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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] and Madhu Davies[2]

[1]Department of Oncology and Metabolism, University of Sheffield Medical School, Sheffield, S10 2RX, United Kingdom; and [2]Diurnal Ltd, Cardiff Medicentre, Cardiff, CF14 4UJ, United Kingdom

ORCiD numbers: 0000-0003-4699-420X (E. Daniel); 0000-0001-9222-9678 (R. J. Ross); 0000-0003-2388-4753 (M. Davies).

Background: Immediate-release hydrocortisone granules in capsules for opening in pediatric-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 yogurt compared with direct administration to the back of the tongue.

Methods: Randomized, 3-period crossover study in 18 dexamethasone-suppressed healthy men. In each period, the fasted participants received 5 mg hydrocortisone granules either directly to the back of the tongue or sprinkled onto soft food (applesauce), or yogurt, followed by 240 mL of water. Serum cortisol was measured by liquid chromatography tandem mass spectometry.

Results: The cortisol geometric mean maximum concentration (C_{max}) and area under the curve (AUC) for direct administration, sprinkles onto yogurt, and sprinkles onto soft food were: C_{max} 428, 426, 427 nmol/L and $AUC_{0\text{-}inf}$ 859, 886, 844 h × nmol/L, and $AUC_{0\text{-}t}$ 853, 882, 838 h × nmol/L respectively. The 90% CI for the ratios of C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ for administration with soft food or yogurt to direct administration were well within the bioequivalent range, 80% to 125%. Median time to Cmax (T_{max}) was similar between methods of administration: 0.63 hours administered directly, 0.75 hours on soft food and 0.75 hours on yogurt. No adverse events occurred during the study.

Conclusions: Hydrocortisone granules administered as sprinkles onto soft food or yogurt but not mixed with these foods 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 yogurt.

Freeform/Key Words: hydrocortisone, pediatric, glucocorticoid replacement, adrenal insufficiency, congenital adrenal hyperplasia

Hydrocortisone is the standard treatment for children with adrenal insufficiency who need lifelong glucocorticoid hormone replacement [1, 2]. Congenital adrenal hyperplasia is the most common cause of adrenal insufficiency in children, and hydrocortisone replacement therapy needs to be initiated at diagnosis in the neonate to avoid death resulting from an adrenal crisis. Hydrocortisone doses are calculated according to body surface area and require careful adjustment as children grow to prevent under- or overtreatment. The total daily dose

Abbreviations: AUC, area under the curve; $AUC_{0\text{-}t}$, area under the curve from the time of administration to the final timepoint of serum cortisol measurement at 12 hours; $AUC_{0\text{-}inf}$, AUC from the time of administration projected to infinity; C_{max}, maximum cortisol concentration; FDA, US Food and Drug Administration; T_{max}, time to peak cortisol concentration.

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is usually 8 to 15 mg/m^2 divided in 3 to 4 administrations, with the highest level in the morning; doses as low as 0.5 mg may be needed to appropriately titrate treatment [1–5].

Currently, children are medicated with compounded tablets prepared by pharmacists or carers to achieve pediatric-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 overtreatment [6–8]. Immediate-release hydrocortisone granules in pediatric-appropriate doses of 0.5, 1.0, 2.0, and 5.0 mg have been shown to be well tolerated; easy to administer; and 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.

Coadministration 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 was not known if coadministration of hydrocortisone granules with food affected its bioavailability. This clinical study was performed in dexamethasone-suppressed healthy men to investigate if hydrocortisone granules administered sprinkled onto soft food or yogurt are bioequivalent to hydrocortisone granules administered directly to the back of the tongue.

1. Methods

A. 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 3 treatment periods were included in the pharmacokinetic analysis and safety and tolerability data from all 19 participants were collected and analyzed [13].

The inclusion criteria were: healthy men aged 18 to 45 years with no significant medical history and a satisfactory baseline physical examination, body mass index 18 to 30 kg/m^2, normal baseline safety tests (biochemistry, hematology, electrocardiography, vital signs, urine analysis), negative urine drug screen, negative viral serology for HIV and hepatitis B and C, and use of effective contraception. The exclusion criteria were: use of concomitant medications other than acetaminophen within 14 days before dosing, vaccination within the previous month, any important 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 yogurt, clinically important history of drug or alcohol abuse, positive alcohol screen before dosing, participation in another clinical trial or blood donation or transfusion ≥450 mL within the previous 3 months, smoking within 6 months before the study, inability to communicate well with the investigator, and shift work.

