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SHORT REPORT

Defined daily doses in pediatric dosing- a theoretical example

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Abstract

A defined daily dose for children (cDDD) taking body weight into account, was proposed as a better measure of drug utilization in children than the World Health Organization's DDD. There is no global definition of DDDs for children, and it is unclear which standard doses should be used for children when conducting drug utilization studies. We used doses according to the authorized medical product information and body weight according to national pediatric growth curves to calculate theoretical cDDD for three common medicines in children in a Swedish setting. These examples demonstrate that the concept of cDDD may not be optimal for drug utilization studies in children, especially not for younger children and when dosing is done according to weight is crucial. Validation of cDDD in real-world data is warranted. When conducting pediatric drug utilization studies, accessibility to individual-level data on body weight and age combined with dosing information is needed.

KEYWORDS
body weight, child, defined daily dose, drug utilization, pediatric prescription

1 | INTRODUCTION AND BACKGROUND

Defined daily dose (DDD) is a unit of measurement developed by the World Health Organization (WHO) defined as "the presumed average daily dose when the drug is used by an adult at the main indication of the medicinal product".[1] DDD is given as the amount of active drug substance and may differ for medications that have more than one route of administration or several formulations where the bioavailability differs largely. If available, prescribed daily dose (PDD) is preferable in pediatric drug utilization studies.[1]

For optimal use of medications in children, several different factors such as age, weight, ethnicity, the course of the disease and pharmacokinetics must be considered. The weight of the pediatric patient may span from 500 g to 150 kg from a small premature infant to an adolescent with obesity. The pharmacokinetic phases (absorption, distribution, metabolism, and elimination) and pharmacodynamic processes (physiological and biological responses) of medicines differ compared to adults, but there are also maturation aspects during the pediatric years that give rise to differences within the developmental period. These factors often need to be taken into consideration when choosing medications and dosage for children.

Over 10 years ago, a defined daily dose for children (cDDD) taking body weight into account, was proposed as a better measure of drug utilization in children than the adult DDD already in use.[2] The cDDD was defined as "the assumed average maintenance dose per day per unit body weight for a drug used for its main indication in children". The cDDD has been subsequently used in studies of drug utilization in children, but despite this, most studies are still using other measures (DDD for adults, number of prescriptions for example). A recently suggested approach was to calculate cDDD from adult DDDs based on the child's age.[3] The use of antibiotics in the pediatric population was stratified into five age groups according to the child growth standards of WHO as suggested by the Chinese new edition of pharmacology.[3] However, there is still no global

definition of defined daily doses for children, and it is unclear which standard doses should be used for children when conducting drug utilization studies. Our aim was to theoretically calculate cDDD for three common medicines in children and discuss the usefulness in a Swedish setting.

2 | MATERIALS AND METHODS

Using information from national age and sex-specific pediatric weight curves[4,5] combined with dosage information from authorized product information for three commonly used pediatric medicines among children in Sweden, we calculated theoretical cDDDs and the proportion of the WHO DDD (cDDDs/WHO DDDs) for boys and girls aged 1, 5, 12 and 16 years.[1]

We used the mean weight +/− two standard deviations and dosage information for phenoxymethylpenicillin[6] (tonsilitis 12.5 mg/kg 3 times per day, otitis 25 mg/kg 3 times per day), paracetamol[7] (fever and pain 15 mg/kg 4 times per day) and desloratadine[8] (allergic symptoms age 0–5 years 1.25 mg/day, age 12+ years 5 mg/day). The WHO DDDs are 2 g for phenoxymethylpenicillin, 3 g for paracetamol and 5 mg for desloratadine.

TABLE 1 Average weight +/−2 standard deviations (SD) for Swedish children according to age and sex.[4,5]

Mean weight (±2 SD)		
Age	**Boys (kg)**	**Girls (kg)**
1 year	10.5 (8.5–13)	10 (8–12)
5 years	19.5 (15.5–24.5)	19 (15–25)
12 years	42 (32–54)	42 (32–56)
16 years	64 (49–83)	58 (44–76)

3 | RESULTS

The weight information of our theoretical example of children, retrieved from Swedish national pediatric growth curves, are described in Table 1.

We found that cDDDs for phenoxymethylpenicillin and paracetamol among boys and girls 1 year of age were approximately 20%, and over 100% for adolescents 16 years of age, of the WHO DDD, respectively (Table 2). Similarly, the cDDD for phenoxymethylpenicillin for indication tonsilitis was 120% and 109% out of WHO DDD, respectively, among boys and girls aged 16 years, i.e., the theoretical

TABLE 2 Calculated daily doses from the Summary of product characteristics (SmPC) and daily doses as percent of WHO DDD by age and sex for phenoxymethylpenicillin, paracetamol and desloratadine.

