GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) A Critical Appraisal System for antimicrobial PKPD studies – Development and Application in Paediatric Antibiotic studies

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Abstract

Introduction

There are limited data on optimal dosing of antibiotics in different age groups for neonates and children. Clinicians usually consult paediatric formularies or online databases for dose selection, but these have variable recommendations, are usually based on expert opinion and are not graded based on the existing pharmacokinetic-pharmacodynamic (PKPD) studies. We describe here a potential new tool that could be used to grade the strength of evidence emanating from PKPD studies.

Areas covered

A scoring system was developed (GAPPS tool) to quantify the strength of each PK assessment and rate the studies quality in already published articles. GAPPS was evaluated by applying it to paediatric PKPD studies of antibiotics from the 2019 Essential Medicines List for children (EML_C), identified though a search of PubMed.

Expert opinion

Evidence for most antibiotic dose selection decisions was generally weak, coming from individual PK studies and lacked PKPD modelling and simulations. However, the quality of evidence appears to have improved over the last two decades.

Incorporating a formal grading system, such as GAPPS, into formulary development will provide a transparent tool to support decision making in clinical practice and guideline development, and guide PKPD authors on study designs most likely to influence guidelines.

Keywords: Antibiotic dosing, Grading Evidence, Paediatric Dosing, PKPD, WHO EMLc

INTRODUCTION

Recently the WHO essential medicines list for children (EMLc) has classified antibiotics into the following groups: Access, Watch, Reserve (AWaRe). This provides a new metric for antimicrobial stewardship to monitor appropriate use of antibiotics in children, as antibiotics are the most commonly prescribed drug class in this population [1-11]. However, data on optimal dosing in different paediatric age groups are sparse for most of these drugs. Information on paediatric dosing has often been omitted from drug labelling information, although regulatory authorities now demand this information in paediatric investigational plans for newly registered drugs [12]. Further compounding the lack of information on antibiotic dosing for older drugs is that unlicensed and off-label use of medicines in paediatric clinical practice is globally widespread [13]. Formularies are one of the tools available to clinicians to inform dosing but vary between countries and usually lack referencing or grading of their stated recommendations [14]. Part of the problem has been the lack of a widely accepted method to grade pharmacokinetic-pharmacodynamic (PKPD) studies. We therefore have developed a simple tool to grade dose recommendations for antibiotics regarding their PKPD evidence, which can provide a transparent rationale for evidence-based clinical recommendations.

Evidence-based dosing in children

Dose recommendations for children have mostly been derived from adult PK studies [15,16]. Assuming linearity between drug exposure and body weight, as in some early recommendations, does not correctly account for growth and maturation processes [17,18], lacks empiric evidence, and may result in inappropriate systemic drug exposures of many drugs in neonates, infants and children [19,20]. Extrapolation of

dosing from adults is better accomplished by acknowledging the standard principle, that PK processes scale with allometric size in children, and include terms for expected maturation in neonates and infants [21,22].

Globally, the most widely referred to paediatric formularies on antibiotic dosing are the WHO Pocket Book on Hospital Care in Children, the USA Red Book, the UK British National Formulary for Children (BNFc), and the European Blue Book [23-25]. In addition, several national formularies have been developed and published in the country's official language. Although formularies have been well established in clinical practice and their content is reviewed by a board of experts in the field, the quality of the evidence included from PKPD studies is generally not formally assessed. The Dutch Paediatric Formulary provides a comprehensive reference list associated with each recommendation [26], based on advice from an editorial board, but again the strength of the evidence is not given.

To assess what is needed for adequate reporting on clinical pharmacokinetic studies Kanji et al. [27] performed a Delphi survey resulting in a checklist with 24 necessary items. The checklist can be seen as a good basis to establish standards for clinical pharmacokinetics, as it facilitates reporting clinical pharmacokinetic studies in a more standardized way and therefore also aids in grading their evidence by a standard conduct.

The lack of a standardized approach to assessing PKPD evidence likely contributes to variation in guidance, and therefore in clinical practice. Due to increasing rates of antimicrobial-resistant infections, robust evidence-based prescribing guidance to support optimal dosing strategies in important. Critical appraisal of the design conduct and analysis of PKPD studies is essential to optimal dosing, particularly with the increasing use of population analyses in paediatric dosing studies. Critical appraisal methods are now needed to assess PKPD evidence along with the evaluation of study quality in order to assess the quality of evidence for each drug.