B. Study Design

This was an open-label, randomized, single-dose, single-center, three-period crossover study in dexamethasone-suppressed healthy men to determine the bioavailability of three methods of administration of hydrocortisone granules (Alkindi®, Diurnal Ltd., Cardiff, United Kingdom): (i) hydrocortisone granules administered directly to the back of the tongue; (ii) hydrocortisone granules sprinkled onto 5 mL of soft food (applesauce) and swallowed within 3

minutes of preparation; or (iii) hydrocortisone granules sprinkled onto 5 mL of yogurt and swallowed within 3 minutes of preparation. All doses were followed by 240 mL of water.

Primary end points were the pharmacokinetic parameters: maximum cortisol concentration (C_{max}), area under the curve from the time of administration to the final timepoint of serum cortisol measurement at 12 hours ($AUC_{0\text{-}t}$), AUC from the time of administration projected to infinity ($AUC_{0\text{-}inf}$) of 5-mg hydrocortisone granules administered as sprinkles onto soft food and yogurt compared with 5-mg hydrocortisone granules administered as dry granules to the back of the tongue.

Secondary endpoints were time to maximum cortisol concentration (T_{max}), safety, and tolerability. The study design was based on the European Medicines Agency and the US Food and Drug Administration (FDA) 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 authorization was obtained from the Medicines and Healthcare Regulatory Agency before the start of the study in accordance with Part 3, Regulation 12, of the UK Statutory Instrument.

The study was performed at Simbec Research Ltd., Cardiff, United Kingdom. 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 22:00 on day −1 to 12:00 on day 0 and received three doses of 1 mg dexamethasone with 240 mL water at 22:00 on day −1 and 06:00 and 12:00 on day 0 for suppression of their endogenous cortisol production. On day 0 of each treatment period, 5-mg hydrocortisone granules were administered at 08:00 by one of the three administration methods. The sequence of administration methods for each participant was determined by a randomization code generated by SAS® software, version 9.3 (SAS Institute Inc., Cary, NC). For each dosing, one 5-mg capsule was opened, the contents either poured out onto a spoon or sprinkled onto soft food or yogurt, and the capsule inspected for residual granules. Participants remained seated upright for 4 hours 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 ~100 minutes) [13]. Poststudy 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.

C. Sample Collection and Analysis

Three blood samples were taken 5 minutes apart starting at 30 minutes predose to monitor cortisol suppression. Further blood was collected predose and up to 12 hours postdosing on day 0 for quantification of serum cortisol concentration [a total of 20 samples for each individual and treatment period with postdose samples at 0 (−2 minutes), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 11, and 12 hours]. The blood samples were processed and kept at −20°C and analyzed for serum cortisol concentration by liquid chromatography tandem mass spectrometry at Seirian Laboratories, Simbec Research Ltd, with assay performance data as previously reported [4].

D. Pharmacokinetic Parameters

All participants received dexamethasone for suppression of endogenous cortisol levels to <1.8 μg/dL (<50 nmol/L). The mean of 3 samples taken 5 minutes apart 30 minutes predose confirmed suppression; 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}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, elimination rate constant, terminal half-life, clearance, and 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, MO). The actual time of blood sampling was used in the calculation of the derived pharmacokinetic parameters.

E. Statistical Analysis

Statistical analysis was performed using SAS software, version 9.3. For the comparative pharmacokinetic analysis, the reference administration method was hydrocortisone granules placed directly to the back of the tongue; the test administration methods were hydrocortisone granules sprinkled onto soft food or yogurt. Following logarithmic transformation C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ values were subjected to ANOVA, including fixed effects for sequence, period, treatment, and subject nested within sequence. Point estimates and 90% two-sided CI for the differences 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.

2. Results

A. Participants and Demographics

Nineteen male participants were randomized, 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 for the 19 participants who enrolled into the study was 31.4 years (SD, 8.71; range, 21 to 44) and mean body mass index was 25.96 (SD, 2.75; range, 20.7 to 29.7). All participants had adequate baseline cortisol suppression with mean predose serum cortisol concentrations $<1.8\mu g/dL$ (<50 nmol/L) at each of the three treatment days (day 0) before administration of hydrocortisone granules. Overall median baseline cortisol for each administration method (direct/yogurt/soft food) was 15.3 (range, 10.6 to 72.4)/15.9 (range, 12.5 to 26.6)/14.6 (range, 9.85 to 81.8).

