therefore the open

label design conferred minimal risk of introducing bias into the study. Further strengths of this study are the accurate measurement of cortisol with LC-MS/MS and the complete suppression of endogenous cortisol levels in all participants ensuring that cortisol measured was the result of treatment and not endogenous production. The study population was healthy young men and this can be a potential limitation as hydrocortisone granules are designed for the paediatric population; however, the absorption of hydrocortisone granules was previously studied in twenty-four young children and the results were comparable to the adult population (9). Children may have differences in physiology and pharmacokinetics but clinical studies are performed in children only under exceptional circumstances and this approach is considered adequate by regulatory agencies (13,15,17). Dexamethasone has been reported *in vivo* and *in vitro* to induce CYP3A4 of which hydrocortisone is a substrate (42-44). It is possible that dexamethasone could alter the pharmacokinetics of hydrocortisone but as each limb of the trial was treated in the same way this shouldn't affect the comparative bioavailability under different modes of administration.

In conclusion it has been demonstrated that hydrocortisone granules can be administered either directly or sprinkled onto soft food (applesauce) or yoghurt which, when consumed within 3 minutes, did not result in any significant or clinically relevant change of overall drug exposure and rate of absorption. Based on the data shown patients have the flexibility of multiple administration methods and prescribers can safely recommend sprinkled administration of hydrocortisone granules. Carers and children may welcome the flexibility of different options for administering hydrocortisone to young children on multiple-time daily dosing and it would be interesting to see if this flexibility improves adherence to treatment, disease management and clinical outcomes.

Corresponding author: Professor Richard J Ross, The University of Sheffield, The Medical School, Sheffield S10 2RX, UK. E-Mail: r.j.ross@sheffield.ac.uk

Disclosure summary:
RJR is a Director of Diurnal Ltd and owns stock, JQ & MD are employed by Diurnal Ltd, and BV & DD have received Consulting fees from Diurnal Ltd

References
1. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE, Ritzen M, White PC, Endocrine S. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology and metabolism 2010; 95:4133-4160
2. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism 2016; 101:364-389

3.   Joint LWPES/ESPE CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. The Journal of clinical endocrinology and metabolism 2002; 87:4048-4053

4.   Whitaker MJ, Spielmann S, Digweed D, Huatan H, Eckland D, Johnson TN, Tucker G, Krude H, Blankenstein O, Ross RJ. Development and testing in healthy adults of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency. The Journal of clinical endocrinology and metabolism 2015; 100:1681-1688

5.   Daniel E, Sandrk M, Blankenstein O, Neumann U, Claahsen-Van der Grinten H, Van der Linde A, Darendeliler F, Pyrazoglu S, Mendonca BB, Bachega TSS, Miranda MC, Acerini C, Guran T, Birkebaek NH, Cools M, Milenkovic T, Bonfig W, Tomlinson JW, Ahmed SF, Elsedfy H, Balsamo A, Hannema SE, Higham C, Atapattu N, Lichiardopol C, Krone RE, Mohnike K, Krone N. 2017 Defining the dose, type and timing of glucocorticoid and mineralocorticoid replacement in 256 children and adults with congenital adrenal hyperplasia (CAH) in the I-CAH registry. Poster presented at ESPE 2017; 2017.

6.   Neumann U, Burau D, Spielmann S, Whitaker MJ, Ross RJ, Kloft C, Blankenstein O. Quality of compounded hydrocortisone capsules used in the treatment of children. European journal of endocrinology / European Federation of Endocrine Societies 2017; 177:239-242

7.   Webb EA, Watson C, Kerr S, Davies JH, Stirling H, Batchelor H. 2017 Hydrocortisone tablets: human factors in manipulation and their impact on dosing accuracy. British Society for Paediatric Endocrinology and Diabetes; 2017; Newcastle, UK.

8.   Barillas JE, Eichner D, Van Wagoner R, Speiser PW. Iatrogenic Cushing Syndrome in a Child With Congenital Adrenal Hyperplasia: Erroneous Compounding of Hydrocortisone. The Journal of clinical endocrinology and metabolism 2018; 103:7-11

9.   Neumann U, Whitaker MJ, Wiegand S, Krude H, Porter J, Davies M, Digweed D, Voet B, Ross RJ, Blankenstein O. Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency. Clinical endocrinology 2018; 88:21-29

10.   Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract 2012; 20:191-198

11.   van Riet-Nales DA, Ferreira JA, Schobben AF, de Neef BJ, Egberts TC, Rademaker CM. Methods of administering oral formulations and child acceptability. International journal of pharmaceutics 2015; 491:261-267

12.   Gardiner P, Dvorkin L. Promoting medication adherence in children. Am Fam Physician 2006; 74:793-798

13.   European Medicines Agency. Guideline on the Investigation of bioequivalence. www.ema.europa.eu: EMA;2010.

14.   FDA. Guidance for the Industry: Statistical Approaches to Establishing Bioequivalence. Center for Drug Evaluation and Research (CDER);2001.