We therefore aimed to describe the development and initial application of a new Grading and Assessment system for PKPD studies (GAPPS) to evaluate the strength of the evidence underlying dosing recommendations for antibiotics used widely in the treatment of paediatric infections.

METHODS

Literature Search

The data used were from a systematic review on PKPD studies on antibiotic use in neonates and children. In brief, the literature searches in Pubmed and EMBASE were from 1966 to 31 May 2018. Only PK related studies were included. Studies on Therapeutic Drug Monitoring or reporting plasma concentration without any PK parameters calculated were excluded. Study eligibility was independently assessed by two authors (from AR, SG, YH, CJ) and disagreements resolved by a third reviewer (YH). Full details are given in Rashed et al. *Pharmacokinetics of the antibiotics in the Access and Watch groups of the 2019 WHO Model List of Essential Medicines for Children: A systematic review*, Expert Review of Clinical Pharmacolgy, submitted 08/2019.

Developing GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies)

In accordance with the GRADE systems methodology [28], scoring systems were developed for GAPPS to account for the analytical strength of the methods used to derive reported PK Parameters for each PKPD evidence (Dosing Evidence Score, DES), as well as the quality of the underlying study (Quality of Evidence Level, QoE). The results of both assessments were then summarized to give one of three strength of recommendation levels (“weak”, “intermediate”, “strong”). There are several decisions made in selecting the best model when conducting a PK study. Any PK model is inherently a simplification of reality and each model makes some concessions. PKPD studies differ in their analytical approach, observational quality and model validation.

Each of these qualities was incorporated into the GAPPS analysis (Figure 1). Introductory descriptions of each of the metrics assessed by the GAPPS system and can be found in Supplement 1.

Scoring evidence using PKPD Dosing Evidence Score

Studies were scored using the PKPD Dosing Evidence Score (Figure 1). The scoring system accounts for the

i) Analytical Approach (target identification, simulation-based dosing recommendations); Observation Quality (meta-analysis with prospective or retrospective data pooling);

ii) Model Appraisal and Validation (Observation-based and simulation-based diagnostics),

iii) Consistency of the model structure with other available evidence.

It was developed by an expert group, that comprised of paediatricians, paediatric clinical pharmacologists and pharmacists based in Europe as part of the Global Research in Paediatrics (GRiP) work plan [29].

Evaluation of Quality of Evidence using the GAPPS Grading System

The QoE score was used to rate the underlying study design. The highest achievable quality level is given by a meta-analysis performed on the raw PK-data of previously published prospective studies, level 1a. If a study was performed on data from prospective data warehousing or pooling, level 1b was assigned.

Data from retrospective pooling or analysis was given the level 2a. When external data was available for validation purposes only, the study was rated level 2b. Dose

recommendations based on simulation or bridging methods without extra data pooling were assigned QoE level 2c.

The QoE level 3 was assigned for individual PK studies with no simulations performed, level 4 was given if a case study was reported with PK or TDM described.

Assigning Strength of Recommendation using the GAPPS Grading System

Levels from the GAPPS assessment of QoE were grouped into three categories of strength of recommendation. The strength of recommendation was determined by assigning the corresponding category for QoE Scores: Strong with QoE levels 1a, 1b, 2a or 2b; Intermediate with QoE levels 2c or 3 or Weak with the QoE level 4.

RESULTS

Antibiotic studies

A total of 237 studies were identified that reported on the 28 selected antibiotics from the EMLc 2019 (13 beta lactams, 10 non-beta lactams). The most commonly studied antibiotics were gentamicin 53/237 (22.4%), vancomycin 41/237 (17.3%) and amikacin 19/237 (8.0%). Non-beta lactams 159/237 (67.1 %) were more studied than beta lactams 78/237 (32.9%). There were 5 antibiotics (phenoxymethylpenicillin, procaine benzylpenicillin, doxycycline, nitrofurantoin and spectinomycin) for which no suitable study was retrieved, leaving 23 Antibiotics for analysis.

