Hydrocortisone suspension formulations are not necessarily the same in the treatment of children with congenital adrenal hyperplasia

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Dear Editor,

We wish to congratulate the authors of the paper entitled 'Paediatric population pharmacokinetic modelling to assess hydrocortisone replacement dosing regimens in young children' (1) in which a sophisticated modeling approach was applied to cortisol concentrations in children with congenital adrenal hyperplasia (CAH). It nicely demonstrates how information from other studies and other populations can inform sparsely sampled data in pediatrics. There was, however, a statement that requires additional commentary as it perpetuates a myth regarding hydrocortisone therapy in children with CAH.

The authors state that hydrocortisone suspensions 'have been shown not to be bioequivalent to the hydrocortisone tablet' and base this statement on an article from 2001 by Merke *et al.* (2). The article reported that patients who used a commercially available hydrocortisone cypionate suspension required higher daily hydrocortisone doses, had higher 17-hydroxyprogesterone and androstenedione levels and increased weight gain and hypertension compared to the tablets. Because of the report, hydrocortisone cypionate suspension was taken off the market. However, Merke *et al.* indicated their study results were specific only to the bioavailability of hydrocortisone cypionate, and not to all hydrocortisone suspension formulations. Indeed, the authors clarify with the statement that 'The stability and dosage uniformity of hydrocortisone suspensions prepared from tablets and powder were found to provide a uniform dose' (2) and support their statement with a reference by Fawcett *et al.* (3).

Since 2001, other studies have also shown that extemporaneously compounded alcohol-free hydrocortisone suspensions based on published methods have excellent stability (4, 5, 6, 7, 8). Moreover, a 6-hour serial sampling cortisol pharmacokinetic and pharmacodynamic response study in children with CAH (9) found using a dose- and BSA-normalized area-under-the-curve analysis that the absorption of an extemporaneously compounded alcohol-free hydrocortisone suspension (8, 10) was not different compared with commercial hydrocortisone tablets (9). In addition, the study found that adrenal steroid concentrations, mean weight and height z-scores were also comparable between children on tablets and suspension. However, this is not to say that hydrocortisone suspensions are the answer. Extemporaneously compounded drugs are not subject to the same quality control measures as commercial medications licensed by the FDA, which can lead to inconsistent quality among different compounding pharmacies and varied results in patients (11, 12, 13). All of the above highlights the critical need for a commercially available pediatric hydrocortisone formulation that allows for dosage units less than 2.5 mg in young children with CAH. The lowest dose currently available in the US is a scored 5 mg tablet.

As a final thought, the authors' focus on establishing a population pharmacokinetic model of cortisol for the purpose of assessing the ability of various hydrocortisone regimens to keep cortisol concentrations in a physiological range. However, the focus on keeping cortisol concentrations in a range similar to healthy children ignores more relevant 17-hydroxyprogesterone and

androstenedione biomarker information and variability in the sensitivity of the hypothalamic–pituitary–adrenal axis to cortisol. In fact, measurements of cortisol concentrations are not part of standard care nor included in the recommend monitoring guidelines of the Endocrine Society CAH consensus (14). There is simply too much between-subject variability in the pharmacodynamic response to cortisol (15, 16, 17). We know that standard dosing guidelines of 10–15 mg/m²/day will result in some children being over-suppressed, while others will still have elevated androgens. What is critically needed in the field is defining the hydrocortisone dose – exposure – long-term outcome relationships. Accepting comparative normalization of biomarkers to healthy children as the gold standard is not sufficient to address the long-term health deficits observed in affected individuals with CAH that extend into adulthood.

Declaration of interest

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