A PROSPECTIVE STUDY OF CHILDREN 0-7 YEARS WITH CAH AND ADRENAL INSUFFICIENCY TREATED WITH HYDROCORTISONE GRANULES

Uta Neumann[1], Katarina Braune[1], Martin J Whitaker[2], Susanna Wiegand[1], Heiko Krude[1], John Porter[2], Dena Digweed[2], Bernard Voet[2], Richard JM Ross[3], Oliver Blankenstein[1]

[1]Charité Universitaetsmedizin Berlin, Germany. [2]Diurnal Ltd, Cardiff, United Kingdom. [3]University of Sheffield, Sheffield, United Kingdom.

Correspondence: Uta Neumann, Charité-Universitaetsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Email: uta.neumann@charite.de

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Abstract

Context: Children with congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) require daily hydrocortisone replacement with accurate dosing.

Objective: Prospective study of efficacy and safety of hydrocortisone granules in children with AI and CAH monitored by 17-OHP saliva profiles.

Methods: 17 children with CAH (9 male) and 1 with hypopituitarism (male) aged from birth to 6 years, had their hydrocortisone medication changed from pharmacy compounded capsules to hydrocortisone granules. Patients were followed prospectively for 2 years. In children with CAH therapy was adjusted by 3-monthly 17-OHP profiles. The following parameters were recorded: hydrocortisone dose, height, weight, pubertal status, adverse events, and incidence of adrenal crisis.

Results: Study medication was given thrice daily, median duration of treatment (range) was 795 (1-872) days with 150 follow-up visits. Hydrocortisone doses were changed on 40/150 visits, 32 based on salivary measurements and 8 on serum 17-OHP levels. Median daily hydrocortisone dose mg/m^2 (range) at study entry in different age groups: 2-8 years, 1months-2years, <28 days was 11.9 (7.2-15.5), 9.9 (8.6-12.2) and 12.0 (11.1-29.5) and at end of study was 10.2 (7.0-14.4), 9.8 (8.9-13.1) and 8.6 (8.2-13.7). There were no trends for accelerated or reduced growth. No adrenal crises were observed despite 193 treatment-emergent adverse events, which were mainly common childhood illnesses.

Interpretation: This first prospective study of glucocorticoid treatment in children with AI and CAH demonstrates that accurate dosing and monitoring from birth results in hydrocortisone doses at the lower end of the recommended dose range, normal growth, without occurrence of adrenal crises.

Keywords: Congenital Adrenal Hyperplasia, Adrenal Insufficiency, Hydrocortisone, saliva, children

Introduction:

The most common cause of adrenal insufficiency (AI) in young children is congenital adrenal hyperplasia (CAH) (1). Patients require lifelong glucocorticoid replacement therapy (2). The recommended therapy in childhood is hydrocortisone given 3-4 times daily (2). It is necessary to adjust the glucocorticoid dose in the growing child and timed hormone measurements including 17-hydroxyprogesterone (17-OHP) are used to monitor CAH control (2). Successful therapy of AI in childhood requires access to a multidisciplinary team of healthcare professionals and regular clinic visits, and reliable medication to avoid adverse effects (3). Until 2018, the lowest available licenced preparations of hydrocortisone were 10 mg tablets in Europe and 5 mg tablets in the United States (US). As scored tablets are licensed to be divided into halves the lowest possible available dose was 5 mg (Europe) and 2.5 mg (US) respectively. However, these doses are not appropriate to treat neonates, infants and young children with adrenal insufficiency who require a daily dose of 10-15 mg/m² with single doses as low as 0.5 mg (4). Crushed hydrocortisone tablets suspended in water are often used in some countries (2), though accurate dosing is not possible as hydrocortisone does not dissolve well in water and may adhere to plastic material when applied with syringes (5,6). Another common practice in pharmacies is to compound hydrocortisone often mixed with sucrose to overcome the inherent bitterness of hydrocortisone. However, a German study demonstrated that up to 25% of compounded batches do not fulfil the acceptance criteria of the European Pharmacopeia in uniformity of net mass or drug content or are labelled inaccurately (7). In Europe, hydrocortisone granules have now become licensed for children with AI from birth to 18 years of age, and are available in low doses of 0.5, 1, 2 and 5 mg. They were developed to address the age group-specific needs of neonates, infants and young children (8,9). As part of the development programme a single dose clinical trial was undertaken in neonates, infants and children under 6 years with AI, the majority of whom had CAH (10). The children were then invited to participate in a prospective

