Manipulation of hydrocortisone tablets leads to iatrogenic Cushing syndrome in a 6-year old girl with CAH

Heba Al-Rayess¹, Kristin Fleissner¹, Mu’taz Jaber², Richard C Brundage², Kyriakie Sarafoglou¹²

¹Department of Pediatrics, Division of Endocrinology, University of Minnesota
²Department of Experimental and Clinical Pharmacology, University of Minnesota

Key Words: Congenital adrenal hyperplasia, hydrocortisone, Cushing’s syndrome, pharmacokinetics

Corresponding Author:

Kyriakie Sarafoglou, MD
Associate Professor
University of Minnesota Masonic Children’s Hospital
2450 Riverside Ave.
East Bldg., Rm MB671
Minneapolis, MN 55454
Ph: (612) 624-5409
Email: saraf010@umn.edu

Reprints: Please contact corresponding author.

Grant support: Research reported in this publication was partially supported by the Office of Orphan Products Development of the Food and Drug Administration under award number R01FDR0006100. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the FDA nor FDA’s Office of Orphan Products Development.

Disclosure Summary: Dr. Sarafoglou receives research support from Spruce Biosciences, Alexion, Inc and Neurocrine Biosciences. The rest of the authors have no financial disclosures to report.
Abstract:

Currently there are no commercially available hydrocortisone formulations for the treatment of children with congenital adrenal hyperplasia (CAH) that allow for smaller doses (0.1-1.25 mg) and incremental adjustments needed to control excess androgen production and avoid the negative effects of overtreatment. This lack of availability has led physicians to recommend dividing hydrocortisone 5 mg tablets into 4 to 6 pieces, compounding capsules or hydrocortisone suspension, or crushing 5 or 10 mg tablets in 5 or 10 mL of water. We report a case of iatrogenic Cushing’s syndrome in a 6-year 11-month-old girl with SW-CAH treated with hydrocortisone tablets that were administered after crushing and dispersing into water to obtain the prescribed dose. She presented with poor growth, increasing BMI, excess downy hair, round facies and gastric ulcers. Her hydrocortisone dose was 8.1 mg/m$^2$/day. Results for all adrenal steroid concentrations were undetectable at 8 am, 12 hours after her last dose. The year prior to presentation parents began dissolving 10 mg of hydrocortisone in 10 mL water and using this preparation over the course of 24 hours, which coincided with rapid increase of BMI. We switched her to a pharmacy compounded alcohol-free hydrocortisone suspension with total daily doses ranging from 6.5-8.2 mg/m$^2$/d which resulted in resolution of her Cushingoid features, a decrease in BMI and catch-up growth. Our case highlights that manipulation of hydrocortisone tablets by parents can result in great variability in dosing and the need for commercially available pediatric formulations allowing for smaller dosing required in young children.
Introduction:

Patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency require lifelong glucocorticoid therapy. Hydrocortisone is used in growing children because of the negative effects on growth of long-acting glucocorticoids (1). Hydrocortisone has a short half-life especially in children with CAH (2) and is usually given three times a day with a recommended daily dose of 10–15 mg/m²/day (1). In infancy and early childhood, smaller doses and incremental adjustments are required to reach a dose that is enough to prevent increased androgen production and exposure, but not excessive to avoid causing hypercortisolism. However, this balance is very hard to achieve in practice as the smallest FDA-approved commercial formulation currently available in the U.S. is 5 mg hydrocortisone tablet with a single score.

This lack of an appropriate pediatric formulation has led to various manipulations of the 5 mg hydrocortisone tablet in order to deliver prescribed doses under 2.5 mg. Some parents are instructed to split tablets into 4 or more pieces, or to crush tablets to create a solution, both of which could lead to great dose variability with resultant hypo- or hypercortisolemia (3-5). We report a case of iatrogenic Cushing’s syndrome in a patient treated with hydrocortisone tablets that were administered after crushing and dispersing into water by parents to obtain the prescribed dose.