Dosing Evidence

Across all papers analysed, a median DES of 3 was scored, ranging from 1, individual descriptive PK study without any additional information available, to 12, where a full PKPD study with target identification was performed, including information on model performance and validation. A DES of 3 was also the most frequently reported score, followed by a score of 2. The next most frequent scores were 7 and 5. The least frequent reported scores were 11 and 12. The frequencies of the reports' scores are shown in Figure 2, along with the Grading of the DES, that is subsequently used as a measure of quality of evidence.

The median and ranges of the DES for each of the studied antibiotics is summarized in Table 1. The median DES varied somewhat, but low-quality

studies were identified for all antibiotics. Studies rated as providing strong quality evidence based on the DES were identified for 12 of the 28 reviewed antibiotics.

Quality of Evidence

The most frequent QoE grade based on study design and methods was level 3, as 153/237 (64.6%) were performed as an individual PK study with no simulation identified (Table 2, Figure 3). The next most frequent study grade was level 2c with 64/237 (27.0%), where studies included recommendations based on simulation or bridging methods. 7/237 (3.0%) studies were performed as prospective data warehousing/pooling (1b), whereas 7/237 (3.0%) were non-systematic/ retrospective data pooling/analysis (level 2a) and 4/237 (1.7%) studies contained external data collection /validation (level 2b). Only one study 1/237 (0.4%) was rated Level 4, a case study with PK or TDM described, as well as just one study met the highest QoE 1a (meta-analysis of raw PK data).

DISCUSSION

Acknowledging GRADE philosophy [30], that evidence in the medical literature should be rated by finding categories of reliability for individual studies, we developed and employed an explicit, potentially reproducible methodology (the GAPPS system) for the assessment of PKPD studies. We then used GAPPS to assess 237 PKPD studies giving evidence for 23 paediatric antibiotics recommended by the WHO, which is to our knowledge the largest such review to date. This assessment of PK studies using the GAPPS system has demonstrated that there remains a strikingly poor evidence base for paediatric antibiotic dosing.

The GAPPS system can categorize PKPD studies starting with the highest level of most reliable studies, a meta-analysis of raw PK data, to the low level and least reliable case studies and expert opinions based on in-vitro studies. Standardized appraisal of PKPD evidence has an important role in facilitating the prioritization of research and development resources by identifying areas where the least information about optimized dosing exists. Systematic assessment of dosing evidence is a useful tool which can be used for other vulnerable and less studied populations, where significant PK changes are expected, including pregnant women, the elderly or patients suffering from organ failure, needing renal replacement therapy or extracorporeal membrane oxygenation [31-33]. PK parameters, needed for dose finding, cannot be extrapolated in a simple linear way from adults to children. Underlying growth and maturation processes need to be considered by including allometric size scaling and when it comes to neonates and infants, maturation functions of the predominant eliminating organ[34-36]. If the population of interest has additional underlying conditions, such as paediatric haemato-oncology patients, HIV, malnutrition, NICU or PICU patients, additional physiological changes need to be included.

Proper investigation of PK in these settings is feasible but since they involve the use of assumed biological prior knowledge ideally PK data in the population of interest is required, in order to confirm extrapolation results. Our study has now developed a systematic way to grade the evidence arising from extrapolation and clinical PKPD study results.

With a median DES of 3 and median Quality of Evidence level 3, the investigated resources for dose recommendations were dominated by individual PK studies, mostly performed in the 1980s and 1990s, with relevant covariates available but lacking PKPD modelling and simulations to derive appropriate dose recommendations. Nevertheless, it is encouraging that the DES trajectory with time indicates that the quality of paediatric antibiotic PKPD research has probably improved over the last two decades (Figure 4). An increase in DES over the las two decades, independent of the number of studies

published in the respective years, possibly reflects the increasing availability of more formal regulatory guidance documents and software, as well as improving computational power.

In 1999 the US Food and Drug Administration released the first version of their "Guidance for Industry: Population Pharmacokinetics", providing details on how to conduct a population PK analysis [37]. This document has undergone continuous updating in draft status since and serves as one of the major guidance documents for conducting PKPD studies.

With not only industry, but also academic institutions and research organizations, adapting their PK studies' standard conduct modelling and simulation has improved, as well as PK study planning and led to the emergence of PK simulation tools into clinical routine[38,39]. More sophisticated PKPD models are now feasible, including more computationally intensive estimation algorithms and quantitative systems pharmacology approaches, resulting in higher quality of PKPD research[40-42].