follow-up study of continued treatment with hydrocortisone granules. It was not possible to include a control group for the hydrocortisone granules as there is no licenced formulation providing a hydrocortisone dose below 5mg and the regulatory authorities recommended against using compounded medication. This manuscript reports the results of this prospective study.

Methods

Protocol: A prospective follow-up study with patients who had been recruited from a previous single dose pharmacokinetic study of hydrocortisone granules was performed over a duration of 2.5 years. The first three clinic visits were scheduled monthly followed by 3-monthly visits. Children who withdrew early were included in baseline and safety analyses but excluded from further analysis.

Patients: 18 patients, 10 male, and all Caucasian, 1 male with congenital hypopituitarism and the others with genetically confirmed CAH were included. All of them successfully completed the previous study with single dosing of the study medication whose inclusion criteria were: age <6 years, confirmed AI (inappropriately low cortisol level), receiving appropriate adrenocortical replacement therapy (hydrocortisone +/- fludrocortisone), adequately hydrated and nourished status at the screening visit and the ability of the parents/carers to understand and give written informed consent according to the German Medicinal Product Act (AMG §40 3b) (1). Exclusion criteria included: clinical signs of acute infection, fever or current adrenal crisis although subjects could be re-evaluated for eligibility after acute episodes, inability of the child to take oral therapy, any surgical or medical condition that, in the opinion of the Investigator, could have placed the subject at higher risk from his/her participation in the study and parents/carers of subjects unwilling to consent to saving or propagation of pseudonymised medical data for

study reasons. The patients were enrolled into three cohorts according to their age at study entry in the previous study (Table 1).

Treatment: The hydrocortisone dose was given according to the manufacturer's instructions (Alkindi® Summary of Product Characteristics). Children´s hydrocortisone medication was changed from pharmacy compounded capsules to hydrocortisone granules continuing the same dose. Patients were followed prospectively for 2 years. In children with CAH therapy was adjusted by 3-monthly 17-OHP profiles timed prior to each dose. Compliance with intake of hydrocortisone granules was calculated on the basis of the number and strength of capsules dispensed and returned, the number of days between visits and the daily dose of hydrocortisone prescribed for the time interval.

Measurements: At each visit the following measurements were taken: weight, height, blood pressure, heart rate, and a physical examination including pubertal status. In CAH patients, salivary 17-OHP levels were used for dose adjustments in accordance with the clinic's standard practice, based on at-home sampling every three months starting from 3-6 months of age. Patients were trained to chew on a swab (Salivette® Sarstedt, Germany) for at least 3 minutes immediately before each dose of hydrocortisone for two consecutive days, i.e. 6 samples. In children below 1 year of age the parents/carers wiped the oral cavity with the Salivette-swab to collect saliva. Serum measurements of 17-OHP were only made if the child was unable to provide a 17-OHP saliva profile or when renin levels were measured annually as part of routine clinical care. Blood sampling was not timed prior to hydrocortisone intake, as it was performed when children visited the outpatient clinic. Adverse events following the first intake of study medication including stress dosing were recorded at every visit.

Calculations of weight-, height-SDS and parental target height-SDS: Weight and height standard deviation score (SDS) were based on German KIGGS-Data (11). The parental target height was calculated using the method of Hermanussen/Cole (12).