B. Pharmacokinetic Analysis

Following a single 5-mg 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 SD of the serum cortisol concentration-time curves adjusted for baseline cortisol for administration as dry granules, sprinkles onto soft food, and sprinkles onto yogurt. The curves were very similar among the three 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 yogurt, and administration onto soft food, the C_{max} (nmol/L, geometric mean) was 428, 426, and 427; $AUC_{0\text{-}t}$ (nmol $\times$ h/L) was 853, 882, and 838; and $AUC_{0\text{-}inf}$ (nmol $\times$ h/L) was 859, 886, and 844. There were no statistical differences in C_{max} or

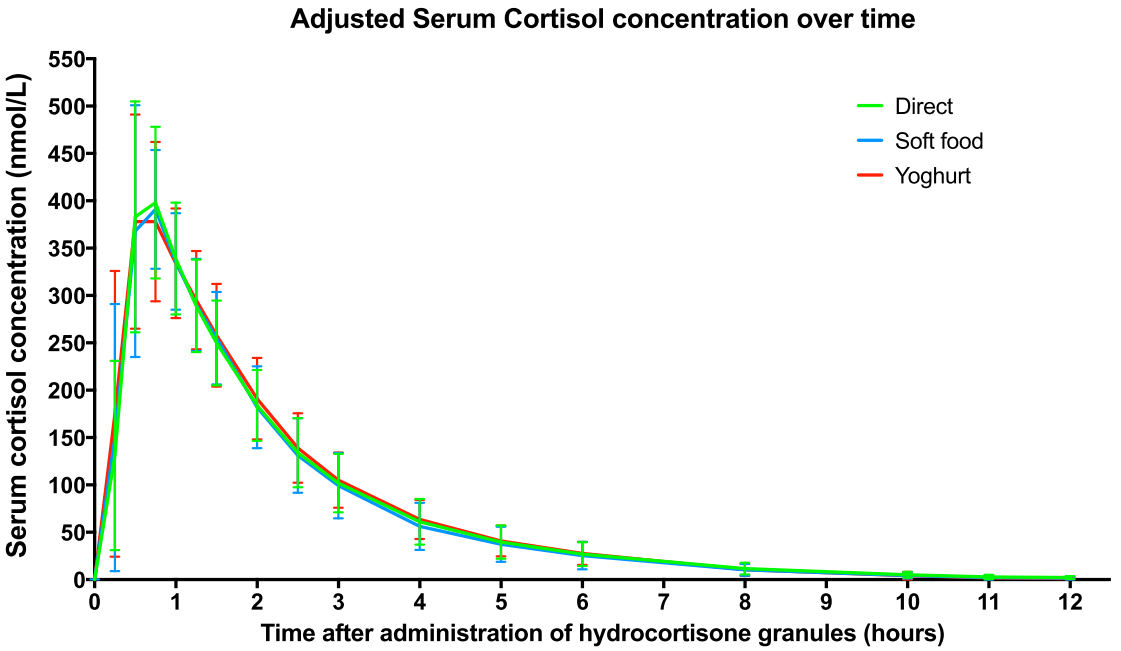

Figure 1. Mean adjusted serum cortisol concentration and standard deviation over time after administration of hydrocortisone granules in 18 fasted, dexamethasone-suppressed healthy men. The serum cortisol concentrations for each participant were corrected for endogenous baseline cortisol by subtraction of the mean predose value.

AUC between methods of administration. T_{max} for dry granules was 0.625 median hours (range, 0.5 to 1.25); sprinkles onto soft food was 0.75 median hours (range, 0.25 to 1.25); and sprinkles onto yogurt was 0.75 median hours (range, 0.25 to 1.5) with no relevant difference among methods of administration.

C. Comparative Bioavailability

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

Table 1. Pharmacokinetic Parameters Calculated From Baseline Adjusted Serum Cortisol After 5-mg Hydrocortisone Granule Dose Administered by Three Methods

	Statistic	Direct Administration	Soft Food	Yogurt
C_{max}, nmol/L	Geometric mean	428	427	426
	SD	82	78	88
$AUC_{0\text{-}t}$, nmol/L × h	Geometric mean	853	838	882
	SD	203	198	161
$AUC_{0\text{-}inf}$, nmol/L × h	Geometric mean	859	844	886
	SD	204	197	162
T_{max}, h	Median	0.63	0.75	0.75
	Range	0.5–1.25	0.25–1.25	0.25–1.5
Elimination rate constant, 1/h	Geometric mean	0.48	0.53	0.55
	SD	0.46	0.24	0.09
Terminal half-life, h	Geometric mean	1.4	1.3	1.3
	SD	0.6	0.4	0.2

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

D. Safety and Tolerability

Hydrocortisone granules were safe and well tolerated. There were no adverse events and no tolerability issues. Safety laboratory tests (biochemistry, hematology, 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.