Strengths and Limitations

The pediatric population is very heterogenous, consisting of large age and weight ranges and, when it comes to antibiotic use, various potential underlying conditions that need to be taken into consideration.

To our knowledge, this is the first PKPD grading system to be applied to paediatric antibiotic studies. We believe that our proposed grading system could form the basis of a generic way to grade all PKPD studies and could be extended to cover analyses performed in adults, as well as various special populations. However, we acknowledge that GAPPS in itself is not evidence based, emerging from a consensus of a small number of experts. It certainly needs to be developed further (e.g. using a Delphi approach amongst a broader range of contributors) and validated before being adopted into practice. For example, the relative superiority of varying modelling approaches is

actively debated amongst PKPD researchers and further discussion of the hierarchy adopted in GAPPS might slightly affect studies' scores. Additionally, variability in study size or even the use of sample size and power estimation methods is not reflected by the current scoring system and will be a valuable addition in future adaptations of the GAPPS system. Furthermore, application of the GAPPS system to studies found through the literature review manually is subject to the reviewer's assessment of the data. Our systematic review may not have identified the entirety of clinical research in this field, but it is unlikely that any missed studies would change the overall result of poor but improving evidence. Recognizing that only one of the 237 assessed resources was graded with a QoE grade of 1a may require reassessment of what is realistically achievable in the context of paediatric PK research.

Possible explanations for the poor evidence-base

There are several possible explanations for the weak evidence base provided by paediatric PKPD studies of antibiotics. Low parental consent rates, heterogenous populations and ethical concerns can lead to small sample sizes [43], which in turn limit the complexity of analytical approaches which can be used. This hurdle can be addressed with innovative clinical trial designs, facilitated by pharmacometrics with the availability of power calculation methods and optimal design methods [44-46]. Broad inclusion criteria and utilization of drugs administered per standard of care, opportunistic drug sampling and scavenged PK samples have been effective tools in the past [33].

Another explanation is the heterogeneity in reporting of PKPD studies which hampers individual patient data meta-analysis of studies. Key guidelines for reporting population pharmacokinetic modelling are the US FDA Guidance for Industry: Population Pharmacokinetics [37] and European Medicines Agency (EMA) Guideline on Reporting

the Results of Population Pharmacokinetic Analyses [47]. In February 2017 a new EMA Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products came into effect. However, there is limited consensus on reporting, and it remains a developing field [27,48,49]. The International Society of Pharmacometrics (ISoP) [50] has now formed working groups for data standards and model evaluation as part of a standards and best practice committee, but further consensus is needed especially for paediatric pharmacokinetic reporting and meta-analytical methodology for traditional and population studies.

Expert Opinion

Information on paediatric dosing, especially across the different age groups is sparse for most antibiotics. As guidance for dose finding is mainly provided by formularies and online data bases, there is a need to grade their evidence base to make recommendations more transparent regarding the underlying analytical approaches and study design.

A grading system such as the GAPPS system can categorize PKPD Studies starting with the highest level of most reliable studies, a meta-analysis of raw PK data, to the low level and least reliable case studies and expert opinions based on in-vitro studies. Most evidence on paediatric dosing in the reviewed paediatric studies on antibiotics comes from individual PK studies. This is reflected in the median dose evidence score of 3, showing that most publications are lacking PKPD modelling and simulations. Nevertheless, with more guidance becoming available and software applications as well as computational power improving, the quality of evidence increased over the last two decades, with more sophisticated

modelling and simulation techniques being use ins study planning and dose finding of more recently approved antibiotics.

Standardized appraisal of PKPD evidence has an important role also in facilitating the prioritization of research and development resources by identifying areas where the least information about optimized dosing exists. Given the poor evidence-base for widely used older antibiotics, there is a need for collaboration between paediatric pharmacokinetic researchers and clinical trial networks internationally to tackle the evidence gaps in a complementary and strategic manner.

As formularies are increasingly becoming available electronically – either as e-books or desktop and mobile applications – direct in-line links to evidence and references for different dosing schedules should be encouraged. Reporting the GAPPS level of evidence and thus making the primary evidence along with its expert grading available to prescribers would allow them to gauge the quality of data underlying the dosing used in practice.