Case presentation:

A 6-year 11-month old female presented to our CAH clinic for a consultation regarding her endocrine management. She was diagnosed with salt-wasting (SW) CAH shortly after birth, when presenting with atypical genitalia (Prader grade 4), hyperkalemia (8.3 mmol/L) and hyponatremia (130 mmol/L). Family history was significant for simple-virilizing CAH in a
paternal 2nd cousin and non-classic CAH in a paternal aunt. Initial evaluation revealed a 46,XX karyotype and elevated baseline adrenal steroids (17-hydroxyprogesterone; 17 OHP = 33,800 ng/dL, androstenedione; D4A = 404 ng/dL, testosterone; T = 353 ng/dL) and plasma renin activity (3677 ng/mL/hr). Pelvic ultrasound showed normal female anatomy. Treatment was started on day of life 6, with hydrocortisone 1.3 mg three times daily (18.7 mg/m²/day), fludrocortisone 0.1 mg daily and sodium chloride 10.2 mEq/kg/day. Hydrocortisone was initially administered using a compounded 2 mg/mL suspension. Her dose was decreased at the age of 4 months to 1.2 mg three times a day (12.6 mg/m²/day) due to undetectable androgen levels. At 5 months of age, patient underwent genital reconstructive surgery, where she was noted to be markedly hypertensive. Workup was negative and included plasma metanephrines and echocardiogram. Dimercaptosuccinic acid scan was performed due to history of Vesicoureteral reflux and showed no scarring. She was discharged on Captopril 15 mg and Amlodipine 2.5 mg daily. Her salt was reduced, her fludrocortisone was decreased to 0.05 mg daily, and her hydrocortisone formulation was changed to tablets that were initially quartered and given 3 times daily, assuming the suspension might have produced inaccurate dosing. As her hydrocortisone doses were further reduced in the following months, parents were instructed to crush tablets and make a solution in water, then draw the prescribed amount (Figure 1 depicts daily hydrocortisone dosing since birth).

At age 12 months parents sought a second opinion due to concerns of poor linear growth (15th percentile) compared to her parental target height (50th percentile) (Figure 2), and persistently undetectable adrenal androgens. At that time her hydrocortisone dose was 6.6 mg/m²/day. Advice was given to target 17-OHP levels between 400-1200 ng/dL, and her doses were titrated accordingly. Until age 4 years, her daily hydrocortisone doses ranged between 4.35-5.8
mg/m²/day divided 3 times daily. At age 3.5 years, she was noted to have “mild global increased lanugo, and slightly rounded cheeks.” Cushingoid features continued to be described in subsequent visits, with increased downy hair growth on face, upper arms and back. At age 4 years, her linear growth dropped to the 4th %ile. At that time, she was taken off fludrocortisone completely and without tapering for a trial period as her treating endocrinologist questioned her diagnosis of SW-CAH based on her low daily hydrocortisone dose and unexplained hypertension. Two days later she developed fatigue, vomiting, hypotension, polyuria, and natriuresis (urine Na 125 mmol/l). Fludrocortisone was restarted with subsequent resolution of her symptoms. Her hydrocortisone was split into 4 doses a day every 6 hours starting at 6 am (5.8 mg/m²/day). Angiotensin-converting enzyme inhibitor was stopped to allow for better monitoring of her fludrocortisone dose. At age 4.4 years, family sought a third opinion. CYP21A2 molecular testing confirmed the diagnosis and revealed compound heterozygosity with three CYP21A2 pathogenic variants (Intron 2G/Intron 2G-P453S), which is consistent with SW-CAH in 85% of the cases (6). The consultant endocrinologist was concerned about the accuracy of the hydrocortisone formulation as parents dissolved 5 mg tablets in 5 mL water, either after crushing or by letting the tablet dissolve over time in warm water at room temperature. Parents would then use that solution for the rest of the day. The endocrinologist advised parents to instead cut tablets into halves and quarters, as it was assumed to produce more accuracy, and her dose was changed accordingly (7.9 mg/m²/d). However, a month later parents were advised by their home endocrinologist to go back to dispersing tablets in water at a dose of 6.5 mg/m²/d.

From age 5 to 6.5 years, her hydrocortisone dose gradually increased from 7.1 mg/m²/d to 12.2 mg/m²/d. Since total daily dose exceeded 5 mg, parents needed to make a 10 mg/10 mL solution using two 5 mg tablets and used that solution over 24 hours. During this period, she
continued to grow along the 5th percentile, and to show increased downy hair growth, poor energy and emotional lability. She also required higher doses of amlodipine (5 mg to 7.5 mg) to control her blood pressure. Her weight increased from 42 lbs at 6 years (30th %ile, -0.51 SD) to 55 lbs at 6.8 years (74th %ile, 0.7 SDS), with a sharp increase in her BMI from 16.5 kg/m² (77th %ile, 0.74 SDS) to 19.38 kg/m² (94th %ile, 1.61 SDS) in the same timeframe (Figure 3; parental consent was obtained for all the photos presented in the figures).

