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Original article

Antimicrobial defined daily dose adjusted by weight: a proposal for antibiotic consumption measurement in children

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Antimicrobial defined daily dose (DDD), has limitations for antimicrobial consumption measurement in paediatrics. An alternative DDD design applicable for children is proposed.
Methods: Children (<16 years-old) from 10 Spanish hospitals during a 12-months period were included. Weight for age (50th percentile) was calculated for the median age of the cohort using standardized World Health Organization tables. DDD (g) for each antimicrobial was calculated by multiplying the obtained weight times the recommended dose (mg/kg) of the antimicrobial for the most common infectious indication.
Results: A total of 40,575 children were included. Median age was 4.17 (IQR: 1.36–8.98) and 4.81 (IQR: 1.42–9.60) years for boys and girls, respectively. Mean weight for this age was 17.08 kg. Standardized DDD for representative antimicrobials were calculated.
Conclusions: A useful method for antimicrobial DDD measurement in paediatrics has been proposed and should be validated in future studies for its use in paediatric antimicrobial stewardship programmes.

Dosis diaria definida ajustada por peso: una propuesta para la medición de consumo antimicrobiano en pediatría

R E S U M E N

Introducción: La dosis diaria definida (DDD), tiene limitaciones para la medición del consumo antimicrobiano en pediatría. Se propone un diseño aplicable en niños.
Métodos: Se incluyeron niños (<16 años) de 10 hospitales españoles durante un periodo de 12 meses. A partir de la mediana de edad de la cohorte, utilizando tablas estandarizadas de la OMS, se obtuvo

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el peso correspondiente al percentil P50 de esa edad. Se calculó la DDD (gr) multiplicando el peso obtenido por la dosis recomendada (mg/kg) de cada antimicrobiano para su indicación más común.
Resultados: Un total de 40575 niños fueron incluidos. La mediana de edad fue 4,17 (RIQ: 1,36–8,98) y 4,81 (RIQ: 1,42–9,60) años para niños y niñas, respectivamente. Peso medio para la edad: 17,08 kg. DDD estandarizadas fueron calculadas para antimicrobianos representativos.
Conclusiones: Se ha propuesto un método útil para monitorizar consumo antimicrobiano en pediatría utilizando DDD adaptadas, que deberá validarse en futuros estudios.

Introduction

Antimicrobials are among the most commonly prescribed drugs in paediatrics. However, up to 50% of in-hospital antimicrobial prescriptions are inappropriate.[1] The relationship between inadequate use of antimicrobials and the emergence of bacterial resistance has been clearly established, resulting in increased mortality and costs.[2] Antimicrobial stewardship programmes (ASP) were successfully implemented to optimize antimicrobial use in hospitalized patients.[3] Though, development of ASP in paediatrics has been limited, due in part to the lack of a standardized method for comparing antimicrobial use.[4]

Defined Daily Dose (DDD) is one of the established metrics used by ASP, allowing the assessment of antimicrobial consumption. The World Health Organization (WHO) expresses DDD as the average standard daily dose of a drug used in a 70 kg adult for the most common indication.[5,6] However, the validity of DDD WHO definition is questionable in hospitalized children, in which dosing is based on body weight.[1,5] This study aims to establish a methodology for antimicrobial DDD measurement in the paediatric population.

Methods

Data collection

An observational retrospective study was performed. Children from 10 Spanish hospitals (9 tertiary and 1 secondary) aged 1 month to 16 years old, with at least one episode of hospital admission into a paediatric ward, whether receiving antibiotics or not, during a 12-months period (January to December 2013) were included. Each patient hospital admission was considered an "episode". For the study purposes, different hospital admissions through the study period and/or change of in-hospital ward during the same hospital admission period were considered as different episodes. Studied variables were age and sex, obtained through the hospitals' admission records.

Data analysis

Mean age, median and range were calculated for each sex. Weight (kg) for DDD calculation was selected for the obtained median age by sex using the 50th percentile according to the WHO weight for age graphs in paediatrics.[7] Overall cohort weight was the mean between the female and male selected weight values. Finally, paediatric DDD (g) for each antimicrobial was calculated through the multiplication of the overall cohort weight (kg) and the recommended dose for the most common indication of each antimicrobial (mg/kg) previously agreed.