Methods of hormone measurements: Hormones were measured using the clinic's standard practices. Serum 17-OHP was measured using the IDS-ISYS 17-OHP assay (Immunodiagnostic Systems Limited, UK) with a lower limit of quantification 0.31 ng/mL. Salivary 17-OHP was measured using the Demeditec free 17-OHP in saliva ELISA kit (Demeditec Diagnostics GmbH, Kiel, Germany), both according to the manufacturer's instructions. Performance parameters for the assays (serum/saliva) are: Intra-Assay variability: 2.4% / 5.2%; Inter-assay variability: 6.2% / 5.3%; LLOQ: 0.3 ng/ml / 11.3 pg/mL.

Hydrocortisone dosing and dose titration: Hydrocortisone dose in newborn babies was determined by the treatment centre. This was 2mg hydrocortisone thrice daily for the main centre, while the two newborns from satellite centres were treated with 2-1-1 mg and 1-1-1 mg respectively. Initially the dose was adjusted by serum 17-OHP; reducing the dose as soon as serum 17-OHP was normalized until a minimum of 2-1-1 mg in two patients and 1-1-1 mg in the third newborn baby. From about 6 months of age, dosing of hydrocortisone was adjusted using timed saliva 17-OHP profiles in patients at the central clinic, while the patients from satellite centres were monitored by serum 17-OHP. The central clinic has established daytime specific target ranges for pre-dose salivary 17-OHP based on the reference range for healthy children (3.0-32.9 pg/mL). Target ranges for CAH patients were defined as follows:

- Between 2am and 10am: <2,5-fold of the upper reference limit (RL) was considered "overtreatment", 2,5 to 5-fold "good disease control", 5 to 10-fold "acceptable" and >10-fold levels as "undertreatment".

- Between 10am and 2am the ranges were reduced by 50% as follows: <1,25-fold of the upper reference limit (RL) was considered “overtreatment”, 1,25 to 2.5-fold “good disease control”, 2,5 to 5-fold “acceptable” and >5-fold levels as “undertreatment”.

Hydrocortisone doses were adjusted according to the pre-dose 17-OHP salivary profiles. If the value for 17-OHP was out of range, the dose 8 hours before that sample timepoint was adjusted. Doses were adjusted by smallest increment possible, usually 0.5mg-1.0mg depending on how close the current daily hydrocortisone dose was to the target range of 10 mg/m²/day. Hydrocortisone dose in mg per body surface area was always calculated but was not the sole basis for dose adjustment.

Sick day rules, adrenal crisis: Parents/carers were trained in using the clinic’s standard sick day rules for children with AI in case of fever and illness and increased their daily hydrocortisone dose according to local guidelines: For fever >38°C double hydrocortisone dose, for fever >39°C triple dose, and for fever >40°C five-fold dose. A repeated full dose was recommended in case of vomiting, and a prednisolone suppository (100mg) and urgent presentation to a doctor was indicated when the vomiting continued. Adrenal crisis was defined as a profound impairment of general health and at least two of the following conditions: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, hyponatraemia, hypoglycaemia and hyperkalaemia (13).

Ethics: The study was conducted in accordance with the ethical principles in the Declaration of Helsinki (1996) and in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the Independent Ethics Committee (IEC, 15/0375 – EK 15) and BfArM (the German regulatory authority) requirements. All parents/carers gave their written informed consent and all children >3 years of age were separately informed about study procedures.

Subjects remained enrolled in the study unless they met the study withdrawal criteria or until hydrocortisone granules became commercially available.

