
Article:
Porter, J., Withe, M. and Ross, R.J. orcid.org/0000-0001-9222-9678 (2018) Immediate-release granule formulation of hydrocortisone, Alkindi®, for treatment of paediatric adrenal insufficiency (Infacort development programme). Expert Review of Endocrinology & Metabolism, 13 (3). pp. 119-124. ISSN 1744-6651

https://doi.org/10.1080/17446651.2018.1455496

Immediate-release granule formulation of hydrocortisone, Alkindi®, for treatment of paediatric adrenal insufficiency (Infacort Development programme).

Short title: Alkindi® (development name Infacort)

Keywords:

- **Adrenal Insufficiency**
- **Congenital Adrenal Hyperplasia**
- **Paediatric Use Marketing Authorisation**
- **Paediatrics**
- **Granules**

Word Count: 2694

Acknowledgements: Funded by the European Commission under the Framework 7 programme (Grant Agreement No. HEALTH-F5-2011-281654 -TAIN)

Drug summary box

Drug name Hydrocortisone **Phase** IV **Indication** Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old). **Pharmacology description/mechanism of action** Synthetic form of naturally occurring glucocorticoid hormone cortisol. Pleotropic effects through activation of the glucocorticoid receptor in multiple tissues. **Route of administration** Oral **Pivotal trial(s)** Infacort 003 Single arm pharmacokinetic study of drug in children aged from birth to 6 years with adrenal insufficiency. To our knowledge first published interventional pharmacokinetic study in this age and patient group.

Background and overview of the market:

The 2017 European commission report on paediatric medicines stated: “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" (1). Despite this guidance, children with adrenal insufficiency in Europe still receive crushed adult tablets or individually compounded preparations of hydrocortisone. Adrenal insufficiency results from failure to synthesise adequate levels of the stress hormone cortisol from the adrenal gland and is either primary due to failure of the adrenal gland or secondary due to failure of the pituitary; in children the commonest cause is Congenital Adrenal Hyperplasia (CAH)(2).

Patients with adrenal insufficiency will die from an adrenal crisis unless cortisol is replaced and children with CAH have the additional problem that the compensatory pituitary drive to the adrenal results in excess adrenal androgen secretion leading to pseudo-precocious puberty and virilisation in both male and female children. Until the 1950s patients with adrenal insufficiency inevitably died through adrenal crisis, and the discovery and introduction of glucocorticoid therapy was life-saving. However, treatment maybe complicated by excess glucocorticoid replacement which puts children at risk of poor growth, osteoporosis later in life, obesity, hypertension, depression and increased risk of cardiovascular disease (3). Guidance for use of replacement glucocorticoids in children is to use the lowest possible dose, and to use the native hormone, hydrocortisone (cortisol), rather than synthetic steroids such as prednisolone and dexamethasone which have a greater suppressive effect on growth (4). The challenge for paediatric patients and their health care providers is that hydrocortisone is only licensed in 10 and 20mg tablet doses in the European Union and children require much smaller doses (of the order of 1-2mg three times daily in infants), and are unable to swallow tablets designed for adults (5). Current clinical practice is for pharmacists to compound hydrocortisone either by tablet crushing or using hydrocortisone base to produce a powder or special solutions of hydrocortisone or in some countries, such as the United Kingdom, for parents to crush tablets (6-8). All such practice is unlicensed and not subject to the level of regulation and quality control of licensed drug manufacture where Good Manufacturing Practice (GMP) regulations mean that every aspect of manufacturing must be described, controlled and regularly assessed with a quality management system in place at each step. This means for instance that the active ingredient in a product should be controlled within strict parameters, usually 95-105% of the label claim (9). By contrast the production of compounded medicine is much less regulated and not subject to GMP, resulting in the Food and Drug Administration (FDA) warning that; "FDA does not verify the safety,

or effectiveness of compounded drugs" (9). A recent study, reported that 21.4% of pharmacist-compounded hydrocortisone batches failed to meet European pharmacopeia guidelines and a further 3.6% of batches contained no hydrocortisone (7). When parents rather than pharmacists crush hydrocortisone tablets the results are worse: data from a UK study of parents of children with adrenal insufficiency showed that >50% of doses were at least 10% out of specification (8). Parents find crushing tablets difficult: 27% report not having been instructed in how to prepare doses, and for those that did have instruction, only 10% reported having repeat training. Moreover, changes in manufacturing of hydrocortisone products can lead to difficulties with crushing or splitting tablets (10). The inconsistency in hydrocortisone dose created by compounding can lead to severe clinical consequences with poor disease control due to undertreatment (7) and Cushings syndrome due to overtreatment (11,12). Hydrocortisone is bitter and sucrose or lactose are often added to compounded tablets to improve palatability, however this has adverse effects on dental health and in children with lactose deficiency (13). EMA guidance for developing new medicines for children advises against sweeteners of all forms (14). Thus, there is a need for a licensed paediatric appropriate formulation of hydrocortisone.

