Compounded hydrocortisone preparations for children with congenital adrenal hyperplasia: are they safe ?

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Abstract

Children with congenital adrenal hyperplasia (CAH) or adrenal insufficiency (AI) need hydrocortisone and sometimes fludrocortisone in appropriate doses to survive. Low dose hydrocortisone preparations and fludrocortisone are not commercially available on the Belgian market so pediatricians have to rely on tablet splitting or crushing and pharmacy compounding. These methods can create substantial dosage errors with important clinical implications and are not subject to the quality controls and pharmacovigilance requirements that govern approved drug preparations. In addition, repeated supply shortages of the active pharmaceutical ingredients have occurred in the last years. Commercial low dose hydrocortisone and fludrocortisone products and modified-release hydrocortisone preparations, reliably produced under GMP regulations, could improve the safety risk associated with compounded medication but are not yet available in Belgium.

Classic congenital adrenal hyperplasia (CAH) is a rare (1:15000) hereditary autosomal recessive condition affecting adrenal steroidogenesis. Most of the cases (90–95%) are caused by mutations in the 21-hydroxylase gene (*CYP21A2*) leading to reduced cortisol synthesis. Additionally, aldosterone synthesis is impaired in about 75% of the patients resulting in salt-wasting CAH. The reduced feedback of cortisol causes a surge in ACTH which stimulates adrenal androgen production (1-3).

Hydrocortisone treatment in CAH substitutes the glucocorticoid deficiency and blunts the ACTH secretion. In addition, mineralocorticoid deficiency is treated with fludrocortisone.

Hydrocortisone treatment in classic CAH is a balance between overtreatment with multiple adverse side effects on growth and on metabolic, cardiovascular and bone health, and undertreatment, which carries risks for life-threatening adrenal crises, virilization and reduced adult height. Both over- and under treatment also affect reproductive function in both sexes.(2). The physiological production of hydrocortisone in humans is 6-8 mg/m^2/day and this quantity, divided in 3 or 4 doses, is used for patients with primary adrenal insufficiency. A higher dose is needed to suppress ACTH production in patients with CAH especially early in the morning. Consensus guidelines propose a dose of 10-15 mg/m^2/per day divided in 3 doses in children (3). This translates to doses of 1 and 2 mg hydrocortisone in toddlers and young children (e.g. 2-1-1 mg per day) (4). The recommended dose of fludrocortisone is 50-200 microgram in 1 or 2 doses (3).

Currently, only a 20 mg hydrocortisone tablet is available on the Belgian market and there is no commercially available form of oral fludrocortisone. A survey of pediatric endocrinologists from 16 countries in Europe 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 (5).

Dosage errors

Several methods are used to arrive at these low doses: tablet splitting, crushing and dissolving in liquids or individualized compounding in the pharmacy. European Pharmacopoeia guidelines on subdivision of tablets require that the parts meet the following criteria “at least 194 of 200 parts resp. 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical weight of a tablet part”(6). The accuracy of tablet splitting depends, among others, on the tablet type and size, the presence of a scoring line, the splitting device (by hand, kitchen knife or tablet splitter) (7,8).

Saimbi et al. measured the accuracy of splitting 2 types of 10 mg hydrocortisone tablets and found that the dose of halved tablets ranged from 41 to 55% for tablet A and 29- 70 % for tablet B .Quartering the tablets gave doses between 17-35% for tablet A and 12-42 % for tablet B instead of the 25% expected (9). In another experiment, more than 40% of the quartered tablets were outside the European Pharmacopoeia weight variation allowance when splitting a 10 mg hydrocortisone tablet in 4 with a standard pill splitter in lab conditions (10).

Thirty unexperienced participants were asked in a study to prepare a 2.5 mg hydrocortisone dose by splitting 10 mg tablets. When the tablet was scored, 70% of the doses ranged between 2,0 and 3,0 mg (20% variability of the intended dose). When unscored tablets were used, only 57 % of the doses were within this 2,0 – 3,0 mg dose range. Worrisome, more than 25% of the parents of children with CAH were not able to produce a dose within 20% of the theoretical value even after a training session(11).

Dispersion of tablets into liquid and withdrawal of the required volume is another popular method to prepare pediatric doses but it is also associated with large errors (7). Hydrocortisone is poorly soluble in water (0,28 mg/ml at 25°C) so most of the product is suspended or precipitates when caregivers prepare an aqueous solution. Saimbi et al crushed a 10 mg hydrocortisone tablet with a spoon, dissolved it in 10 ml of water and took 2 ml with a syringe. The mean actual dose ranged from 1,3 to 1,7 mg instead of 2,0 mg (9). In another study, only 67% and 87% of the liquid doses prepared using tablet A or tablet B respectively were within a ± 20% tolerance limit. (11).

A commercial oral suspension (Cortef suspension, Pfizer) was recalled from the market because it was not bioequivalent to tablets and failed to provide adequate control in children with CAH (12). Although an improved suspension has been proposed (13) the Endocrine Society Clinical Practice Guidelines on congenital adrenal hyperplasia (CAH) still recommend against using hydrocortisone suspensions (3).