The Delphi method was used to find a joint agreement for antimicrobial dose discrepancies. This method is a structured process that uses a series of questionnaires or "rounds" to gather information, which are held until group consensus is reached.[8]

Agreement process was as follows: First, one pharmacist and one paediatric infectious diseases specialist from each participating centre established the recommended dose for the most common indication for each antimicrobial. In the second round, these doses were anonymously sent to each of the 20 experts who were asked to review again their proposed dose. In case of disagreement after this round, the antimicrobial dose was established using the database from the Medicines Committee of the Spanish Association of Paediatrics (Pediamecum).[9] Agreement percentage was calculated using as numerator the number of hospitals that selected the agreed dose and as denominator the number of hospitals that proposed a dose. Data analysis was performed using SPSS statistical software, version 19 (IBM SPSS, Armonk, New York).

Ethics

The study was approved by the Spanish Agency for Medicines and Sanitary Products. It was classified as "Post-authorization study with other designs different from prospective design" on May 11th, 2015 (ID number: GAT-TEI-2015-01). Subsequently, it was approved by the Hospital Universitario Virgen del Rocio and Hospital Universitario Virgen Macarena Ethics Committee on October 24th, 2016, (ID number: 0620-N-15).

Results

A total of 40,575 patients were included: 23,877 (58.8%) males, 16,698 (41.2%) females. The median age was 4.17 (IQR: 1.36–8.98) years old for boys and 4.81 (IQR: 1.42–9.60) for girls. The 50th percentile of weight for that age was 17.08 kg (males 16.6 kg and females 17.8 kg). The selected antimicrobials with their respective calculated DDDs and agreement percentages are shown in Table 1 (intravenous route) and Table 2 (oral route). In 9 of 52 antimicrobials, a second round was necessary for dose agreement, achieving it in 4 of them. For oral amoxicillin, amoxicillin-clavulanic acid, ampicillin, cefuroxime and intravenous ceftriaxone; dose was agreed using Pediamecum data. Total agreement percentage was 77.9% (360/462): 79.3% (242/305) and 75.2% (118/157) for intravenous and oral antimicrobials, respectively.

Discussion

Paediatric DDDs for antimicrobials have been designed in this multicentre study. The best metric for aggregate antimicrobial consumption evaluation in paediatrics has not yet being defined.[4,10] DDD measurement in children is limited due to weight variability, thus, other methods like Point Prevalence Surveys (PPS) have been proposed.[2,11,12] PPS can assess antimicrobial consumption in short periods of time basis, using retrospective, prospective or mixed designs.[10,12] The Antibiotic Resistance and Prescribing in European Children Project (ARPEC) and the European Surveillance of Antimicrobial Consumption (ESAC), have used this metric to monitor

Table 1

Paediatric defined daily dose of intravenously administered antimicrobials according to the results of Delphi method.

Antimicrobial	Proposed dose											Agreement percentage (%)	Agreed dose (mg/Kg/day)	Paediatric DDD (g/day)	Adult DDD[13] (g/day)
	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hospital 10	Pediamecum				
Amikacin	15	15	15	15	X	15	15	15	20	15	15	88.9	15	0.26	1
Amoxicillin	80	X	80	100	50	X	80	X	X	80	80	57.1	80	1.37	1
Amoxicillin-clavulanic acid	100	100	150	100	100	100	100	100	100	100	100	90	100	1.71	3
Ampicillin	100	100	200	100	200	100	100	200	200	100	100	60	100	1.71	2
Liposomal amphotericin B	3	3	5	3	X	3	3	5	3	5	5	66.7	3	0.05	0.035
Azithromycin	10	10	10	10	10	10	10	10	10	10	10	100	10	0.17	0.5
Aztreonam	120	120	120	120	X	120	120	150	150	120	120	77.8	120	2.05	4
Cefazolin	100	100	75	100	100	100	100	100	100	50	50	80	100	1.71	3
Cefepime	150	150	100	150	X	150	100	150	150	150	150	77.8	150	2.56	2
Cefotaxime	150	150	150	150	100	200	150	150	200	150	150	80	150	2.56	4
Ceftazidime	150	150	150	150	100	200	150	150	150	150	150	80	150	2.56	4
Ceftriaxone	80	50	50	100	100	100	80	50	50	50	50	50	50	0.85	2
Cefuroxime	100	100	100	150	60	100	100	150	150	100	100	60	100	1.71	3
Ciprofloxacin	20	20	15	20	20	20	20	30	30	15	15	60	20	0.34	0.5
Clindamycin	40	30	30	40	30	40	40	30	30	30	30	60	30	0.51	1.8
Cloxacillin	100	100	100	100	100	150	100	100	100	100	100	90	100	1.71	2
Daptomycin	8	X	10	8	X	8	8	8	8	X	8	85.7	8	0.14	0.28
Erythromycin	40	40	40	40	X	40	40	X	40	40	40	100	40	0.68	1
Fluconazole	6	6	6	6	6	6	6	6	6	6	6	100	6	0.10	0.2
Fosfomycin	200	100	100	200	200	200	200	200	200	100	200	70	200	3.42	8
Gentamicin	6	5	6	6	5	5	5	5	5	6	6	60	5	0.09	0.24
Imipenem-cilastatin	100	100	60	100	X	100	60	100	60	100	100	66.7	100	1.71	2
Itraconazole	5	5	X	5	X	5	5	X	2,5	5	5	85.7	5	0.09	0.2
Levofloxacin	20	X	10	20	20	20	20	20	10	X	15	75.0	20	0.34	0.5
Linezolid	30	30	30	30	30	30	30	30	30	30	30	100	30	0.51	1.2
Meropenem	60	60	60	60	60	60	60	60	120	60	60	90	60	1.02	2
Metronidazole	30	30	30	30	30	30	30	30	30	30	30	100	30	0.51	1.5
Micafungin	2	2	X	2	X	2	2	1	2	2	2	87.5	2	0.03	0.1
Penicillin G sodium*	1,000,000	1,000,000	250,000	600,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	80	600	0.6	3.6
Piperacillin - Tazobactam	300	X	300	300	X	300	300	300	300	300	300	100	300	5.12	14
Teicoplanin	10	10	8	10	X	10	10	10	10	6	6	77.8	10	0.17	0.4
Tobramycin	5	7,5	5	5	X	5	5	X	4	5	5	75	5	0.09	0.24
Vancomycin	40	40	40	40	45	40	40	40	40	40	40	90	40	0.68	2

