Journal of Clinical Epidemiology 68 (2015) 1221−1231

Journal of Clinical Epidemiology

REVIEW ARTICLES

Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children

Perrine Janiaud[a], Audrey Lajoinie[b], Fleur Cour-Andlauer[b], Catherine Cornu[a,b,c], Pierre Cochat[a,d], Michel Cucherat[c], François Gueyffier[a,b], Behrouz Kassai[a,b,c,*]

[a]*UMR 5558 CRNS Lyon, University of Lyon 1, France*
[b]*Clinical Investigation Center, EPICIME, INSERM CIC 1407/UMR 5558 CNRS, Bron, France*
[c]*Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, France*
[d]*Department of Pediatric Nephrology, Hopital Femme Mere Enfant, Lyon, France*

Accepted 29 June 2015; Published online 9 July 2015

Abstract

Objective: Our main objective was to see whether the therapeutic benefit observed in placebo controlled randomized controlled trials (RCTs) is different between adults and children.

Study Design and Setting: We searched three electronic databases for meta-analyses that included double-blind, placebo-controlled RCTs with separate results for adults and children. The selected reviews were classified according to disease and drug used. The heterogeneity of treatment response between adults and children was measured using ratio of odds ratios (RORs).

Results: We selected 89 meta-analyses and calculated RORs for 124 drugs. Heterogeneity in the direction of the treatment effect was observed in one drug and heterogeneity in the quantity of the treatment effect for 13 drugs, indicating significantly different treatment effect in adults when compared with children. RORs were not significantly different from 1 for 110 drugs. For 36 of these drugs, the treatment effect was confirmed in both populations.

Conclusion: We found different treatment benefits estimated by clinical trials performed in adults compared with those performed in children for 14 of 124 drugs. Data on dose adjustment and child age groups from RCTs were not adequately reported to investigate their influence on the treatment benefit dissimilarities.

Keywords: Meta-epidemiological study; Extrapolation; Treatment benefit; Pediatrics; Adults; Data reporting

1. Introduction

It has been widely recognized that children cannot be provided with safe and efficacious drugs compared with those available for adults without involving them in clinical trials. EU pediatric regulations (Regulation [EC] 1901/2006) now require that clinical trials in minors be planned and conducted for all new products [1]. The main objectives of the pediatric European regulation were to ''achieve high-quality ethical pediatric clinical research, increase availability of authorized medicines that are appropriate for children, and produce better information on medicines'' [2]. Since 2008, nearly 500 pediatric investigation plans have been approved by the European Medicines Agency, but few of them have been completed [3]. Therefore, many drugs used to treat children in hospitals are either not licensed for use in children or are prescribed outside the terms of their product license (off-label prescribing) because of the lack of clinical trials in this population [4−6]. This may be explained by a lack of knowledge on drug evaluation methodology, the need for large multicenter international trials to evaluate the effectiveness of medicines in children suffering from rare diseases, ethical concerns on treatment randomization, the use of placebos, time consuming or invasive explorations, difficulties for recruiting participants because parents are reluctant to allow their children to participate, and insufficient funding due to the high cost of drug development for a limited market [7,8].

Consequently, care givers are left with the choice to either deprive children from potentially innovative therapies or to prescribe potentially ineffective or harmful drugs.

Conflicts of interest: P.J. is currently receiving a salary from GlaxoSmithKline, France, for her 3 years Ph.D. at the UMR 5558 CNRS. The remaining authors have no conflicts of interest.

* Corresponding author. Hospices Civils de Lyon, Groupement hospitalier Est, Bâtiment Les Tilleuls, 59 boulevard Pinel, 69003 Lyon, France. Tel.: +33(0)4 27 85 77 32; fax: +33(0)4 72 35 73 64.

E-mail address: behrouz.kassai-koupai@chu-lyon.fr (B. Kassai).

http://dx.doi.org/10.1016/j.jclinepi.2015.06.021
0895-4356/

What is new?

