Development of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency

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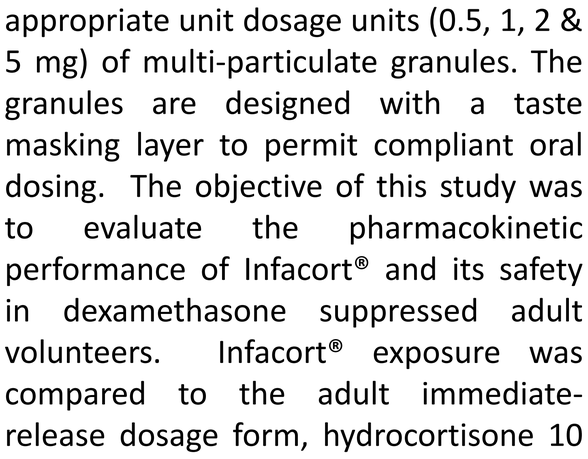
Background

Current treatment in Europe for adrenal insufficiency in neonates and infants is unsatisfactory as unlicensed adult dosage formulations are used. These are difficult to administer and may give rise to inconsistencies in dose as the content uniformity of the dosage form cannot be verified. As there is no licensed hydrocortisone formulation for children < 6 years hydrocortisone is often compounded by pharmacies using adult hydrocortisone tablets. In a recent study of compounded hydrocortisone up to 20% of the batches did not meet European Pharmacopeial accuracy and precision criteria (ECE 2014 Abstract #1278). This medication safety study investigated hydrocortisone individually and extemporaneously compounded for paediatric use in adrenally insufficient patients, meaning the current therapy is inadequate in up to every 5th child treated. Thus, there is a need for specifically designed and licensed hydrocortisone formulations for this vulnerable paediatric patient group especially neonates and infants.

Methods

Infacort® is a newly developed immediate release formulation of hydrocortisone that is provided in child appropriate unit dosage units (0.5, 1, 2 & 5 mg) of multi-particulate granules. The granules are designed with a taste masking layer to permit compliant oral dosing. The objective of this study was to evaluate the pharmacokinetic performance of Infacort® and its safety in dexamethasone suppressed adult volunteers. Infacort® exposure was compared to the adult immediate-release dosage form, hydrocortisone 10 mg tablets. This was a single centre, open-label, randomised crossover study in 16 dexamethasone suppressed healthy adults. The study was approved by the South East Wales Research Ethics Committee and each potential study subject provided their freely given informed consent. EudraCT number: 2013-000260-28

Figure 1: Cross-sectional diagram of a multi-layered Infacort® granule formulation



Results

Infacort® and hydrocortisone tablets were administered to subjects at 07:00 (fasted) with 200mL water. Blood samples were taken at hourly intervals for 12 hours and serum cortisol concentration was determined by tandem mass spectrometry LC-MS-MS (Applied Biosystems, US). Pharmacokinetic end-points were derived from the individual serum cortisol concentration-time data using WinNonlin Phoenix 32.

Infacort® and hydrocortisone tablets at a dose of 10 mg are bioequivalent as reflected by the geometric LSmean 90 % CI for ratios of Cmax, AUC_{0-t} and AUC_{0-inf} within 0.8 – 1.25. The majority of subjects described Infacort® as, "not good or bad", for smell (81.3% to 87.5 % of subjects), feel in the mouth (68.8 % of subjects) and taste (68.8 % to 81.3 % of subjects) using a palatability questionnaire

Figure 2: Comparison of the cortisol pharmacokinetic profile between 10mg hydrocortisone tablet (HC) and 10mg Infacort® (n=16)

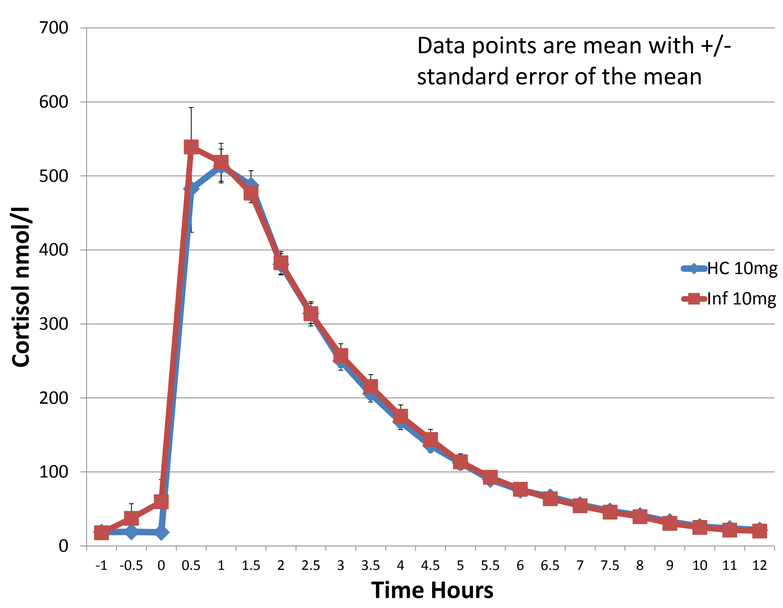


Figure 3: Dose-response to 0.5mg - 10mg Infacort® in dexamethasone suppressed healthy volunteers (n=16)