To avoid these dosage errors, pediatricians often prescribe individualized doses of hydrocortisone for the pharmacist to prepare in capsules. Unfortunately, huge dose errors have also been described for this method. A group from Ghent University reported that a significant amount of the hydrocorti-

sone is lost during the preparation of the capsules and more than 1% remains in the capsule after emptying them (14). Neumann et al analyzed the hydrocortisone content of 1125 capsules sent in by 56 patients. In this real world analysis, more than 20 % of the batches revealed insufficiency in uniformity of net mass or drug content as defined by the European Pharmacopoeia and the capsules of 2 patients did not contain any hydrocortisone (15) (**Figure 1**).

Clinical implications of dosage errors

The extent of health problems related to the quality and safety of compounded drugs is unknown, as there is no requirement to report adverse effects of compounded drugs. However, regulatory agencies such as the FDA (Food and Drug Administration, USA) continuously receive reports of serious and sometimes deadly adverse events especially in children (16).

Overtreatment of CAH patients with hydrocortisone causes short stature, weight gain, decreased bone mineral density, hypertension and glucose intolerance . Undertreatment results in hyperandrogenism, low blood pressure and, in extreme cases, an adrenal crisis (1,2,3). Iatrogenic Cushing syndrome has been described in a child with congenital adrenal hyperplasia due to a hydrocortisone dose in the compounded medication that was 5 to 10 times the prescribed dose (17). Al Rayess et al described a 6 y old girl with CAH who became severely Cushingoid and developed gastric ulcers. The caregivers dissolved tablets in hot water and withdrew the desired volume from the bottom of the container. Due to the poor solubility of hydrocortisone the dose was much larger than expected (18). In the Netherlands, several cases of adrenal crisis have been reported by patients to the pharmacovigilance website LAREB (19).

Differences between approved and compounded medications

Approved drugs are manufactured under good manufacturing practice (GMP) regulations that govern the production and testing of pharmaceutical materials. The regulatory agencies regularly inspect pharmaceutical manufacturing facilities to ensure compliance with GMPs. Pharmacies are exempt from GMP regulations and are seldom inspected (20). **Table 1** lists other important differences in the requirements for approved drugs and compounded preparations.

Because there is less assurance that compounded products provide a constant product quality the rules stipulate that a compounded product cannot be prescribed when an approved product is available on the market.

Table 1: Regulatory differences between approved and compounded drugs

Approved drugs	Compounded drugs
Must follow GMP regulations	Exempt from GMP regulation
Efficacy (or bioequivalence) and safety tested	No testing
Retesting of bulk ingredients mandatory	Rely on Certificate of Analysis
Labeling and inserts required and approved	No labelling and information needed
Adverse events reporting mandatory	No adverse event reporting needed

Supply chain interruptions

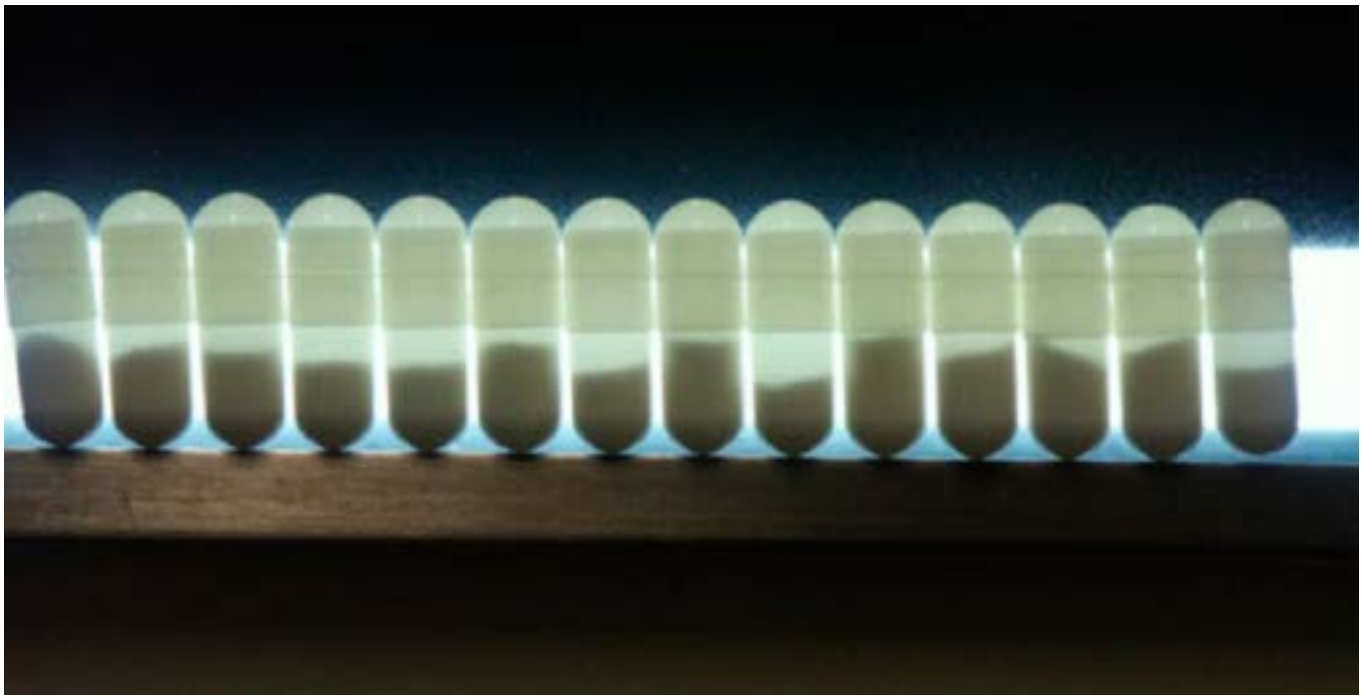
Hydrocortisone and fludrocortisone are essential and life-saving medications and their supply should be guaranteed for patients that need them. However, hydrocortisone and fludrocortisone used for compounding are often produced abroad and shortages have been reported in several countries in recent years (21-23). This brings an additional safety risk to patients with CAH and AI.