	Boys		Girls	
Calculated daily doses according to average weight (±2 SD)	**Daily dose g per kg mean bodyweight (±2 SD)**	**Daily dose per kg mean bodyweight (±2 SD) as % of WHO DDD**	**Daily dose g per kg mean bodyweight (±2 SD)**	**Daily dose per kg mean bodyweight (±2 SD) as % of WHO DDD**
Phenoxymethylpenicillin tonsilitis (12.5 mg/kg 3 times per day)				
1 year	0.39 (0.32–0.49)	20 (16–24)	0.38 (0.30–0.45)	19 (15–23)
5 years	0.73 (0.58–0.92)	37 (29–46)	0.71 (0.56–0.94)	36 (28–47)
12 years	1.58 (1.20–2.03)	79 (60–101)	1.58 (1.20–2.10)	79 (60–105)
16 years	2.40 (1.84–3.11)	120 (92–156)	2.18 (1.65–2.85)	109 (83–143)
Phenoxymethylpenicillin otitis (25 mg/kg 3 times per day)				
1 year	0.79 (0.64–0.98)	39 (32–49)	0.75 (0.60–0.90)	38 (30–45)
5 years	1.46 (1.16–1.84)	73 (58–92)	1.43 (1.13–1.88)	71 (56–94)
12 years	3.15 (2.40–4.05)	158 (120–203)	3.15 (2.40–4.20)	158 (120–210)
16 years	4.80 (3.68–6.23)	240 (184–311)	4.35 (3.30–5.70)	218 (165–285)
Paracetamol (15 mg/kg 4 times per day)				
1 year	0.63 (0.51–0.78)	21 (17–26)	0.6 (0.48–0.72)	20 (16–24)
5 years	1.17 (0.93–1.47)	39 (31–49)	1.14 (0.9–1.5)	38 (30–50)
12 years	2.52 (1.92–3.24)	84 (64–108)	2.52 (1.92–3.36)	84 (64–112)
16 years	3.84 (2.94–4.98)	128 (98–166)	3.48 (2.64–4.56)	116 (88–152)
Desloratadine (Age 0–5 years 1.25 mg per day, age 12+ years 5 mg per day)				
1 year	1.25	25	1.25	25
5 years	1.25	25	1.25	25
12 years	5	100	5	100
16 years	5	100	5	100

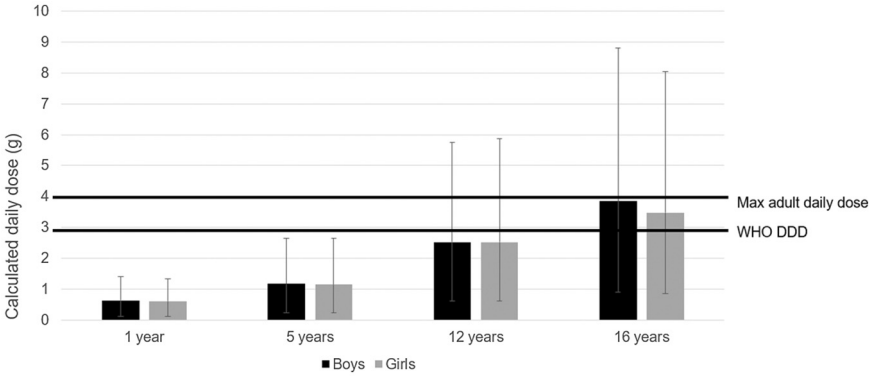

FIGURE 1 Calculated daily doses from the Summary of product characteristics (SmPC) for paracetamol to children by age group and sex. The bars represent the dose for average weight and the whiskers +/− 2 standard deviations from the average weight.

cDDD exceeds the maximal recommended dose for adults. The cDDD for desloratadine was 25% of WHO DDD among children 1 and 5 years of age and 100% among children 12 and 16 years of age.

The calculated daily dose for paracetamol ranged from 0.6 g for children aged 1 year to 3.84 g for boys 16 years of age (Figure 1). The calculated daily dose for boys and girls aged 16 years corresponds to 128% and 116% of WHO DDD, respectively.

4 | DISCUSSION

Using a theoretical calculation of cDDDs for three medicines commonly used in pediatrics, we demonstrate that the cDDDs vary largely in relation to WHO DDDs. For phenoxymethylpenicillin, the doses are dependent both of the indication and body weight. Children with a body weight 40 kg and above are given the same doses as for adults. The WHO DDD is reflecting individuals with a weight of at least 40 kg treated for tonsillitis. When treating otitis, approximately twice the dose for tonsilitis is used, which may overestimate the number of individuals using phenoxymethylpenicillin. Desloratadine is prescribed according to age and not body weight which make it possible to use WHO DDD for children 12 years of age and above. In the example of paracetamol, the maximum daily dose from 12 years of age is 4 g according to the authorized medical product information, but the WHO DDD is only 3 g. This is another example of where WHO DDD is not accurate for children. Using the WHO DDD in drug utilization studies among individuals 12 years and above will thus overestimate the number of DDDs and, hence, the number of individuals using paracetamol.

These examples demonstrate that the concept of DDD is not optimal for drug utilization studies in children, especially not for younger children and when dosing is done according to weight. Since the national healthcare register does not include information on weight, we used theoretical calculations from weight curves in combination of doses according to the authorized medical product information as a proxy for the actual dose used. Using WHO DDD as a drug utilization measure will underestimate the number of users among children and overestimate the number of users among adults.[9] New studies of drug utilization across different age groups in the pediatric population are important—but a more refined approach may be necessary to provide the insights needed. The discrepancy between the theoretical DDD and actual dosage is another issue that deserves more research and validation of cDDD in real-world data is needed.

To adequately develop drug utilization measures in the pediatric population, individual-level data on body weight and age combined with dosing information when a medicine is prescribed is warranted.

AUTHOR CONTRIBUTIONS

Elin Kimland (EK) and Elin Dahlén (ED) developed the hypothesis with input from Jenny Marianne Kindblom (JMK). ED managed data and did the analysis with contribution from EK. All authors contributed to study concept and design, analysis, and interpretation of data, and drafting or critical revision of the manuscript for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

All data related to this study are available online through websites listed in references 1, 4, 6–8.

DISCLAIMER

ED and EK are employed at the Swedish Medical Products Agency, the views expressed in this study are the personal views of the authors and not necessarily the view of the Government agency.

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