Infacort Programme- development of a paediatric appropriate immediate-release granule formulation of hydrocortisone:

Alkindi® (Diurnal Ltd.) is a formulation of hydrocortisone developed under an EU-FP7 grant, The TAIN (Treatment of Adrenal Insufficiency in Neonates) Project, to meet the needs of paediatric adrenal insufficiency patients. Alkindi® is a multiparticulate granule formulation with maximum granule diameter controlled by passing through a 0.8mm sieve i.e. well below the FDA Guidance to industry on sprinkle formulation limits of 2.5mm diameter, and allows for swallowing of granules even by neonates (15). The granules are

presented within a transparent capsule that is opened for dosing, this allows for accurate paediatric dosing with dose strengths of 0.5, 1.0, 2.0, and 5.0 mg (Figure 1). The granules are so small that even the 0.5 mg capsule contains ~900 granules. Each granule has an inert cellulose core, a spray coat of hydrocortisone and a taste masking layer to prevent the bitter taste of hydrocortisone being experienced by the patient.

Hydrocortisone has been in use as a human medicine for over 60 years and is the pharmaceutical form of the natural glucocorticoid hormone cortisol. Cortisol binds the cytosolic glucocorticoid receptor which, translocates to the cell nucleus, and regulates gene expression through either transactivation or transrepression. Glucocorticoids also mediate actions through non-genomic mechanisms (16). Hydrocortisone is rapidly absorbed from the gut with almost 100% bioavailability reaching peak concentrations around an hour after being taken fasted (17) . Circulating hydrocortisone is approximately 90% protein bound mostly by cortisol binding globulin, but also by albumin. The binding proteins are saturable leading to non-linear pharmacokinetics whereby higher doses of hydrocortisone are cleared quicker (17,18). Hydrocortisone is metabolised by 11b-Hydroxysteroid dehydrogenase type 2 (11b-HSD2) to inactive cortisone in the kidney and other tissues and the reverse conversion occurs in liver and adipose tissue due to 11b-HSD1. Both cortisol and cortisone are renally excreted and hydrocortisone can be sequentially metabolised to allo-tetrahydrocortisol, tetrahydrocortisol and tetrahydrocortisone, also renally excreted (19).

Safety data gathered from pharmacovigilance of glucocorticoids generally reflects the widespread use of steroids as anti-inflammatory agents and not the rare condition of adrenal insufficiency. Anti-inflammatory doses of steroids are frequently ten-fold those used in replacement therapy and as most adverse effects are dose related these are less relevant when

prescribing hydrocortisone for adrenal replacement therapy. However, psychiatric adverse effects have been described in patients treated for adrenal insufficiency (20). Drug-drug interactions are seen in patients with adrenal insufficiency: potent CYP3A4 inducers such as anti-convulsants increase the clearance of steroids and require dose adjustment of hydrocortisone upwards, whereas enzyme inhibitors such as azole anti-fungals and erythromycin increase cortisol concentrations requiring a reduction in hydrocortisone dose (21-23).

Clinical studies with Alkindi®:

Development of Alkindi® was under a Paediatric Investigation Plan (EMEA-001283-PIP0-12) to support a hybrid marketing authorisation application for a Paediatric Use Marketing Authorisation (PUMA). The plan allowed for demonstration of bioequivalence to a marketed hydrocortisone (Auden Mckenzie Hydrocortisone 10mg) at phase 1 followed by a phase 3 study demonstrating appropriate exposure in paediatric adrenal insufficiency patients. To demonstrate bioequivalence between Alkindi® and the reference hydrocortisone product healthy adult male volunteers were treated with dexamethasone to suppress their hypophyseal-pituitary-adrenal axes. The study was a single centre, open label, randomised, crossover study in 16 dexamethasone-suppressed healthy adult male volunteers which compared the pharmacokinetics of Alkindi® with the reference hydrocortisone tablets at a single dose of 10mg and also evaluated the dose proportionality of Alkindi® at doses of 0.5, 2.0, 5.0 and 10 mg. The study demonstrated bioequivalence of Alkindi® to immediate release hydrocortisone (Figure 2)(5).

