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PEDIATRIC PHARMACOLOGY/DRUGS AND CHILDREN

Use of available clinical evidence to extrapolate drug effects from adults to children

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Summary The extrapolation of the benefit risk ratio from adults to children is performed during drug development and often implicitly used by many paediatricians when prescribing off-label drugs in children. This is due to the specific constraints of paediatric clinical research leading to a lack of safety and efficacy data in children. Extrapolation frameworks for drug development have been proposed by several regulatory agencies. Using a meta-epidemiological approach, we explored the similarities and differences of the benefit, the benefit risk ratio and the perceived placebo effect between adults and children from meta-analyses including randomized double-blinded placebo-controlled trials evaluating a drug intervention in an indication in adults and children with separate data for both populations. We also explored the use of the effect model using adult data to predict the treatment effect in children and to calibrate future paediatric clinical trials. Our research highlights the importance of using all available evidence and quantitative methods before extrapolating the benefit risk ratio from adults to children and carrying out new studies in the context of the existing evidence. More generally, this should be applied to any research to avoid a waste of time and resources invested.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
ADRs	adverse drug reactions
CONSORT	consolidated standards of reporting trials
EMA	European medicine agency
FDA	Food and drug agency
OR	odds ratio
PD	pharmacodynamics
PK	pharmacokinetics
NEAR-OR	net efficacy adjusted for risk odds ratios
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCTs	randomized, double-blinded, placebo-controlled trials
ROR	ratio of the odds ratios
RR	relative risk
SPIRIT	standard protocol items: recommendations for interventional trials

Introduction

It has been widely recognized that to be able to prescribe drugs to children with an appropriate benefit risk ratio, clinically relevant and robust data are needed. Such data are essentially obtained through randomized controlled trials [1]. However, paediatric clinical research is often confronted to methodological, ethical, operational, and financial barriers. Children are a heterogeneous population (from birth to adulthood) [2] with heterogeneous diseases and potentially heterogeneous outcomes and galenic formulation needs, according to the paediatric age group [1]. This heterogeneity leads to subdividing an already small population, compared to adults, which may further increase recruitment difficulties. The small sample sizes in paediatrics may result in inadequately powered trials, inconclusive trial results, and failure to detect a small but clinically relevant beneficial treatment effect [3].

The importance of extrapolation in children

Considering the scarcity of paediatric clinical data, off-label use is common in children [4,5]. A recent survey in two neonatal intensive care units in Lyon, France, reported that 95% of the 910 included neonates were exposed to at least one off-label or unlicensed drug [6]. It is even more worrisome since off-label use in children has been shown to be significantly associated with adverse drug reactions (ADRs) (relative risk [RR] 3.44; 95%CI [1.26; 9.38]) [7].

Off-label prescriptions are due to direct extrapolation of the benefit risk ratio observed in adult trials to children after adjustment of the dose according to the body weight or body surface area with no additional supporting evidence. However, as the common adage says: ''Children are not just small adults'' [8]. Such an extrapolation is often inaccurate due to pharmacological and physiological differences. There are obvious physiological dissimilarities that have an impact on the ''absorption, distribution, metabolism, and excretion'' (ADME) and therefore on the drug's pharmacokinetics (PK, i.e. how the organism affects the drug) and pharmacodynamics (PD, i.e. how the drug affects the organism). In addition, children are a heterogeneous group of patients whose organ maturation and development do not happen in a linear fashion [9], potentially altering drug PK and PD several times through childhood.

In addition to regulatory requirements and incentives to promote the quantity and quality of paediatric drug development, approaches to extrapolate adult clinical data to children have been proposed by the European medicine agency (EMA, EU) and the Food and drug administration (FDA, US). When robust similarities exist between adults and children, extrapolation from adult evidence may help reduce the paediatric data requirements and thus reduce the number and complexity of paediatric trials [10—12].

The following definition of extrapolation has been proposed by the EMA: ''Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product. The primary rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency, and to allocate resources to areas where studies are the most needed.'' [11].

According to the EMA framework, extrapolation is based on three fundamental evidence based assumptions: similar disease progression, clinical responses and exposure-response relationship in adults and children. The rationale for extrapolating the treatment benefit should be based on a body of evidence that takes into account the scientific knowledge of all aspects of the disease and its natural history in adults and children. On the other end, the FDA has developed a decision tree defining three levels of extrapolation: no extrapolation (none of the assumptions verified); partial extrapolation (uncertainties on at least one); and full extrapolation (all three verified) [10,13].

The degree of extrapolation depends on how much of the source data can be used to predict the PK, PD and efficacy of a drug in children. The decision requires a timely availability of source data and to find a balance between the uncertainties underlying the extrapolation concept and the additional number of patients required to carry out further studies. Overall, the extrapolation rationale should be updated and the assumptions retested as new data become available [11].

The rational use of available evidence before extrapolating to children

The extrapolation of the benefit risk ratio from adults to children occurs during drug development through modelling and simulation techniques [14,15]; in 2016, up to 52 agreed paediatric investigation plans had explicit extrapolation measures [16]. It is obvious that paediatricians cannot apply