Medication safety study investigating hydrocortisone individually and extemporaneously compounded capsules for paediatric use in CAH

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Background and Objectives

Treatment of congenital adrenal hyperplasia (CAH) usually consists of substitution of endogenous cortisol with hydrocortisone (HC) [1]. Individual and exact dosing is a prerequisite for beneficial treatment outcome, especially in neonates and children. Currently, no licensed formulation for children < 6 years is available. Therefore, hydrocortisone capsules have to be compounded individually by local pharmacies (usual dose strength: 0.5–9.5 mg HC). During compounding three critical steps occur: (i) saturation of the mortar with filling material before usage (else leading to lower drug amount in the capsules), (ii) sufficient homogenisation (else leading to imprecision of drug content), and (iii) homogeneous distribution of the mixture to capsule casings (else leading to imprecision of mass) [2]. The aim of this study was to characterise mass and content of these capsules in order to assess medication safety for effective and nontoxic dosing in terms of precision of mass and drug concentration as well as accuracy of drug content in the compounded capsules.

Methods

➢ 20 batches of 18 - 21 hydrocortisone capsules each were collected from patients across Germany
➢ Batches were analysed according to European Pharmacopoeia [3]:

Precision/Variability of net capsule mass

➢ Net mass of capsule filling was investigated gravimetrically (capsule casing was substracted from total capsule mass)