The phase 3 study was undertaken in the Charite hospital in Berlin (6). The study was a sequential age cohort design to maximise subject safety. Initially 12 patients with adrenal

insufficiency aged 2 years to 6 years were studied. Following analysis of safety outcomes, a further 6 infants with adrenal insufficiency aged 1 month to 2 years were studied, and finally 6 neonates aged less than 28 days with adrenal insufficiency were studied. The protocol was similar in all cohorts with patients receiving a morning dose of Alkindi® identical to their usual morning dose of compounded hydrocortisone. Dosing was at least 8 hours after the patients' previous dose of hydrocortisone, and was at least 2 hours after food in children aged twelve months or more, and 45 minutes after food in those aged less than 12 months. Following dosing the children had blood sampling at 0, 60 and 240 minutes with the primary endpoint being maximum serum cortisol concentration up to 240 minutes after Alkindi® administration as measured by liquid chromatography-mass spectrometry. Secondary endpoints included palatability of Alkindi® (for which new 5 point Likert questionnaires were developed for parents and patients), adverse events and vital signs recorded during the study. 23 of the 24 children studied had Congenital Adrenal Hyperplasia and one patient had hypopituitarism, the median age was 3 years and 3 months, 54.2% were male and all subjects were white. All children were successfully dosed with a median dose of 2mg. In all children cortisol increased from baseline to a C_{max} at 60 minutes (Figure 3). The absolute geometric ± SD (standard deviation) mean cortisol concentration at C_{max} was 575.8 ± 299.5 nmol/L for the overall population (> 2years cohort: 547.1 ± 82.9 nmol/L; 1 month to 2 years cohort: 450.1 ± 88.9 nmol/L; < 28 days cohort: 815.7 ± 474.9 nmol/L). The rapid absorption and clearance of cortisol was similar to findings in previous studies of children dosed with immediate release hydrocortisone (24). The hydrocortisone C_{max} was similar to peak concentrations of cortisol in children with intact hypophyseal-pituitary-adrenal axes (25). Alkindi® was generally well received by parents and children alike. 82.6% of parents agreed/strongly agreed that their child found swallowing Alkindi® easy and 95.5% said that they would prefer Alkindi® for their child's treatment over their usual hydrocortisone

formulation. Six of the 12 children in the oldest cohort responded to an adjusted palatability questionnaire, with ≥50% subjects reporting that the taste, feel in mouth and ease of swallowing were very good and that they were likely to take the medicine again. No serious adverse events were seen throughout the study, and the adverse events seen were mild (most common reported were diarrhoea, vomiting and rash) and not attributed to investigational product (6).

Following the phase 3 Alkindi® study subjects could choose to continue in a safety extension study. 18 subjects elected to continue, and at time of writing 12 patients remain on treatment. Drop outs from the study related to problems with dosing of the older children who were used to taking a sweetened compounded hydrocortisone liquid in the evening. These subjects were aged between 2-6 years and the investigators felt treatment refusal was related to age appropriate behavioural development rather than rejection of the specific therapy. Following a change of advice to allow sprinkling of granules on yoghurt or fruit mousse there have been no further drop outs. Indeed, one patient who initially refused Alkindi® then demanded to go back on Alkindi®. At one year, patients on Alkindi® had good disease control, no abnormal progression in pubertal status and growth was as expected.

Current status of Alkindi®:

Alkindi® received a centralised paediatric use marketing authorisation in the European Union on 9th February 2018 for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old)(Reference Alkinid SmPC Diurnal Ltd.). Alkindi® is also being investigated under an Investigational New Drug programme in the United States of America.

Conclusions:

Alkindi® is a novel paediatric formulation of immediate release hydrocortisone licensed for use in paediatric adrenal insufficiency with doses of 0.5, 1.0, 2.0 and 5.0 mg (reference Alkindi SmPC Diurnal Ltd). Alkindi® provides a consistent licenced treatment option for accurate dosing in children with adrenal insufficiency where compounded adult tablets of hydrocortisone are unsuitable.