Patient presented at our CAH clinic at age 6.9 years with a weight of 25.1 kg (74th %ile and 0.7 SDS), height of 113.8 (9th %ile and -1.3 SDS) and a BMI of 19.38 (94th %ile and 1.61 SDS) (Figures 2-3). Her physical exam was significant for round facies, a buffalo hump, and downy body hair over the upper back with a large whorl, as well as on arms, legs, forehead and sideburns (Figures 4-5). She had no acanthosis nigricans or hyperglycemia. Her blood pressure was at the 92%ile systolic and 96%ile diastolic based on the August 2017 AAP Clinical Practice Guideline, despite treatment with amlodipine. Her CAH regimen consisted of 2 mg hydrocortisone at 6 am, 1.75 mg at noon, 1.5 mg at 6 pm, and 2 mg at midnight (8.1 mg/m²/day), and fludrocortisone 0.1 mg daily.

In order to determine her cortisol pharmacokinetic (PK) and pharmacodynamic (PD) response, patient underwent 6-hour timed serial measurements of her cortisol, 17OHP and D4A after receiving her prescribed hydrocortisone dose at 8 am. Her baseline 17OHP concentration was 43 ng/dL and her adrenocorticotropic hormone (ACTH), cortisol, and D4A concentrations were undetectable, even though her last dose of hydrocortisone was given the previous evening at 8 pm (12 hours prior to her 8 am dose), suggesting chronic over-suppression of her hypothalamic-pituitary-adrenal (HPA) axis. Throughout the test her 17OHP and D4A levels
remained undetectable. Her cortisol PK was significant for low clearance (Figure 6 and Table 1). Her growth factors and thyroid function tests were in the normal range.

Based on our findings we changed her formulation to an extemporaneously compounded alcohol-free hydrocortisone suspension based on a published method (7) made by our compounding pharmacy that has been found to have comparable bioavailability to tablets (8). Her regimen was changed to 2 mg at 6 am, 1.2 mg at 8 am, 1.8 mg at 2 pm, 1.2 mg at 9 pm (6.9 mg/m²/day). Over the next year, her daily hydrocortisone dose ranged between 6.5-8.2 mg/m²/d, divided 4 times a day at the same intervals, using the compounded suspension.

On her follow up visit at age 8 years, her linear growth started catching up and was tracking along the 10th %ile (Figure 1). Her hypertension improved and her local nephrologist weaned the amlodipine down to 3 mg, from 7.5 mg at initial presentation to our clinic. Her cushingoid features significantly improved compared to her initial presentation (Figure 4). Her body hair had decreased in density and pigmentation (Figure 5). Her BMI decreased to 16.79 kg/m² (68th %ile, 0.48 SDS), after reaching a peak of 20.46 (96th %ile, 1.81 SDS) at age of 7 (Figure 3).

Discussion:

Our patient’s clinical and biochemical presentation was consistent with iatrogenic Cushing’s syndrome although her total daily hydrocortisone dose (8.1 mg/m²/day) was below the recommended range of 10-15 mg/m²/day (1). Her case highlights the health risk of parents manipulating hydrocortisone tablets (splitting, crushing and dissolving) to give prescribed doses in increments less than 2.5 mg and the need for a commercially available pediatric formulation that allows small incremental doses.
Hydrocortisone tablets have poor aqueous solubility (0.28 mg/mL at 25°C) that makes forming a stable homogenous mixture in water very difficult. This leads to sedimentation and unequal distribution of the drug particles in different zones of the container resulting in increased variability of the intended dose. In our case, the patient was receiving higher than intended doses that led to overtreatment. Her sharp increase in weight and BMI corresponded to her total daily dose exceeding 5 mg, thus requiring the parents to use 2 tablets (5 mg) to make a 10 mg/10 mL hydrocortisone solution that resulted in unequal distribution and higher ingested doses than intended. Dispersion of tablets into liquid followed by withdrawal of the required volume is associated with variability in dosing (9). Watson, et al, found that parents who administer 10 mg hydrocortisone tablets dispersed in water that the dose the children received was outside the ±20% range of the target dose of 2.5 mg in more than half of the cases, with some individual doses reaching beyond 250% of desired target dose (5).