15.   The Association of the British Pharmaceutical Industry. Guidelines for phase 1 clinical trials. http://www.abpi.org.uk2012 edition.

16.   FDA. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. www.fda.gov: Center for Drug Evaluation and Research (CDER);2002.

17.   FDA. Guidance for the Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. Center for Drug Evaluation and Research (CDER);2003.

18.   van Riet-Nales DA, Wang S, Saint-Raymond A, Robert JL. The EMA quality guideline on the pharmaceutical development of medicines for paediatric use. International journal of pharmaceutics 2012; 435:132-134

19.   FDA. Guidance for Industry: Size of Beads in Drug Products Labeled for Sprinkle. Center for Drug Evaluation and Research (CDER);2012.

20.   Musiime V, Fillekes Q, Kekitiinwa A, Kendall L, Keishanyu R, Namuddu R, Young N, Opilo W, Lallemant M, Walker AS, Burger D, Gibb DM, Team C-T. The Pharmacokinetics and Acceptability of Lopinavir/Ritonavir Minitab Sprinkles, Tablets, and Syrups in African HIV-Infected Children. Jaids-J Acq Imm Def 2014; 66:148-154

21.   Garnett WR, Levy B, McLean AM, Zhang Y, Couch RA, Rudnic EM, Pellock JM, Belendiuk GW. Pharmacokinetic evaluation of twice-daily extended-release carbamazepine (CBZ) and four-times-daily immediate-release CBZ in patients with epilepsy. Epilepsia 1998; 39:274-279

22.   Boinpally R, Chen L, Zukin SR, McClure N, Hofbauer RK, Periclou A. A novel once-daily fixed-dose combination of memantine extended release and donepezil for the treatment of moderate to severe Alzheimer's disease: two phase I studies in healthy volunteers. Clin Drug Investig 2015; 35:427-435

23.   Kernitsky L, O'Hara KA, Jiang P, Pellock JM. Extended-release divalproex in child and adolescent outpatients with epilepsy. Epilepsia 2005; 46:440-443

24.   Adjei A, Teuscher NS, Kupper RJ, Chang WW, Greenhill L, Newcorn JH, Connor DF, Wigal S. Single-dose pharmacokinetics of methylphenidate extended-release multiple layer beads administered as intact capsule or sprinkles versus methylphenidate immediate-release tablets (Ritalin((R))) in healthy adult volunteers. J Child Adolesc Psychopharmacol 2014; 24:570-578

25.   Pentikis HS, Simmons RD, Benedict MF, Hatch SJ. Methylphenidate bioavailability in adults when an extended-release multiparticulate formulation is administered sprinkled on food or as an intact capsule. J Am Acad Child Psy 2002; 41:443-449

26.   Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT, Ross RJ. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clinical endocrinology 2004; 61:367-375

27.   Mennella JA, Roberts KM, Mathew PS, Reed DR. Children's perceptions about medicines: individual differences and taste. BMC Pediatr 2015; 15:130

28.   Boztepe H, Ozdemir H, Karababa C, Yildiz O. Difficulties experienced during preparation and administration of oral drugs. Turk Pediatri Ars 2014; 49:231-237

29.   Nahata MC, Allen LV, Jr. Extemporaneous drug formulations. Clinical therapeutics 2008; 30:2112-2119

30.   Merke DP, Cho D, Calis KA, Keil MF, Chrousos GP. Hydrocortisone suspension and hydrocortisone tablets are not bioequivalent in the treatment of children with

congenital adrenal hyperplasia. The Journal of clinical endocrinology and metabolism 2001; 86:441-445

31. Goyal A, Bhadravathi MC, Kumar A, Narang R, Gupta A, Singh H. Comparison of Dental Caries Experience in Children Suffering From Epilepsy with and without Administration of Long Term Liquid Oral Medication. J Clin Diagn Res 2016; 10:ZC78-82

32. Nagavelli LR, Lionberger RA, Sayeed VA, Yu L, Allgire J, Smith A, Wokovich A, Westenberger BJ, Buhse L. Analysis of bead sizes for MR capsules labeled for sprinkle. AAPS PharmSciTech 2010; 11:1508-1510

33. Sutcliffe K, Stokes G, O'Mara A, Caird J, Hinds K, Bangpan M, Kavanagh J, Dickson K, Stansfield C, Hargreaves K, Thomas J. Paediatric medication error: A systematic review of the extent and nature of the problem in the UK and international interventions to address it. Social Science Research Unit.