New treatment modalities on the horizon

The described safety issues with the current treatment modalities underscore the need for licensed pediatric hydrocortisone formulations. This is also endorsed by a 2017 European Commission report on pediatric medicines that states : "there is a broad consensus that children deserve access to medicines that have been specifically developed and researched for their use "and" crushing adult tablets and using only a portion comes with the risk of inefficacy and/or adverse reactions in children" (24).

At the request of the care platform BijnierNET/AdrenalNET, ACE Pharmaceuticals recently introduced hydrocortisone tablets (Acecort®) of 2, 3 and 10 mg, produced under GMP regulations on the Dutch market the 2 and 3 mg tablets have been registered in the meantime (25). Each tablet strength has a different color to minimize dosing errors and has a neutral taste. The same company also produces GMP fludrocortisone tablets (Fludrace®) of 62,5 microgram, from locally produced fludrocortisone (26). ACE Pharmaceuticals registered both products in Belgium and their market introduction awaits a viable price setting.

Figure 1: A "real world" batch of compounded hydrocortisone capsules dispensed for a child with CAH. Each capsule should contain the same dose, but it is clear that there is great variation in capsule content(13)(reproduced with permission from Uta Neumann).



Hydrocortisone granules (0.5mg, 1mg, 2mg and 5mg) with immediate release and taste masking (Infacort, Alkindi®, Diurnal Pharma) have been approved in Europe in 2018 but are not yet available in Belgium (27).The absorption of Infacort was studied in 24 neonates and small children age 1 day to 6 years with CAH replacing their usual morning dose of hydrocortisone. Serum cortisol levels measured 1hr after dose administration were more than 150 nmol/L in all children, with a geometric mean of 575.8 ± 299.5 nmol/L (28) . Neumann et al treated 18 children (17 with CAH and 1 with congenital hypopituitarism) with Alkindi for up to 2 years. The dose of hydrocortisone was titrated based on salivary 17-OH-progesterone levels as recommended. At the last visit, the hydrocortisone doses were at the lower end of the recommended dose range without any adrenal crises. There were no treatment related severe adverse events and the participants had normal growth trajectories (29). Biopredictive modeling demonstrated that the hydrocortisone granules can be mixed with fruit juices and yoghourt and a pharmacokinetic study in adults confirmed a similar bioavailability when administered either as dry granules or sprinkled on top of soft food such as yoghurt or apple sauce facilitating the administration to young children(30)(31). Alkindi is unfortunately not available in Belgium.

Modified release tablets have been developed to alter the absorption profile of hydrocortisone after administration. Duocort (Plenadren®, Shire/Takeda 5 and 20 mg tablets) combines a slow release core with an immediate release layer of hydrocortisone After ingestion in the morning serum cortisol peaks after 40-50 min and remains detectable during the afternoon and evening . The hydrocortisone profile more closely resembles the physiological profile and allows a once a day administration (32). The lower total cortisol exposure compared to 3 times daily immediate release hydrocortisone tablets, had a less adverse effect on blood pressure and body mass index and improved quality of life in adults (33). A major drawback is the very low hydrocortisone level during the night and early morning which makes it less suitable for patients with CAH.

Chronocort (Efmody®, Diurnal) is designed to have a delayed and sustained release of hydrocortisone (34). The peak levels occur 5 hours after ingestion (35). It is taken in two daily doses and the evening dose generates a hydrocortisone peak in the early morning. In clinical trials in adults, Efmody suppressed ACTH and 17-OH-progesterone levels at a lower daily dose than hydrocortisone (36). A physiologically based pharmacokinetic model showed that the profile in adults and adolescents is identical and the European Medicines Agency therefore licensed its use from age 12 onwards (37). However, Efmody is so far not available on the Belgian market.

Conclusion

The established practice to obtain small hydrocortisone doses for children with CAH by splitting, crushing, dissolving or compounding available tablets is fraud with errors that can result in serious complications. Commercial low dose hydrocortisone and fludrocortisone products, reliably produced under GMP regulations, are urgently needed.

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