Other methods of manipulation besides dispersing tablets in water, such as splitting scored tablets can also lead to wide variability of dosing. Verrue et al., found that tablet splitting devices were superior to knives or scissors yet there were still large dose deviations (10). Madathilethu et al., reported that splitting 10 mg hydrocortisone tablets, which are quarter scored, allowing them to be divided into halves and quarters, were found to produce unacceptable dose variations (3). A survey that targeted physicians from 16 countries in Europe (11) revealed that 60% of them used divided adult hydrocortisone tablets and 55% used unlicensed individualized capsules, with the prescribed doses reported to be as small as 0.5 mg. Another survey in the UK showed that the parents are usually advised to either disperse the 10 mg tablets in water to obtain the required dose or to quarter them to obtain 2.5 mg (5).
A commercially available hydrocortisone cypionate suspension was removed from the market in 2001 following a study that showed that patients required higher daily hydrocortisone doses, had higher D4A levels and increased weight gain and hypertension compared to the tablets (12). However, the authors indicated their study results were specific to the bioavailability of hydrocortisone cypionate, but not to other forms of hydrocortisone suspension such as alcohol-free hydrocortisone suspension prepared from tablets or powder by a compounding pharmacy.

Multiple compounded liquid formulations of hydrocortisone have been studied and have been shown to be stable (13-17). These formulations were made by adding inactive ingredients that increase solubility of hydrocortisone such as polysorbate 80, B-cyclodextrin,(14,18) or included 1:1 mixture of suspending vehicles with high colloidal activity, such as Ora-plus, and Ora Sweet, a flavoring vehicle to improve palatability (17,19). Alcohol-free compounded solutions of either 2 mg/mL (17) and 1 mg/mL (19) have been shown to be stable in amber plastic bottles and syringes stored at 4 C or 25 C for 90 days with excellent dose repeatability. Sarafoglou, et al. compared the bio-availability of extemporaneously compounded alcohol-free hydrocortisone suspension to tablets and found that based on a mg/m² dose-normalized AUC analysis, the absorption of the alcohol-free hydrocortisone suspension was not different compared to commercial hydrocortisone tablets in children with CAH (8). The study found that C_max values, and T_max values were also similar to those taking tablets, strongly supporting the notion of comparable bioavailability (8). In addition, adrenal steroid concentrations, weight gain and growth were comparable between children on tablets and suspension. Despite all this cumulating evidence on the suitability of hydrocortisone suspensions for treatment of children
with CAH, there has been no effort to commercially market an alcohol-free suspension. Currently, such formulation is only available through compounding pharmacies.

Compounding is an important part of the healthcare system, as it can allow for flexibility in dosing and individualized therapy, which can be of great benefit on a small scale. However, compounded drugs are less strictly regulated than licensed medications by the FDA and are exempt from good practice manufacturing regulations, which can be concerning for inconsistent quality among different compounding pharmacies (20). It is important that the prescribing physician is familiar with the reliability of their local compounding pharmacy. There have been reports of compounded hydrocortisone capsules associated with iatrogenic Cushing (21,22). In Neumann, et al, examination of 61 batches of hydrocortisone capsules showed that 21.4% failed the uniformity analysis with 3.6% not containing hydrocortisone at all (21), underscoring the need for the development of licensed pediatric hydrocortisone formulations that provide a safe and accurate method for hydrocortisone administration to children with CAH. Preventing cortisol under- or over-exposure during early childhood is critical to ensure optimal growth and weight gain and prevent adverse outcomes on cardiovascular and bone health and glucose metabolism due to insulin resistance associated with over-treatment (23-30). A pediatric formulation in development, but not yet available in the U.S. is hydrocortisone granules (0.5 mg each) (alkindi), which has been reported to have good absorption and bioavailability (11,31).
References

1. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(11):4043-4088.
2. Sarafoglou K, Zimmerman CL, Gonzalez-Bolanos MT, Willis BA, Brundage R. Interrelationships among cortisol, 17-hydroxypregesterone, and androstenedione exposures in the management of children with congenital adrenal hyperplasia. J Investig Med. 2015;63(1):35-41.
3. Madathilethu J, Roberts M, Peak M, Blair J, Prescott R, Ford JL. Content uniformity of quartered hydrocortisone tablets in comparison with mini-tablets for paediatric dosing. BMJ Paediatr Open. 2018;2(1):e000198.
4. Daniel E, Whitaker MJ, Keevil B, Wales J, Ross RJ. Accuracy of hydrocortisone dose administration via nasogastric tube. Clin Endocrinol (Oxf). 2019;90(1):66-73.
5. Watson C, Webb EA, Kerr S, Davies JH, Stirling H, Batchelor H. How close is the dose? Manipulation of 10mg hydrocortisone tablets to provide appropriate doses to children. Int J Pharm. 2018;545(1-2):57-63.
6. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev. 2000;21(3):245-291.
7. Allen LV. Formulations: Hydrocortisone 2 mg/mL oral liquid. International Journal of Pharmaceutical Compounding. 2004;8(1):56.
8. Sarafoglou K, Gonzalez-Bolanos MT, Zimmerman CL, Boonstra T, Yaw Addo O, Brundage R. Comparison of cortisol exposures and pharmacodynamic adrenal steroid responses to hydrocortisone suspension vs. commercial tablets. J Clin Pharmacol. 2015;55(4):452-457.
9. Abu-Geras D, Hadziomerovic D, Leau A, Khan RN, Gudka S, Locher C, Razaghikashani M, Lim LY. Accuracy of tablet splitting and liquid measurements: an examination of who, what and how. J Pharm Pharmacol. 2017;69(5):603-612.
10. Verrue C, Muhy E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: a common yet not so innocent practice. J Adv Nurs. 2011;67(1):26-32.
11. 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.
12. 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.
13. Santoven A, Llabre's M, Farina JB. Quality control and physical and chemical stability of hydrocortisone oral suspension: an interlaboratory study. Int J Pharm Compd. 2010;14(5):430-435.
14. Fawcett JP, Boulton DW, Jiang R, Woods DJ. Stability of hydrocortisone oral suspensions prepared from tablets and powder. *Ann Pharmacother*. 1995;29(10):987-990.

15. Gupta VD. Chemical stability of hydrocortisone in humco simple syrup and ora-sweet vehicles. *Int J Pharm Compd*. 2010;14(1):76-77.

16. Gupta VDP. Chemical Stabilities of Hydrocortisone in an Oral Liquid Dosage Form without Suspending Agents. *Int J Pharm Compd*. 2007;11(3):259-261.

17. Manchanda A, Laracy M, Savji T, Bogner RH. Stability of an Alcohol-free, Dye-free Hydrocortisone (2 mg/mL) Compounded Oral Suspension. *Int J Pharm Compd*. 2018;22(1):66-75.

18. Orlu-Gul M, Fisco G, Parmar D, Gill H, Tuleu C. A new reconstitutable oral paediatric hydrocortisone solution containing hydroxypropyl-beta-cyclodextrin. *Drug Dev Ind Pharm*. 2013;39(7):1028-1036.

19. Chong G DD, Ensom JHH. Stability of hydrocortisone in extemporaneously compounded suspension. *J Inform Pharmacother*. 2003;13:100-110.

20. Gudeman J, Jozwiaiski M, Chollet J, Randell M. Potential risks of pharmacy compounding. *Drugs R D*. 2013;13(1):1-8.

21. Neumann U, Burau D, Spielmann S, Whitaker MJ, Ross RJ, Kloth C, Blankenstein O. Quality of compounded hydrocortisone capsules used in the treatment of children. *Eur J Endocrinol*. 2017;177(2):239-242.

22. 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.

23. Bomberg EM, Addo OY, Kyllo J, Gonzalez-Bolanos MT, Lteif AM, Pittock S, Himes JH, Miller BS, Sarafoglou K. The relation of peripubertal and pubertal growth to final adult height in children with classic congenital adrenal hyperplasia. *J Pediatr*. 2015;166(3):743-750.

24. Halper A, Hooke MC, Gonzalez-Bolanos MT, Vanderburg N, Tran TN, Torkelson J, Sarafoglou K. Health-related quality of life in children with congenital adrenal hyperplasia. *Health Qual Life Outcomes*. 2017;15(1):194.

25. Halper A, Sanchez B, Hodges JS, Dengel DR, Petryk A, Sarafoglou K. Use of an aromatase inhibitor in children with congenital adrenal hyperplasia: Impact of anastrozole on bone mineral density and visceral adipose tissue. *Clin Endocrinol (Oxf)*. 2019;91(1):124-130.

26. Halper A, Sanchez B, Hodges JS, Kelly AS, Dengel D, Nathan BM, Petryk A, Sarafoglou K. Bone mineral density and body composition in children with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2018;88(6):813-819.