3. Discussion

These data show that hydrocortisone granules sprinkled onto soft food and yogurt 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}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were well within the 80% to 125% limits required to confirm bioequivalence. The maximum 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, because of exposure to different pH [18]. The medicines regulatory agencies in the United States and Europe, the FDA and European Medicines Agency, 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 vs 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 with 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 because hydrocortisone granules having a taste-masking layer added to neutralize 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

Table 2. Bioequivalence Comparison Between the Reference Administration Method[a] and the Test Administration Methods[b]

	Granules Sprinkled Onto Soft Food to Direct Administration of Dry Granules		Granules Sprinkled Onto Yogurt to Direct Administration of Dry Granules	
	Geometric LS Mean Ratio	90% CI	Geometric LS Mean Ratio	90% CI
C_{max}, nmol/L	99.68	93.98–105.72	99.43	94.33–104.80
$AUC_{0\text{-}t}$, nmol/L × h	98.24	94.42–102.21	103.33	94.80–112.62
$AUC_{0\text{-}inf}$, nmol/L × h	98.21	94.24–102.36	103.07	94.55–112.35

Abbreviation: LS, least squares.
[a]Direct administration of dry hydrocortisone granules to the back of the tongue.
[b]Hydrocortisone granules sprinkled onto yogurt and sprinkled onto soft food.

tested the pharmacokinetics of single administration of hydrocortisone granules in varying doses (0.5, 2.0, 5.0, and 10 mg) in 16 dexamethasone-suppressed healthy adult men [4]. The dose tested in our study (5 mg) is part of the dose range used to treat adrenal insufficiency both in pediatric and adult patients [4, 26]. In the pediatric population, the pharmacokinetics of hydrocortisone granules have been studied in 24 young children with adrenal insufficiency (1 month to 6 years of age) 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 neurologic disease [27]. Compounding of medications to administer as powder and mixing medication with food, juice, and sweeteners is a common approach that parents and pediatric nurses take to improve compliance, especially when there are problems swallowing or medications with a bitter taste [10, 12, 28, 29]; joint administration of medicines with food or drink is an effective strategy to ensure swallowing in children [11]. Liquid formulations are favored 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, which can have adverse effects on teeth with long-term use [31]. Food is chewed to <2 mm [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. 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 pediatric-appropriate dosage and the common use of unlicensed, off-label, and/or compounded medicines that do not have appropriate labeling, 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 pediatric-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 substantial inaccuracy in the content of active ingredient, leading to clinically important consequences including Cushing syndrome [6–8].

The FDA defines yogurt products as having a pH of up to 4.6 [37]. The pH of fresh plain yogurt is around 4.3 to 4.6 and decreases rapidly with storage time to 4.0 to 4.2 [38–40]. The pH of different yogurt 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, 3.94 to 3.98 vs 4.09 to 3.94). For comparison, the pH of applesauce is lower than yogurt and is between 3.1 and 3.6. Because the pharmacokinetic analysis in our study showed bioequivalence between sprinkles on yogurt and applesauce, we believe that any commercial yogurt product with a pH in these ranges could be used as a vehicle for the sprinkling of hydrocortisone granules.

The strengths of the study lie in the three-period crossover design that ensures same within-participant control and thus less variability of the data obtained. A double-blind design was not required because the primary objective of the study was to compare the bioavailability of hydrocortisone granules administered via three 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 liquid chromatography tandem mass spectrometry 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, which can be a potential limitation because hydrocortisone granules are designed for the pediatric population; however, the absorption of hydrocortisone granules was previously studied in 24 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 because each limb of the trial was treated in the same way this should not 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 yogurt that, when consumed within 3 minutes, did not result in any substantial 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.

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Correspondence: Richard J. Ross, MD, The University of Sheffield, Room EU14 Floor E, The Medical School, Beech Hill Road, Sheffield S10 2RX, United Kingdom. E-mail: r.j.ross@sheffield.ac.uk.

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References and Notes

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; Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;**95**(9):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. *J Clin Endocrinol Metab*. 2016;**101**(2):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. *J Clin Endocrinol Metab*. 2002;**87**(9):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. *J Clin Endocrinol Metab*. 2015;**100**(4):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. 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 the 10th International Meeting of Pediatric Endocrinology; 14–17 September 2017; Washington, DC. Abstract PT-1503.