➢ Mean net mass per batch and deviations from this mean mass were calculated for each capsule to investigate 'uniformity of net mass'
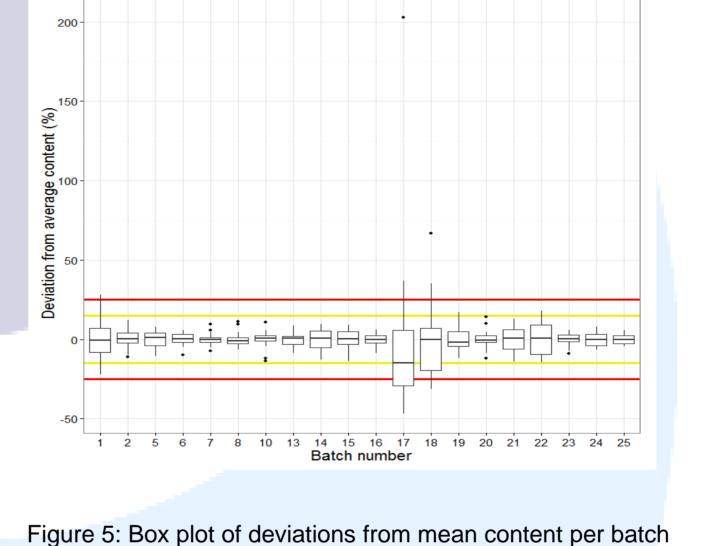
Precision and accuracy of drug content
➢ An HPLC-UV method for simultaneous quantification of hydrocortisone and fludrocortisone (potentially co-compounded) was developed and validated according to EMA Guideline on bioanalytical method validation [4]
➢ Analytical method parameters:
  o ThermoFisher Ultimate 3000, Agilent Eclipse XDB C18 column
  o Mobile phase: H_2O: ACN 70:30 (v/v), flow rate 0.8 mL/min
  o Injection volume 2.5 μL, temperature of column oven 15° C
  o Linearity range: 2.5 - 150 μg/mL
➢ Mean concentration per batch and deviation for each capsule from mean concentration were determined to evaluate 'uniformity of drug content'
➢ Deviations from nominal concentration were calculated to investigate 'accuracy of drug content'
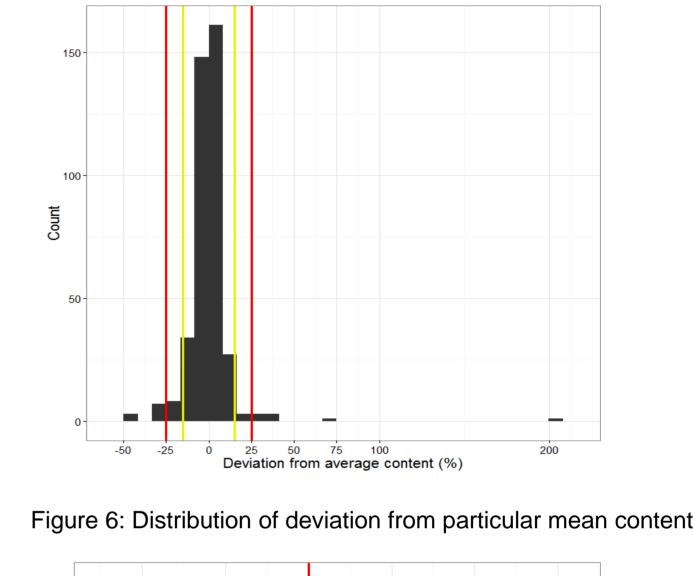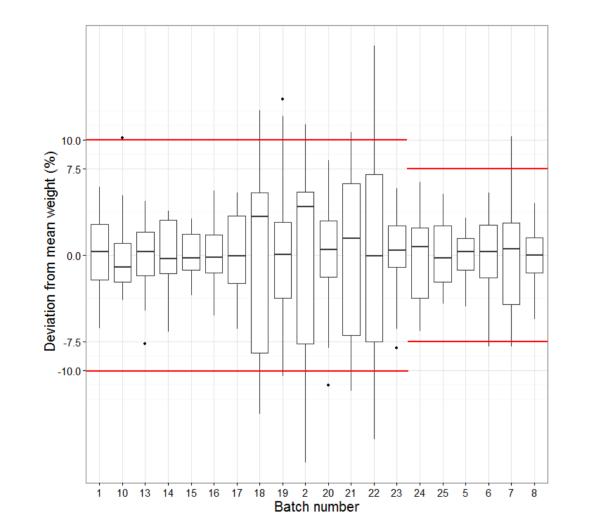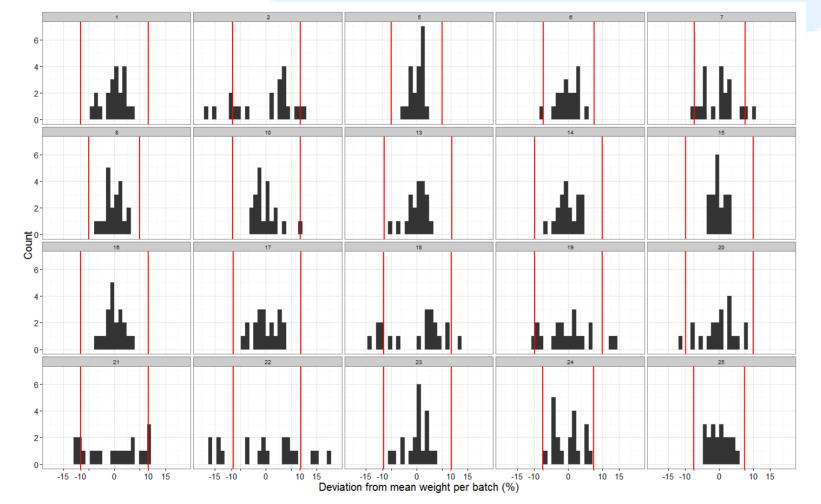
Results

Precision/ Variability of net capsule mass

➢ Summary statistics of investigating mass precision per batch are displayed as box plots and histograms in figures 1 and 2:

➢ Red lines show the borders of acceptable deviation which are allowed to be exceeded by maximal 3 capsules per batch. 4 of 20 batches (20%) failed the test: i.e. batch: 2, 18, 21 and 22.

Figure 1: Box plot of deviations from mean net mass per batch

Figure 2: Distribution of deviation from mean net mass in each batch

➢ Individual deviations of 'uniformity of mass' for all capsules are illustrated in figures 3 and 4: 30 of 399 capsules were outside the particular acceptance borders.