Results:

Patients and visits: 18 patients were recruited. In total, 6 patients withdrew during the study; 4 withdrew within the first month and their data were only included in the baseline and safety analysis, 1 patient withdrew after 5 months and has data included but did not attend the final visit and the growth charts therefore exclude this patient, 1 patient withdrew before first dosing resulting in inclusion of only demographic data. One patient also withdrew before dosing, but subsequently re-enrolled, and the respective data are included from that date onwards. One male patient with hypopituitarism was only included in the demographic data and safety data analysis as growth was impaired by the underlying condition. Seventeen patients (8 females, 9 males), with genetically confirmed classic CAH had salt wasting CAH and were additionally treated with fludrocortisone. All withdrawals were within the older patient cohorts 1 (n=5) and 2 (n=1) and were related to difficulties adapting from sweetened pharmacy-compounded powder to tasteless dry granules for the administration of the night-time dose while sleeping. A protocol amendment was made during the study to allow use of soft food for administration of the granules. Study follow up was up to 2.5 years: median (range) 795 days (1-872 days). Of the 12/17 children with CAH who received hydrocortisone granules for more than one month, the mean number of visits/patient (SD) was 10.7 (4.93) with a median (range) of 13 visits (1-15). Overall, 150 follow-up visits were analysed. The compliance of patients included in the study until withdrawal or until study end was good, with a median of 98.9% of treatment days with correct intake of study medication.

Growth: SDS scores for height and weight in the 11 children with CAH treated with hydrocortisone granules for over 6 months were evaluated over the study period and all but one showed normal growth with no trends for accelerated or reduced growth. The one patient with reduced growth had congenital renal hypoplasia in addition to CAH, which explained the poor growth. When adjusted for target height, two thirds of the children converged towards their expected height centile (Figure 1a). The mean difference between z-scores of actual height and target height (SD) decreased from 1.04 (0.71) to 0.89 (0.72). The z-scores for weight and BMI decreased toward the 50th percentile in half of patients (Figure 1b).

Safety and Sick Day Rules: There were no deaths, no severe treatment-emergent adverse events (TEAEs), no TEAEs leading to withdrawal from the study and no TEAEs with a suspected causal relationship to hydrocortisone granules. No cases of adrenal crisis were reported. Nine severe adverse events (SAEs) were reported in 3 patients (gastroenteritis, vomiting, urinary tract infection, erysipelas), all considered unrelated to hydrocortisone granules. A total of 193 TEAEs were reported by 14 subjects (77.8%) the most commonly occurring of which were pyrexia, n=45 in 10 patients (45/10), gastroenteritis 15/9, viral upper respiratory tract infection 21/7 and vomiting 14/7. In 172 of the 193 treatment-emergent adverse events (13 subjects), and in all 9 SAEs, the hydrocortisone dose was increased using the sick day rules, of these TEAEs 42 were reported by one subject (Table 2). Most common causes of sick day episodes were fever, vomiting or diarrhoea, respiratory tract infections or other (most commonly stress or excitement related symptoms or abdominal pain). In the subject with 42 episodes of implementing sick day rules further investigation found the parents were dosing for excitement and non-specific abdominal pain on multiple occasions, e.g. birthday party or New Year's Eve. With the majority of TEAEs the hydrocortisone dose was increased according to the sick day rules, in seven cases the increased stress dose was given for 7-12 days and in all other events the duration was less than 7 days.

Hydrocortisone dose: The hydrocortisone dose was within the recommended dose for body surface area (BSA) over time and at the lower end of recommended treatment ranges for CAH at the end of the study (Table 3). Doses used at different time points varied from 0.5mg to 10mg and the dose distribution varied from the beginning to the end of the study within age groups with the older patients having a greater proportion of their dose in the morning and night-time (Table 4).

Fludrocortisone dose: Daily fludrocortisone dose was divided in 1-3 single doses per day and adjusted according to the renin level (Table 3).