Abbreviations: DDD: Defined daily dose; X: not used.

Hospital 1: Hospital Universitario Virgen del Rocío, Sevilla; Hospital 2: Hospital Regional Universitario de Málaga; Hospital 3: Complejo Hospitalario Universitario de A Coruña; Hospital 4: Hospital Universitario Cruces, Baracaldo; Hospital 5: Hospital Universitario Infanta Sofía, Madrid; Hospital 6: Complejo Hospitalaria Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria; Hospital 7: Hospital Universitario Reina Sofía, Córdoba; Hospital 8: Hospital Universitario Gregorio Marañón, Madrid; Hospital 9: Hospital Universitario Vall D'Hebrón, Barcelona; Hospital 10: Hospital Universitario de Jerez, Cádiz.

* Sodium penicillin G is expressed in fixed dose, not per kilogram of body weight.

Table 2
Paediatric defined daily dose of orally administered antimicrobials according to the results of Delphi method.

Antimicrobial	Proposed dose											Agreement percentage (%)	Agreed dose (mg/Kg/day)	Paediatric DDD (g/day)	Adult DDD[13] (g/day)
	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hospital 10	Pediamecum				
Amoxicillin	60	50	50	50	80	80	80	80	50	40	50	40	50	0.85	1
Amoxicillin-clavulanic acid	50	50	40	50	80	80	40	80	40	40	40	30	40	0.68	1
Ampicillin	X	X	X	X	100	100	X	X	30	X	50	0	50	0.85	2
Azithromycin	10	10	10	10	10	10	10	10	10	10	10	100	10	0.17	0.3
Cefadroxil	40	30	X	X	X	40	X	30	30	30	30	66.7	30	0.51	2
Cefixime	8	8	X	8	8	8	8	8	8	8	8	100	8	0.14	0.4
Cefuroxime	20	20	20	30	60	30	15	30	30	20	15	10	15	0.26	0.5
Ciprofloxacin	20	20	20	20	20	20	20	20	30	20	20	100	20	0.34	1
Clarithromycin	15	15	15	15	15	15	15	15	15	15	15	100	15	0.26	0.5
Clindamycin	30	30	30	30	30	40	40	30	30	30	30	80	30	0.51	1.2
Cloxacillin	X	50	100	100	X	100	100	100	100	50	100	75	100	1.71	2
Erythromycin	40	40	40	40	X	40	40	40	40	40	40	100	40	0.68	1
Fluconazole	6	6	6	6	6	6	6	6	6	6	6	100	6	0.10	0.2
Fosfomycin	X	100	100	X	200	200	200	100	200	X	100	57.1	200	3.42	3
Itraconazole	5	5	X	X	X	5	5	X	5	5	5	100	5	0.09	0.2
Levofloxacin	15	X	X	X	20	20	10	10	10	15	15	42.9	10	0.17	0.5
Linezolid	30	30	30	X	30	30	30	30	30	30	30	100	30	0.51	1.2
Metronidazole	30	30	30	30	30	30	30	30	30	30	30	100	30	0.51	1.5
Vancomycin	X	X	X	X	45	40	40	X	X	X	40	66.7	40	0.68	2