Figures 3 and 4: Distribution of deviations from mean mass (>/< 300 mg)

Results (cont.)

Precision and accuracy of capsule content

➢ Summary statistics of investigating 'uniformity of HC content' is demonstrated as box plot and histogram in figures 5 and 6, indicating extremely high variabilities in deviation of -47 up to 203%.

➢ Yellow lines show 15% deviation (exceedable by maximal 3 capsules per batch, red lines illustrate 25% deviation from mean content (no capsule should exceed). 3 of 20 batches (15%) missed the acceptance criteria.

Figure 5: Box plot of deviations from mean content per batch

Figure 6: Distribution of deviation from particular mean content

➢ A histogram of accuracy of mean drug content per batch is shown in figure 7. Red line show 15% deviation from particular nominal HC concentration: 5 of 20 batches (25%) had a higher deviation.

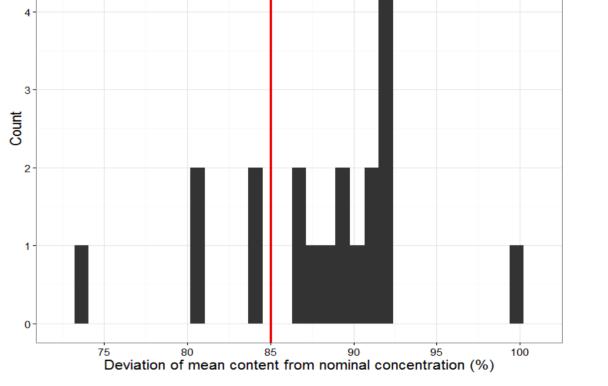➢ Average deviation from nominal concentration was -11.7%. No positive deviation occured.

Figure 7: Deviation of mean contents from nominal drug content
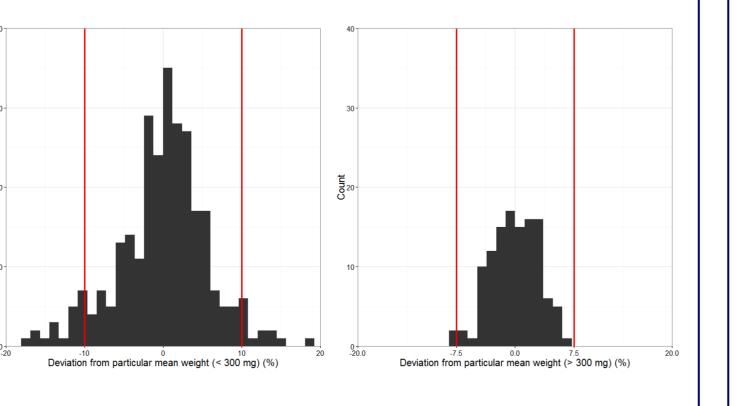
Discussion and Conclusions

➢ In total, 6 of 20 batches (30%) missed the acceptance criteria for precision of mass and/or content of the European Pharmacopoeia.

➢ Additional, 2 batches failed due to an HC concentration of less than 85% of nominal concentration.

➢ Imprecisely, inaccurately and highly variably produced capsules could lead to inadequate therapy, disease progression or, alternatively, to adverse drug effects in case of overdosings in every 4th of 10 child.

➢ The study demonstrates the need for improved medication safety for patients treated with capsules compounded individually by local pharmacies- not only for CAH patients.

➢ More precise Standard Operation Procedures for compounding i.e. HC capsules or development of a suitable paediatric formulation might help to improve medication safety.

➢ As next steps, more batches will be investigated to gain a larger database for an unbiased overview over the current therapy situation of neonates and young children suffering from CAH.

References:
[1] P.W. Speiser et al., Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency:
An Endocrine Society Clinical Practice Guideline, Journal of Clinical Endocrinology and Metabolism (2010)
[2] Deutscher Arzneimittel Codex/ Neues Rezepturformularium (2013)
[3] European Pharmacopoeia, 8th ed. (2013)
[4] European Medicines Agency, Guideline on bioanalytical method validation (2012).

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