Monitoring by saliva and blood sampling: Salivary profiles were collected at home prior to 54% of study visits (82/150). The 17-OHP salivary profile was in range during the whole day profile in 44% (36/82), at two time points in 28% (23/82) and at only one time point in 16% (13/82). In 12% (10/82) the whole daily profile of salivary 17-OHP was out of range. Hydrocortisone doses were changed in 40/150 visits, in 32 visits based on the results of salivary measurements collected at home before the visit and in a further 8 visits due to serum 17-OHP levels. In 21 of those visits, a single dose was changed, in 13 visits two doses and in 6 visits all three were changed amounting to 65 dose changes in total. In 82% the morning or night-time dose were changed resulting in an altered dose distribution across the day with lowering of the midday dose. In 12 of 32 cases where dose was adapted based on 17-OHP saliva sampling a repeat sampling was done within 4 weeks and in 8/12 cases these control samples were in range.

Discussion:

We have prospectively studied a group of children with AI from 0 to nearly 8 years of age treated with hydrocortisone granules for a total duration of up to 2.5 years. To our knowledge, this is the largest prospective interventional study to date in neonates, infants and young children with AI. Individualised treatment by titration in these patients was in line with the treating centre's normal practice. The availability of a lowest unit dose of 0.5mg allowed doses to range from 0.5 to 10mg at individual time points during the day. In 21.3% of all administrations 0.5mg doses were used. The daily dose per BSA at the end of the study period across the patient group was at the lower end of that recommended for the treatment of CAH, and similar to that recommended for adrenal replacement therapy. Despite this relatively low dose, disease control remained good as demonstrated by normal growth and lack of pubertal development. The children experienced common childhood illnesses resulting in a large number of adverse events reported, none of which were considered related to the study medication, and no adrenal crises occurred.

Recommended hydrocortisone dosing for children with CAH is 10–15 mg/m^2/day given 3 times daily although cohort studies show higher doses generally being used in children (14-16). In this study, accurate dosing with hydrocortisone granules using dose changes down to 0.5mg allowed dosing at the lower bound of the recommended dose range. The thrice daily, individualized, 8-hour dosing-regimen used in this study has been used for many years in the main centre. While it appears clear that twice daily dosing is less effective in attainment of physiological cortisol concentrations than thrice daily dosing, no evidence to date has shown a benefit for differently timed regimens for hydrocortisone delivery (14). Pharmacokinetics studies of hydrocortisone in children with AI reveal significant times of high and low cortisol exposure with frequently very low cortisol levels between dosing (17), and therefore this was likely in this study.

This is the first prospective study in young children of stress dosing and adrenal crisis and demonstrates that children with AI under 8 years of age encountered multiple intercurrent illnesses, however, despite the hydrocortisone dose being towards the lower end of the recommended dose range, no adrenal crises were seen during this period. CAH has been associated with increased risk of mortality. In a cohort of 588 patients with CAH from the Swedish national registry, adrenal crisis has been reported as the leading cause of death followed by cardiovascular disease, which is the leading cause of death in adults globally (18). Prevention of adrenal crises in CAH patients is one of the key elements of appropriate glucocorticoid dosing under normal and stress-related situations (14), and the main risk of lowering doses of steroid in conditions with AI is the possible increase in life threatening adrenal crises. A long-term study of adrenal crises in patients with CAH found that receiving lower hydrocortisone doses had associated higher rates of stress dosing and illnesses and were a risk factor for adrenal crises (19). Patients with CAH and adrenal insufficiency and their carers are taught sick day rules (20), and are recommended to increase their glucocorticoid intake by doubling, tripling or five-fold increasing the dose whenever they feel unwell with a fever or flu-like illness. In case of vomiting, diarrhoea or severe worsening of illness use a prednisolone suppository or an injection of hydrocortisone is recommended. There is no universal accepted sick day rules regimen. The protocol used in this study, according to the German CAH guidelines, has been successfully used by the main centre for several years, and worked well for the study cohort. Up until recently, very little information on the underlying causes that prompt parents to institute stress dosing have been assessed systematically. A retrospective study of El-Maouche et al. found an increased number of illnesses and necessary stress dosing in children compared to adults with highest rates particularly in the younger children (21). The follow-up period of our study allowed us to gather such data, with adverse events and stress dosing discussed during regular three-monthly visits, and it was reassuring that in most cases the stress

dosing was being used for physiological stresses. However, one patient in this cohort had an excess number of events treated with stress dosing, and administered higher doses, e.g. for excitement and non-specific abdominal pain on multiple occasions. We believe that gathering data on stress dosing can help paediatric endocrinologists to identify families where stress dosing is being used more frequently than expected and counselling and support can be instituted to avoid the child being exposed to excessive steroid doses.