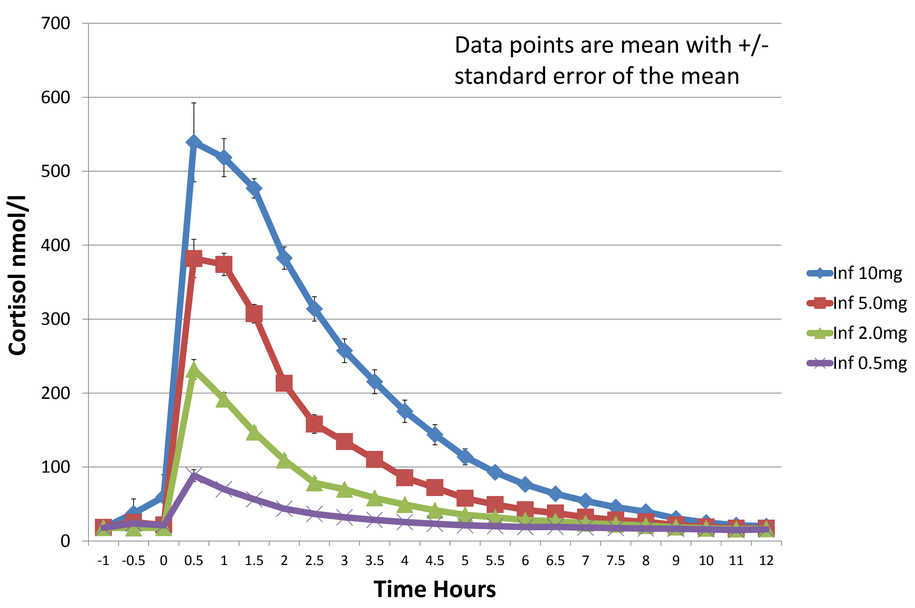


Table 1: Bioequivalence of 10mg Infacort® to 10mg Hydrocortisone Tablets

	Infacort® 10mg Geomean	Hydrocortisone Tablets 10mg Geomean	Ratio Infacort® to Hydrocortisone (90% Confidence Interval)
C_{max} (nmol/l)	566	598	95 (84-107)
AUC_{0-inf} (hr*nmol/l)	1602	1576	101 (96-107)
$T_{max\ (hr)}$	0.75	1.00	0.0 (-0.5-0.3)

Figure 4: Dose linearity (AUC) from 0.5 to 10mg Infacort®

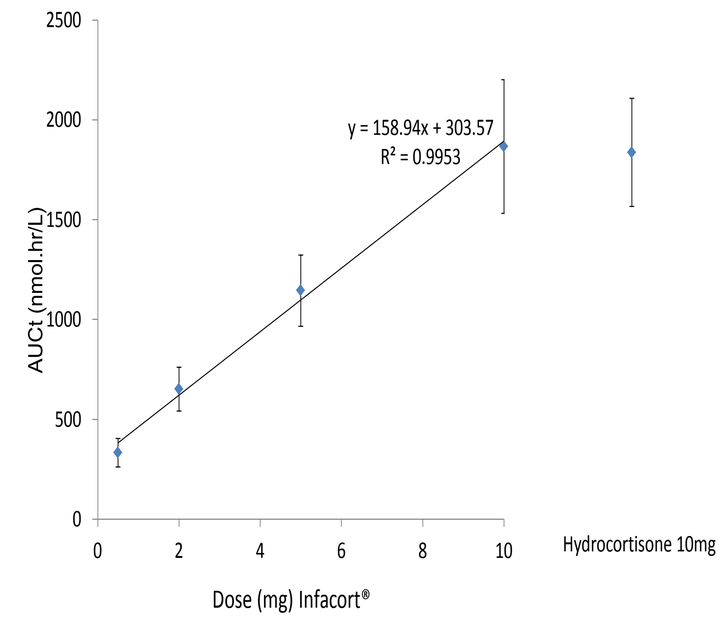
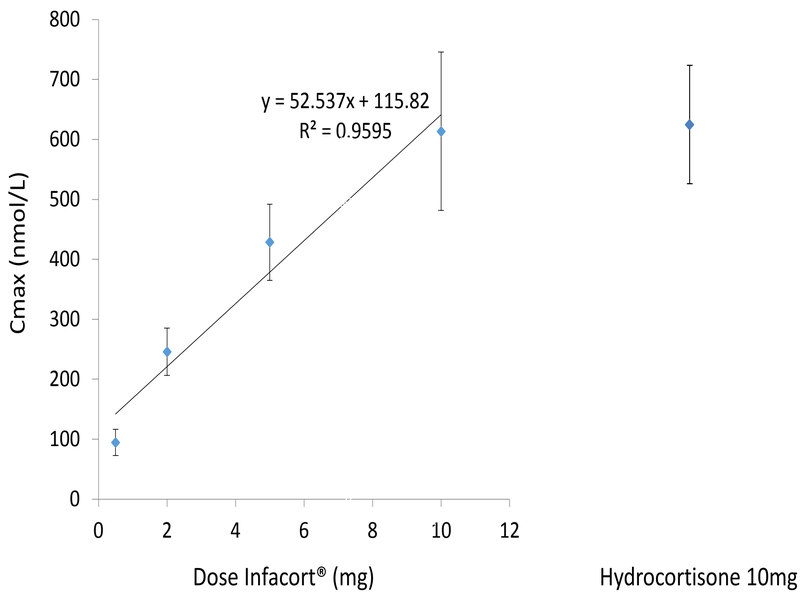


Figure 5: Dose linearity (Cmax) from 0.5 to 10mg Infacort®



Conclusions and Discussion

Infacort® was safe, well tolerated and of neutral taste when administered as a single oral dose of 10 mg. Infacort® 10mg was bioequivalent to 10mg hydrocortisone tablets with respect to C_{max} and AUC . Infacort® demonstrated dose-linearity between 0.5 mg and 10mg.

Infacort® has the potential to be the first, regulatory approved, specially developed paediatric formulation for the treatment of children suffering from adrenal insufficiency under 6 years of age in Europe. The study was performed under a Paediatric Investigation Plan approved by the European Medicines Agency (EMEA-001283-PIP01-12) and further studies in the target patient group are planned.

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