Expert commentary:

Adrenal insufficiency was inevitably fatal before the introduction of glucocorticoid replacement therapy in the 1950s. Hydrocortisone replacement therapy is life-saving, however there has been little innovation since its introduction in the 1960s and there is increasing recognition that both children and adults with adrenal insufficiency have an increased morbidity and mortality related to under or over treatment with glucocorticoid (3). Treatment of paediatric patients with adrenal insufficiency is challenging due to the lack of appropriate glucocorticoid preparations for children and the use of either pharmacy- or parent-compounded hydrocortisone tablets. Paediatric patients suffer from over- and under-treatment (7), growth outcomes in congenital adrenal hyperplasia are suboptimal (26), and for parents there is the continuous stress of managing a child at risk of adrenal crisis if they don't receive the correct medication and this is most stressful in the youngest children (27). Compounding hydrocortisone has multiple issues beyond inconsistent dosing including the practical problems for parents who compound the drug themselves or travel long distances to a compounding pharmacy and the cost of compounding by the pharmacy. Alkindi® is a licenced formulation providing accurate dosing and allows paediatricians to titrate doses to the needs of the growing child. The Alkindi® formulation is easily administered to young children or older children who find taking tablets difficult.

Five-year view:

In 2017 the European Commission reported on the status of paediatric medicines ten years after the introduction of paediatric medicines legislation (1). Although there had been an increase in the number of successfully completed paediatric investigation plans this was mainly in areas where the needs of paediatric and adult patients overlapped, and progress in rare childhood disease areas has been slow. The commission is investigating how to improve this situation, and it seems likely that there will be increasing provision of medicines for children. In adrenal insufficiency the development of Alkindi® is an important first step in improving the care of children with adrenal insufficiency and its PUMA is only the fourth approved PUMA under this route. However, replacing the natural circadian rhythm of cortisol is not addressed by Alkindi® (28). A modified release formulation of hydrocortisone is under development for CAH by Diurnal Ltd that more closely mimics the overnight physiological pattern of cortisol release and in a phase 2 study improved biochemical control in patients with CAH (29,30). It is anticipated that this product will be developed for children. Finally, a number of non-glucocorticoid products are under development that may address the excess of androgens in CAH (31). These are in early stage trials, but may improve control and reduce steroid requirements in patients with CAH.

Key issues:

- Currently children with adrenal insufficiency are dependent on compounded hydrocortisone formulations which do not provide accurate dosing, are bitter to taste and associated with poor disease control resulting in under and over treatment, adrenal crises and poor growth.
- Alkindi®, is an immediate release hydrocortisone formulation with taste masking, licenced under a PUMA, and provides an easy to administer, well tolerated, paediatric formulation which allows accurate dose titration in neonates, infants and children.

Figures:

Figure 1: Alkindi® is a granule formulation of immediate release hydrocortisone that can be dosed in neonates. Figure shows that by combining capsules incremental doses can be used as the child grows. (Source Diurnal Ltd.)

Empty first capsule (2mg) onto spoon

Empty second capsule (0.5mg) onto spoon

Give complete dose (2.5mg) to child following administration instructions

Figure 2: Alkindi® was bioequivalent to hydrocortisone tablets in adult phase 1 trials. Figure shows Alkindi® at doses 0.5 to 10mg compared to a standard 10mg hydrocortisone tablet. (Whitaker et al. JCEM 2015)