The drop-out rate in the study can be explained by two major factors depending on age of the children. In neonates, patients were recruited from all over Germany and parents were not willing to travel the long distance to the study centre in the follow up study. In children >2 years of age those withdrawing generally did not accept the change to a non-sweetened hydrocortisone medication and so withdrew early. In the remaining study cohort, compliance was high with a median of >98% of treatment days where study medication was administered as recommended, and might reflect the clinic's approach of patient empowerment and education of the patients, parents, and carers.

Therapy was predominantly monitored by salivary profiles. If parents provide a child's salivary 17-OHP profile before the clinic visit, we do not perform serum 17-OHP. However, at the yearly blood sample to check for renin values we always measure serum testosterone and 17-OHP These blood samples are not timed and therefore, in our experience, of limited value as sometimes the serum 17-OHP is increased despite the 17-OHP home salivary profile two days before being in range. This might be due to blood sampling inducing an increase in 17-OHP. Additionally, it is difficult to adjust individual doses during the day according to a single serum 17-OHP measurement. When dosing was adjusted by 17-OHP salivary profile the hydrocortisone dose before each sampling timepoint was evaluated and changed as required. When dosing was adapted by the serum 17-OHP measurement, the overall dose was adjusted

according to the international guidelines by calculating the dose by 10-15 mg/m² body surface area divided in 3 single doses (14). Monitoring of CAH is an area where little data exists to provide practice guidelines. According to our experience, salivary sampling in young children worked well with salivary profiles available at more than half of the clinic visits, so that blood sampling could be minimised. Monitoring by 17-OHP salivary profiles was started at 3-6 months of age. An advantage of 17-OHP saliva sampling is that the collection can be performed at home without further stress for the children and allows individual titration of therapy for each patient. However, more research is required to develop best practice guidance on monitoring in CAH, with our data suggesting that salivary sampling can be considered as a viable alternative to blood sampling.

Based on our findings from this study, which is the largest interventional study in the orphan condition of childhood adrenal insufficiency to date, the use of hydrocortisone granules resulted in effective treatment of the children's adrenal insufficiency as demonstrated by the absence of adrenal crises and a normal growth profile. No safety issues were detected. Over the course of 2.5 years, the patients' doses of hydrocortisone remained stable within the recommended range and decreased at the end of study to the lower end of the recommended treatment range for CAH. In conclusion, hydrocortisone granules are an effective treatment for childhood adrenal insufficiency providing the ability to accurately prescribe paediatric appropriate doses.

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Figure legends

Figure 1: Height and weight of individual patients at start and finish of study in patients that had more than 6 months treatment (n=11): a) Height SDS compared to parental target height; b) weight SDS.

*This child had renal hypoplasia in addition to CAH

Table 1: Patient characteristics at baseline, median (range). Classification in 3 cohorts according to age at study entry in previous study: cohort 1 (2-<6 years), cohort 2 (1 month-2 years) and cohort 3 (<28 days).

Table 2: Implementation of Sick Day Rules. The percentage subjects overall was calculated from the overall subject number n=18.

Table 3: Daily dose of Hydrocortisone (HC) and Fludrocortisone (FC) at beginning and end of study in different age groups, median (range), N. Classification in 3 cohorts according to age at study entry in previous study: cohort 1 (2-<6 years), cohort 2 (1 month-2 years) and cohort 3 (<28 days).