Abbreviations: DDD: Defined daily dose; X: not used.
Hospital 1: Hospital Universitario Virgen del Rocío, Sevilla; Hospital 2: Hospital Regional Universitario de Málaga; Hospital 3: Complejo Hospitalario Universitario de A Coruña; Hospital 4: Hospital Universitario Cruces, Baracaldo; Hospital 5: Hospital Universitario Infanta Sofía, Madrid; Hospital 6: Complejo Hospitalaria Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria; Hospital 7: Hospital Universitario Reina Sofía, Córdoba; Hospital 8: Hospital Universitario Gregorio Marañón, Madrid; Hospital 9: Hospital Universitario Vall D'Hebrón, Barcelona; Hospital 10: Hospital Universitario de Jerez, Cádiz.

antimicrobial consumption in children.[10,11] However, PPS specific time-point data is susceptible to case-mix complexity, seasonality and variability of the sample.

Current recommendation for paediatric ASP metric is Days of Therapy (DOT).[5] This metric counts the number of days a patient receives antibiotics, avoiding weight variability. Nonetheless, DOT measurement poses problems in the setting of drugs with a long half-life, variable pharmacodynamics, or in patients with renal failure.[5] In addition, DOT favours patients who receive less antimicrobials even if that involves the use of broader spectrum antimicrobials,[5] while the optimal length of treatment for most of paediatric infections varies widely.[12]

Few studies have used the DDD methodology in children.[4] A recent systematic review found up to 26 distinct measures across 79 studies including paediatric patients (DDD or similar metrics in 38 studies).[4] Limitations were found for all metrics and authors conclude that the best metric remains to be identified.[4] In our study, weight variability was overcome by selecting the average weight for the obtained sample. The availability of a normalized DDD value could allow its application for ASP monitoring in paediatrics. Nevertheless, the average weight obtained in our sample, does not allow comparisons with other series that may report a different median age and consequently a different average weight. Future strategies could include constructing confidence intervals for the calculated DDDs or designing specific DDDs for paediatric age subgroups of interest (neonates, infants, children, adolescents).

Centre participation was high for the selected dose agreement method, therefore, the lack of dose values for some antimicrobials does not reflect data loss, it could be due to the variability of antimicrobial use in the included centres. Thus, it is possible that some agreed DDDs of occasionally used drugs are less reliable, as well as for those antimicrobials for which there were more discrepancies between centres. Nevertheless, dose agreement data was high for most of the antimicrobials included, and further confirmation would be expected when this tool undergoes validation.

Of note, 4 out of 52 antimicrobials had a greater paediatric DDD when compared to adult DDD. For amoxicillin and liposomal amphotericin B, the DDD value established by WHO is smaller than the dose used in clinical practice according to the specific antimicrobial drug label instructions.[13] For cefepime and oral fosfomycin the agreed doses where greater in paediatrics probably because these antimicrobials are used mostly for infections that require higher doses in children.[14]

Main limitations of our study include the lack of validation of this strategy and low external validity of the method. To overcome this, a new multicentre study has been projected to validate this tool in real-life patients who receives antimicrobial prescriptions under usual clinical practice. Currently, the project is looking for internal validity in our country including representative centres of several Spanish regions. If good results are obtained, further international multi-centre studies will be proposed to standardize this metric.[5,6] Although standardized Spanish weigh for age and sex charts exist,[15] WHO charts were used with the aim to provide a tool potentially applicable in different populations.

To the best of our knowledge, this study provides one of the largest sample size to define specific DDD for paediatric population, in a multicentre setting. Neonatal patients were excluded, as they have different pharmacokinetics and pharmacodynamics compared to paediatric patients. A parallel project is underway to design neonatal DDD applying a similar methodology.

In conclusion, this study has designed a suitable paediatric DDD for antimicrobial consumption assessment. Further validation of this tool standardizing the age ranges is required in future studies, as this metric could help to design paediatric ASP strategies to prevent the emergence and dissemination of antimicrobial resistance in children.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. The Paediatric Antimicrobial Defined Daily Dose Study Group (KiDDDs)

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