Hydrocortisone Granules Are Bioequivalent When Sprinkled Onto Food or Given Directly on the Tongue

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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 spectrometry.

Results: The cortisol geometric mean maximum concentration (Cmax) and area under the curve (AUC) for direct administration, sprinkles onto yogurt, and sprinkles onto soft food were: Cmax 428, 426, 427 nmol/L and AUC0-inf 859, 886, 844 h × nmol/L, and AUC0-t 853, 882, 838 h × nmol/L respectively. The 90% CI for the ratios of Cmax, AUC0-inf and AUC0-t for administration with soft food or yogurt to direct administration were well within the bioequivalent range, 80% to 125%. Median time to Cmax (Tmax) 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.

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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; AUC0-inf, area under the curve from the time of administration to the final timepoint of serum cortisol measurement at 12 hours; AUC0-inf, AUC from the time of administration projected to infinity; Cmax, maximum cortisol concentration; FDA, US Food and Drug Administration; Tmax, time to peak cortisol concentration.
is usually 8 to 15 mg/m² 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/m², 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\text{max}), area under the curve from the time of administration to the final timepoint of serum cortisol measurement at 12 hours (AUC\text{0,12}), AUC from the time of administration projected to infinity (AUC\text{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\text{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 21 to 12:00 on day 0 and received three doses of 1 mg dexamethasone with 240 mL water at 22:00 on day 21 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 \(\sim 100\) 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 \(-20\)\(^\circ\)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\ \mu\text{g/dL} (<50 \text{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 $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\text{inf}}$, 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 $C_{\text{max}}$, $AUC_{0-t}$, 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]. $T_{\text{max}}$ 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 $<1.8 \mu g/dL (<50 \text{ nmol/L})$ 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 $C_{\text{max}}$ (nmol/L, geometric mean) was 428, 426, and 427; $AUC_{0-t}$ (nmol × h/L) was 853, 882, and 838; and $AUC_{0-\text{inf}}$ (nmol × h/L) was 859, 886, and 844. There were no statistical differences in $C_{\text{max}}$ or
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 $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ 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 $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were well within the 80% to 125% limits, which confirmed that 5-mg hydrocortisone granules administered as

![Adjusted Serum Cortisol concentration over time](image)

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.

| Statistic | Direct Administration | Soft Food | Yogurt |
|-----------|-----------------------|-----------|--------|
| $C_{max}$, nmol/L | Geometric mean | 428 | 427 | 426 |
| | SD | 82 | 78 | 88 |
| $AUC_{0-t}$, nmol/L × h | Geometric mean | 853 | 838 | 882 |
| | SD | 203 | 198 | 161 |
| $AUC_{0-inf}$, 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 $C_{\text{max}}$, 99.68 (93.98 to 105.72), $AUC_{0-t}$, 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: $C_{\text{max}}$, 99.43 (94.33 to 104.80), $AUC_{0-t}$, 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 $C_{\text{max}}$, $AUC_{0-t}$, 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 $C_{\text{max}}$ and AUC was the same for the three administration methods and there was no relevant difference in the rate of absorption measured by $T_{\text{max}}$. 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 |
| $C_{\text{max}}$, nmol/L | 99.68 | 93.98–105.72 | 99.43 | 94.33–104.80 |
| $AUC_{0-t}$, nmol/L $\times$ h | 98.24 | 94.42–102.21 | 103.33 | 94.80–112.62 |
| $AUC_{0-\text{inf}}$, nmol/L $\times$ 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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Disclosure Summary: R.J.R. is a director of Diurnal Ltd and owns stock. J.Q. and M.D. are employed by Diurnal Ltd. B.V. and D.D. have received consulting fees from Diurnal Ltd. The remaining author has nothing to disclose.

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