Key findings

- Extrapolation of the therapeutic benefit from adults to children is not misleading in some cases, but differences in the direction and amount of the treatment benefit are not uncommon.

What this adds to what was known?

- This work emphasizes the importance of reporting data separately for each age groups, and the need to consider all available evidence in adults and children before the extrapolation of the treatment benefit is warranted.

What is the implication and what should change now?

- Extrapolation of efficacy from adults to children should be based on all available evidence including RCTs.

In most cases, data are extrapolated from adults to children after adjusting the dose for weight or body surface area. Such extrapolation is often inaccurate due to pharmacological and physiological differences between adults and children of different age groups [9,10]. Because of the complexity of drug action mechanisms and organism responses, it is difficult to predict the treatment benefit in children only based on pathophysiological and pharmacological knowledge.

Adults and children may respond differently to drugs. Randomized controlled trials (RCTs) evaluating drugs versus placebo are the best available evidence to appraise the difference on the therapeutic benefit between adults and children. Our main objective was to explore the available evidence from placebo-controlled RCTs included in meta-analyses to see if the benefit in adults could be extrapolated to children for each drug.

2. Methods

2.1. Literature search

Three electronic databases (PubMed, EMBASE, and the Cochrane Library) were searched for meta-analyses (from 1998 for Cochrane Library and from 1966 for PubMed and from 1947 for EMBASE), with no limitation on diseases or treatments. The last bibliographic search was performed in February 7, 2014. The following search terms were used: (Child or preschool or infant or adolescent) and (adult*) and placebo. For PubMed, we specified the type of study (''meta-analysis''). For EMBASE, we specified the following filters: ''human'' and ''meta-analysis.''

2.2. Meta-analyses selection

Meta-analyses were eligible when they included RCTs in adults and RCTs in children that were double-blinded, placebo-controlled and reported separately their results in adults and children. All types of treatments were eligible, except for homeopathic treatments and nondrug interventions. All age ranges were included. The age limit between adults and children, when necessary, was arbitrarily set at 16 years. Adult trials may also include a few adolescents (>12 years). Meta-analyses conducted in adults or in children but evaluating the same drug in the same indication were also included. Once all the inclusion criteria were met, the RCTs from the included meta-analyses were organized according to the active drug used. A review was considered a duplicate when it included the same RCTs. Two authors (P.J. and B.K.) independently reviewed all citation abstracts and excluded irrelevant studies according to predefined exclusion criteria.

2.3. Data extraction

The following information was extracted from the meta-analyses and entered into the database: (1) the conception and design of the study (randomization, parallel group, cross-over, and blinding); (2) patient characteristics (adults or children, disease, number of patients in the placebo and treatment arms, and the number of events and no-events in each arm); (3) the drug used (some meta-analyses gave information for more than one drug, when possible data were extracted for each drug studied in the meta-analysis); (4) the outcome; (5) the dose for adults and the dose adjustment for children when available. When a review studied more than one drug, data for children were extracted for each drug, and the relative benefit for each drug was estimated according to the outcome reported in the meta-analysis.

For each included review, trials were grouped by drug and then as pediatric and adult trials according to the cutoff age used in the reviews. The original RCTs were consulted when data were missing in the meta-analysis report. The doses and dose adjustments were compared to the usual recommendation given in the Theriaque database (http://www.theriaque.org). The pharmacokinetic (PK) parameters (volume of distribution, bioavaibility, half-life, time to peak serum, and clearance) were compared between adults and children using available data in the UpToDate database (http://www.uptodate.com).

The main outcome and the treatment benefit (number of events or effect size in each group) were extracted blindly from the original systematic review by three authors (P.J., A.L., and C.C.). Differences were resolved by consensus.

2.4. Quality assessment

We reported the quality assessment reported by the authors of the meta-analyses for each included RCT. For