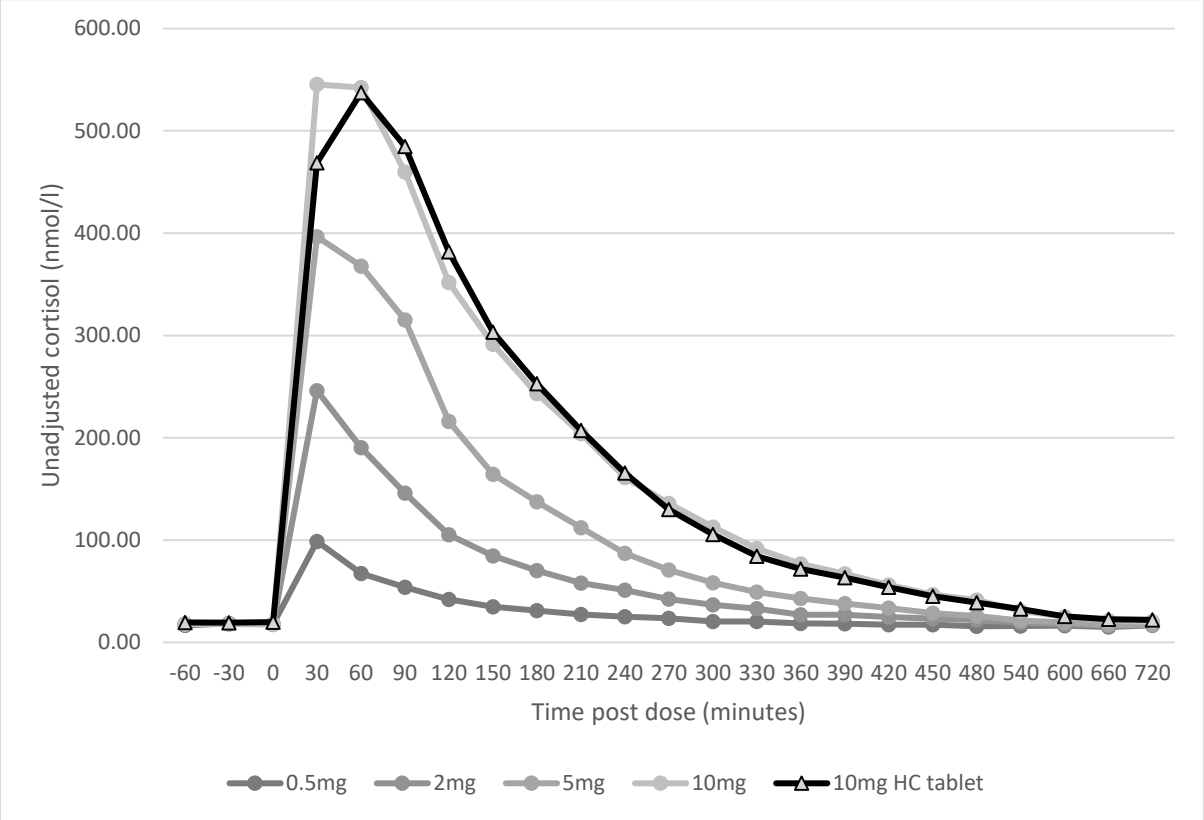
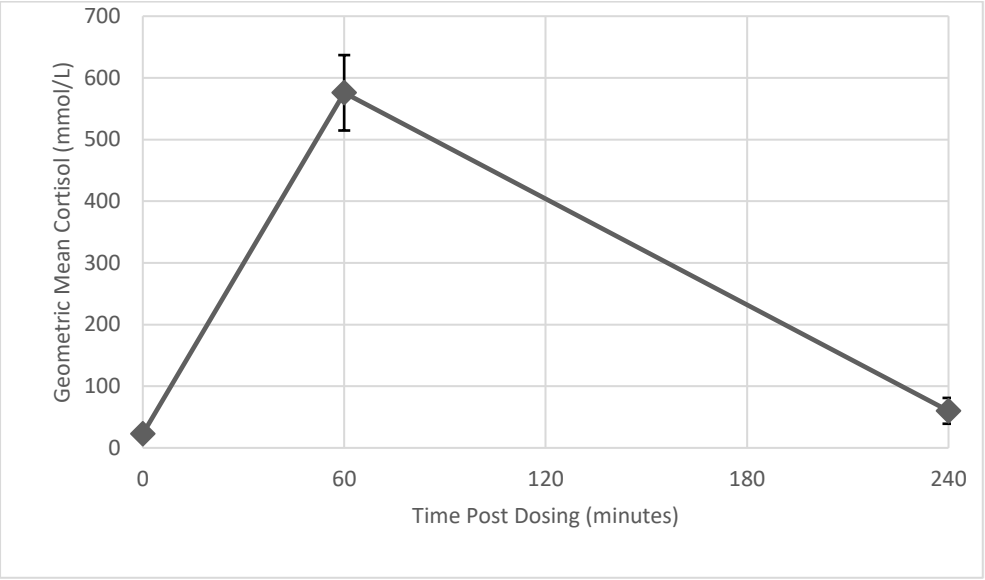


Figure 3: Geometric mean ±SEM cortisol levels following single dose of Alkindi® in neonates, infants and children <6 years. (Data from Infacort003 study Diurnal Ltd.)



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Reference Annotations

**References of considerable importance

EU. State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation COM 2017; 626

This reference is key as it lays out the European view on the importance of medicines for children and the failure to date to adequately cater for children's medicine

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; 100:1681-1688

This reference is key as it describes the initial development and phase 1 trial for the product.

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;

This reference is key as it describes the pivotal phase 3 study for the product

*References of importance

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

This reference is important as it describes the potential problems relating to compounding in a developed European situation

Webb EA, Watson C, Kerr S, Davies JH, Stirling H, Batchelor H. Hydrocortisone tablets: human factors in manipulation and their impact on dosing accuracy. Endocrine Abstracts 2017; 51:OC8.1

This reference is important as it describes the issues relating to parental manipulation of tablets to provide paediatric doses.