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. *Eur J Endocrinol*. 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.*Endocrine Abstr*. 2017;**51:**OC8.
8. Barillas JE, Eichner D, Van Wagoner R, Speiser PW. Iatrogenic Cushing syndrome in a child with congenital adrenal hyperplasia: erroneous compounding of hydrocortisone. *J Clin Endocrinol Metab*. 2018;**103**(1):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. *Clin Endocrinol (Oxf)*. 2018;**88**(1): 21–29.
10. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. *Int J Pharm Pract*. 2012;**20**(3):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. *Int J Pharm*. 2015;**491**(1-2):261–267.
12. Gardiner P, Dvorkin L. Promoting medication adherence in children. *Am Fam Physician*. 2006;**74**(5): 793–798.
13. European Medicines Agency. Guideline on the investigation of bioequivalence. Available at: www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 28 February 2019.
14. US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for the industry: statistical approaches to establishing bioequivalence. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070244.pdf. Accessed 28 February 2019.
15. The Association of the British Pharmaceutical Industry. Guidelines for phase 1 clinical trials. Available at: www.abpi.org.uk/media/1627/guidelines_phase1_clinical_trials.pdf. Accessed 5 February 2018.
16. US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: food-effect bioavailability and fed bioequivalence studies. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf. Accessed 28 February 2019.
17. US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for the industry: bioavailability and bioequivalence studies for orally administered drug products — general considerations. Available at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM154838.pdf. Accessed 28 February 2019.
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. *Int J Pharm*. 2012;**435**(2):132–134.
19. US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for industry: size of beads in drug products labeled for sprinkle.* Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240243.pdf. Accessed 28 February 2019.
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. The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets, and syrups in African HIV-infected children. *J Acquir Immune Defic Syndr*. 2014;**66**(2):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**(3):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**(7):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**(3):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(®)) in healthy adult volunteers. *J Child Adolesc Psychopharmacol*. 2014;**24**(10):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 Adolesc Psychiatry*. 2002;**41**(4):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. *Clin Endocrinol (Oxf)*. 2004;**61**(3):367–375.
27. Mennella JA, Roberts KM, Mathew PS, Reed DR. Children's perceptions about medicines: individual differences and taste. *BMC Pediatr*. 2015;**15**(1):130.
28. Boztepe H, Özdemir H, Karababa Ç, Yıldız Ö. Difficulties experienced during preparation and administration of oral drugs. *Turk Pediatri Ars*. 2014;**49**(3):231–237.
29. Nahata MC, Allen LV Jr. Extemporaneous drug formulations. *Clin Ther*. 2008;**30**(11):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. *J Clin Endocrinol Metab*. 2001;**86**(1):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**(6):ZC78–ZC82.
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**(4): 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. https://eppi.ioe.ac.uk/cms/Portals/0/PDF%20reviews%20and%20summaries/Paediatric%20medication%20error%202014%20Sutcliffe%20report.pdf?ver=2014-11-20-161504-377. Accessed 31 January 2018.
34. Levine SR, Cohen MR, Blanchard NR, Frederico F, Magelli M, Lomax C, Greiner G, Poole RL, Lee CK, Lesko A. Guidelines for preventing medication errors in pediatrics. *J Pediatr Pharmacol Ther*. 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**(9):1029–1035.
36. Giacoia GPM, Taylor-Zapata P, Mattison D. 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**(1):5–8.
37. US Food and Drug Administration. Title 21: food and drugs. Code of Federal Regulations title 21, volume 2: 21CFR131.200. Milk, cream, and yogurt. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=131.200. Accessed 28 February 2019.
38. Tan G, Korel F. Quality of flavored yoghurt containing added coffee and sugar. *J Food Qual*. 2007;**30**(3): 342–356.
39. Kailasapathy K, Harmstorf I, Phillips M. Survival of Lactobacillus acidophilus and Bifidobacterium animalis ssp. lactis in stirred fruit yogurts. *Food Sci and Technol*. 2008;**41**(7):1317–1322.
40. Dave RI, Shah NP. Viability of yoghurt and probiotic bacteria in yoghurts made from commercial starter cultures. *Int Dairy J*. 1997;**7**(1):31–41.
41. Keating KR, White CH. Effect of alternative sweeteners in plain and fruit-flavored yoghurts. *J Dairy Sci*. 1990;**73**(1):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**(24):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 USA*. 1985; **82**(18):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**(4): 1029–1036.