Table 4: Average dose and dose distribution of hydrocortisone (morning – afternoon – night-time-dose) across visits according to the age of the children

Table 1: Patient characteristics at baseline, median (range). Classification in 3 cohorts according to age at study entry in previous study: cohort 1 (2-<6 years), cohort 2 (1 month-2 years) and cohort 3 (<28 days).

	Cohort 1	Cohort 2	Cohort 3	Overall
Number	n=9	n=6	n=3	n=18
female/male	4/5	2/4	2/1	8/10
Age (days)	1316 (1077-2084)	748 (394-923)	46 (36-145)	1000 (36-2084)
Age (months)	43 (35-68)	25 (13-30)	2 (1-5)	33 (1-68)
BMI (kg/m²)	16.4 (13.7-22.1)	17.5 (16.4-20.1)	16.0 (13.2-16.8)	16.83 (13.2-22.1)
BSA (m²)	0.71 (0.58-0.84)	0.56 (0.44-0.60)	0.27 (0.20-0.33)	0.59 (0.20-0.84)

Table 2: Implementation of Sick Day Rules. The percentage subjects overall was calculated from the overall subject number n=18.

Cause	Episodes	Subjects	Percentage subjects overall
Vomiting	14	5	28
Fever	101	13	72
Diarrhea	9	2	11
Other†	47	10	56
No reason given	1	1	6
Total*	172	13	72

*42 episodes in one individual

† Other causes are: Excitement/stress (birthday party, New Year´s Eve, Sleepover in kindergarten, first day at school), Abdominal pain, Infection, Injury (e.g. laceration, injury of teeth after fall), Headache, Exercise, Operation/Procedure, Rash

Table 3: Daily dose of Hydrocortisone (HC) and Fludrocortisone (FC) at beginning and end of study in different age groups, median (range), N. Classification in 3 cohorts according to age at study entry in previous study: cohort 1 (2-<6 years), cohort 2 (1 month-2 years) and cohort 3 (<28 days).

Visit	Cohort 1	Cohort 2	Cohort 3	Overall
First Visit				
HC dose (mg/m^2)				
Median (range)	11.9 (7.20-15.5)	9.9 (8.6-12.2)	12.0 (11.1-29.5)	11.4 (7.2-29.5)
N	9	4	3	16
FC dose ($\mu g/m^2$/day)				
Median (range)	102 (62-159)	146 (124-180)	492 (369-900)	127 (62-900)
N	9	4	3	16
Last Visit				
HC dose (mg/m^2)				
Median (range)	10.2 (7.0-14.4)	9.8 (8.9-13.1)	8.6 (8.2-13.7)	9.7 (7.0-14.4)
N	4	4	3	11
FC dose ($\mu g/m^2$/day)				
Median (range)	61 (45-77)	70 (65-94)	213 (92-216)	72 (45-216)
N	4	4	3	11

Table 4: Average dose and dose distribution of hydrocortisone (morning – afternoon – night-time-dose) across visits according to the age of the children

	Average dose distribution	Mean HC dose	Proportion of administrations containing 0.5 mg granule dose
Children aged 0-3 month	33,3 – 33,3 – 33,3 %	1.5 – 1.5 – 1.5 mg	0 – 0 – 0 %*
Children aged 4 month – <2 years	46 – 22 – 32 %	2.3 – 1.1 – 1.6 mg	0 – 7 – 10 %
Children aged 2-<4 years	40.6 – 18.7 – 40.6 %	2.6 – 1.2 – 2.6 mg	41 – 18 – 23 %
Children aged 4- 8,4 years	36 – 14 – 50 %	3.2 – 1.3 – 4.6 mg	18 – 43 – 15 %

* half of the patients were treated with a hydrocortisone dose of 2-2-2 mg and half of the patients with 1-1-1 mg resulting in a mean dose of 1.5-1.5-1.5 dose.

Figure 1