27. Maccabee-Ryaboy N, Thomas W, Kyllo J, Lteif A, Petryk A, Gonzalez-Bolanos MT, Hindmarsh PC, Sarafoglou K. Hypertension in children with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2016;85(4):528-534.

28. Sarafoglou K, Addo OY, Turcotte L, Otten N, Wickremasinghe A, Pittock S, Kyllo J, Lteif AN, Himes JH, Miller BS. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia-the Minnesota cohort. *J Pediatr*. 2014;164(5):1141-1146 e1141.

29. Sarafoglou K, Forlenza GP, Yaw Addo O, Kyllo J, Lteif A, Hindmarsh PC, Petryk A, Gonzalez-Bolanos MT, Miller BS, Thomas W. Obesity in children with congenital adrenal hyperplasia in the Minnesota cohort: importance of adjusting body mass index for height-age. *Clin Endocrinol (Oxf)*. 2017;86(5):708-716.

30. Mooij CF, Kroese JM, Claahsen-van der Grinten HL, Tack CJ, Hermus AR. Unfavourable trends in cardiovascular and metabolic risk in paediatric and adult patients with congenital adrenal hyperplasia? *Clin Endocrinol (Oxf)*. 2010;73(2):137-146.
31. 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.

**Table 1:** Patient’s cortisol pharmacokinetics.

| Parameter   | Patient Value | Lower Range     | Patient value normalized | Upper Range     |
|-------------|---------------|-----------------|--------------------------|----------------|
| CL          | 52.3 (dL/hr)  | 46-86 (dL/hr/m²) | 58.8 dL/hr/m²            | 136-210 (dL/hr/m²) |
| Vd          | 78.7 (dL)     | 77-126 (dL/m²)  | 88.4 dL/m²               | 187-237 (dL/m²)  |
| Half-life   | 1.0 (hours)   | 0.7-0.9 (hours) |                          | 1.2-1.8 (hours)  |

CL: clearance; Vd: volume of distribution.
Figure Legend:

**Figure 1**: Patient’s total daily hydrocortisone dose in mg and mg/m² since birth. Starting at 65 months of age her total daily prescribed dose increased to greater than 5 mg which necessitated the parents to dissolve 10 mg of hydrocortisone in 10 ml of water rather than 5 mg of hydrocortisone in 5 ml of water. Orange circles represent total daily hydrocortisone dose in mg and blue squares represent total daily hydrocortisone dose in mg/m².

**Figure 2**: Poor linear growth illustrated by patient’s height tracking along the 5th percentile despite mid-parental height being at the 50th percentile. Catch up growth is evident after patient was switched from dispersed hydrocortisone tablets to the pharmacy compounded alcohol-free suspension. A peak of weight gain was also observed prior to presentation. Arrows represent time of switching to pharmacy compounded suspension. MPH: Mid-Parental Height.

**Figure 3**: Rapid BMI increase between ages 6 and 7 years, corresponding with using 10mg of hydrocortisone in 10 mL water. Significant improvement noted after switching to the pharmacy compounded suspension (arrow).

**Figure 4**: A. Patient showing cushingoid facies at time of presentation. B, resolution of cushingoid features a year after switching to alcohol-free hydrocortisone suspension.

**Figure 5**: Increased growth of dark hair on patient’s back while on the homemade hydrocortisone liquid (A and C). Diminished hair growth and pigmentation on the upper back after switching to pharmacy compounded alcohol-free hydrocortisone suspension (B and D).

**Figure 6**: Patient’s cortisol and adrenal steroids timed measurements during a 6-hour period following her morning hydrocortisone dose. 17-hydroxyprogesterone (17 OHP) and androstenedione (D4A) were suppressed at baseline and remained undetectable throughout the test.
Figure 1

![Graph showing hydrocortisone dose over age in months. The graph compares daily HC dose (mg) and HC dose (mg/m2).]
Figure 3

2 to 20 years: Girls
Body mass index-for-age percentiles

Date | Age | Weight | Stature | BMI* | Comments
--- | --- | --- | --- | --- | ---

*To Calculate BMI: Weight (kg) + Stature (cm) + Stature (cm) x 10,000
or Weight (lb) + Stature (in) + Stature (in) x 703

Published May 30, 2000 (modified 10/1/00)
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000),
http://www.cdc.gov/growthcharts

SAFER • HEALTHIER • PEOPLE®