34. Stuart R. Levine MRC, Nicholas R. Blanchard, Frank Frederico, Merrell Magelli, Chris Lomax, Gary Greiner, Robert L. Poole, Carlton K. K. Lee, , Lesko A. Guidelines for preventing medication errors in pediatrics. The Journal of Pediatric Pharmacology and Therapeutics 2001; 6:427-443

35. Sutherland A, Waldek S. It is time to review how unlicensed medicines are used. Eur J Clin Pharmacol 2015; 71:1029-1035

36. Giacoia GPM, Taylor-Zapata PM, Mattison DM. Need for appropriate formulations for children: the national institute of child health and human development-pediatric formulations initiative, part 1. Int J Pharm Compd 2007; 11:5-8

37. FDA. Food For Human Consumption: Milk, Cream and Yoghurt. In: FDA, ed. Vol 21CFR131.200.

38. Tan G, Korel F. Quality of flavored yoghurt containing added coffee and sugar. Journal of Food Quality 2007; 30:342-356

39. Kailasapathy K, Harmstorf I, Phillips M. Survival of Lactobacillus acidophilus and Bifidobacterium animalis ssp. lactis in stirred fruit yogurts. LWT-Food Science and Technology 2008; 41:1317-1322

40. Dave RI, Shah NP. Viability of yoghurt and probiotic bacteria in yoghurts made from commercial starter cultures. International Dairy Journal 1997; 7:31-41

41. Keating KR, White CH. Effect of alternative sweeteners in plain and fruit-flavored yoghurts. Journal of Dairy Science 1990; 73:54-62

42. Pascussi JM, Drocourt L, Gerbal-Chaloin S, Fabre JM, Maurel P, Vilarem MJ. Dual effect of dexamethasone on CYP3A4 gene expression in human hepatocytes. Sequential role of glucocorticoid receptor and pregnane X receptor. Eur J Biochem 2001; 268:6346-6358

43. Watkins PB, Wrighton SA, Maurel P, Schuetz EG, Mendez-Picon G, Parker GA, Guzelian PS. Identification of an inducible form of cytochrome P-450 in human liver. Proc Natl Acad Sci U S A 1985; 82:6310-6314

44. Watkins PB, Wrighton SA, Schuetz EG, Molowa DT, Guzelian PS. Identification of glucocorticoid-inducible cytochromes P-450 in the intestinal mucosa of rats and man. J Clin Invest 1987; 80:1029-1036

Figure 1: Mean adjusted serum cortisol concentration and standard deviation over time after administration of hydrocortisone granules in 18 fasted, dexamethasone-suppressed

healthy men. The serum cortisol concentrations for each participant were corrected for endogenous baseline cortisol by subtraction of the mean pre-dose value.

Table 1: Pharmacokinetic parameters calculated from baseline adjusted serum cortisol following a dose of 5mg hydrocortisone granules administered by three methods

	Statistic	Direct administration	Soft food	Yoghurt
Cmax (nmol/L)	Geometric Mean SD	428	427	426
		82	78	88
AUC0-t (nmol/L*h)	Geometric Mean SD	853	838	882
		203	198	161
AUC0-inf (nmol/L*h)	Geometric Mean SD	859	844	886
		204	197	162
Tmax (h)	Median Range	0.63	0.75	0.75
		0.5, 1.25	0.25, 1.25	0.25, 1.5
λ_z (1/h)	Geometric Mean SD	0.48	0.53	0.55
		0.46	0.24	0.09
t1/2 (h)	Geometric Mean SD	1.4	1.3	1.3
		0.6	0.4	0.2

sd: standard deviation, cv: coefficient of variation, Geom: geometric mean, Cmax: maximum serum cortisol concentration after administration, Tmax: time to Cmax, AUC0-t: area under the serum cortisol concentration time curve from administration to the end of the sampling at 12h, AUC0-inf: area under the serum cortisol concentration time curve from administration extrapolated to infinite time, λ_z: terminal rate constant, t1/2: serum cortisol concentration half-life

Table 2: Bioequivalence comparison between the reference administration method (direct administration of dry hydrocortisone granules to the back of the tongue) and the test administration methods (hydrocortisone granules sprinkled onto yoghurt and sprinkled onto soft food)

	Granules sprinkled onto soft food to direct administration of dry granules		Granules sprinkled onto yoghurt to direct administration of dry granules	
	Geometric LSmean ratio	90% CI	Geometric LSmean ratio	90% CI
Cmax (nmol/L)	99.68	93.98-105.72	99.43	94.33-104.80
AUC0-t (nmol/L*h)	98.24	94.42-102.21	103.33	94.80-112.62
AUC0-inf (nmol/L*h)	98.21	94.24-102.36	103.07	94.55-112.35

Cmax: maximum serum cortisol concentration after administration, Tmax: time to Cmax, AUC0-t: area under the serum cortisol concentration time curve from administration to the end of the sampling at 12h, AUC0-inf: area under the serum cortisol concentration time curve from administration extrapolated to infinite time.

Adjusted Serum Cortisol concentration over time