In 2017, the WHO published a list of antibiotic-resistant "priority pathogens" which pose the greatest threat to human health [51]. The list was drawn up to guide and promote research and development of new antibiotics and more research on the repurposing of older, less well studied drugs. The designation of a list of Access antibiotics by the WHO should provide a focus on the optimal dosing of this important group of medicines for children. A systematic appraisal of PKPD evidence of Access and Watch antibiotics focusses attention on the weakness of the evidence for current dosing guidance. The Blue Book formulary was the first paediatric formulary to alert prescribers to the potential strengths and weakness of the dosing guidance using smiley/sad faces. Prescribers need to be aware that potential treatment failure or unexpected toxicities

could be related to inadequate or over dosing following guidance correctly based on inadequate primary data.

The potential next step is to extend this analysis to other classes of medicines for children. International collaboration is then required between the leading paediatric formularies internationally, potentially convened by the WHO. Following a more thorough analysis of the data, a more harmonized consensus on current guidance can be achieved between formularies. In parallel a more formal process of research prioritization needs to be undertaken and international collaboration between the relevant stakeholders to undertake the relevant clinical studies required. This has been successfully achieved in other clinical areas, such as paediatric HIV and TB, so the principles are well established. Although there is a more considerable challenge when extending to antibiotics, the prioritization of Access antibiotics and these studies have demonstrated a clear path forward.

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Tables and Figures

Table 1

Antibiotics (studies included)	DES median [min - max]
Gentamicin (n=53)	3[1-10]
Vancomycin (n=41)	4[2-11]
Amikacin (n=19)	3[2-11]
Meropenem (n=16)	7[1-9]
Cefotaxime (n=11)	3[2-12]
Ciprofloxacin (n=10)	5.5[2-10]
Ampicillin (n=10)	2.5[1-12]
Azithromycin (n=10)	3[2-9]
Piperacillin-tazobactam (n=9)	7[2-12]
Amoxicillin (n=7)	3[1-12]
Co-amoxiclav (n=7)	2[2-10]
Chloramphenicol (n=7)	3[2-5]
Metronidazole (n=6)	5[1-12]
Cotrimoxazol (n=6)	2.5[2-11]
Ceftriaxone (n=6)	2.5[1-8]
Clindamycin (n=5)	7[2-10]
Cefazolin (n=5)	3[2-10]
Benzylpenicillin (n=3)	6[3-8]
Cefalexin (n=2)	2.5[2-3]
Claritrhomycin (n=1)	2
Cefixime (n=1)	3
Benzathine benzylpenicillin (n=1)	2
Cloxacillin (n=1)	2

Table 2

Quality of Evidence	Number of studies (%)	Strength of Recommendation	Number of studies (%)
1a	1/237 (0.4%)	Strong	19/237 (8.0%)
1b	7/237 (3.0%)		
2a	7/237 (3.0%)		
2b	4/237 (1.7%)		
2c	64/237 (27.0%)	Intermediate	217/237 (91.6%)
3	153/237 (64.6%)		
4	1/237 (0.4%)	Weak	1/237 (0.4%)

Table legends

Table 1 Dose Evidence Score (DES), listed as the median, minimal and maximal achieved DES score. The score metrics are listed by analysed Antibiotic

Table 2 Number of studies by GAPPS Quality of Evidence and Strength of Recommendation – summarized for each category

Figure legends

Figure 1 The GAPPS system uses a three part sequential assessment: PKPD Dosing Evidence Score (DES, numeric scoring 1 -12), Quality of Evidence (QoE, Levels of Quality 1a -4) in summary the Strength of Recommendation in categories weak, intermediate, strong.

Figure 2 Percentages of observed Dosing Evidence Score – Score is summarized over all evaluated antibiotics.

Figure 3 Frequencies of reviewed studies at each Quality of Evidence Level 1a – 4, displayed per Antibiotic.

Figure 4 Evolution of the median Dose Evidence Score over time – black dots represent the median score across all studies reviewed per year, dashed dark grey line represents the general trend via a loeass fit of the median DES, dashed light grey line shows the number of studies reviewed per year