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Perspective

Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children

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Children are often touted as being very important members of society because they represent our future. Optimizing their health outcomes has the potential for a huge impact on public health because children are at an early stage in the life trajectory. But it is often unclear how society allocates its resources or creates policies to ensure that it invests in children's health. The under-investment in pediatric clinical trials is a good example of how our resource allocation may be insufficient.

Over half of the pharmacological interventions we use for hospitalized children are off-label or unlicensed drugs [1,2]. The challenge for clinical care is that health care providers may fail to use medications that are indeed effective, or conversely, continue to use ineffective medications, or even those that bring unintended harm. Child health care providers must often rely on evidence that has been generated on adult populations [3]. However, both the safety and efficacy profiles of medications may be significantly different for children than adults due to differences in developmental physiology, disease pathophysiology, or developmental pharmacokinetics and pharmacodynamics [4,5].

The Challenges from the Past

History has shown that children may be exposed to serious unintended harms from medications if adequate research is not performed. Examples of such harm include the use of chloramphenicol for neonates producing the grey baby syndrome, the use of verapamil for treatment of infants with supraventricular tachycardia resulting in refractory hypotension and death, serious extrapyramidal dysfunction and bladder retention leading to hospitalization after domperidone, and many more [5–7].

To address the lack of randomized controlled trials (RCTs) and pharmacokinetic and pharmacodynamic evidence in children, Europe and the United States have enacted legislative and regulatory changes to encourage pharmaceutical companies to invest in research involving children, to provide the needed data on safety and efficacy of new agents [8,9]. The outcome of such legislative and regulatory changes has been an increase in the number of pediatric studies performed; however, a significant number of these studies have not yet been published [10]. An overall examination of the pediatric studies performed under this new legislation has shown that the types of drugs studied have tended to mirror those most commonly used by the adult market rather than drugs commonly used by children [11].

While there is evidence that children have been harmed by medication that has not been adequately studied, or by medication that has demonstrated differences in pharmacokinetics and pharmacodynamics in children as compared to adults, it has been more difficult to demonstrate significant and important differences in treatment effects between adults and children. In an examination of Cochrane systematic reviews dealing with interventions for diseases occurring in both children and adults, we identified 408 reviews. Only 52% of these included data from children. We could find no significant differences in effect sizes between these two groups, because all of the comparisons lacked statistical power with wide confidence intervals, and hence it was not possible to rule out clinically important differences [3].

Epilepsy as a Case Study

A new study by Philippe Ryvlin and colleagues in this issue of

Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P (2008) Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 5(8): e166. doi:10.1371/journal.pmed.0050166

In a systematic review of antiepileptic drugs, Philippe Ryvlin and colleagues find that children with drug-resistant partial epilepsy enrolled in trials seem to have a greater response to placebo than adults enrolled in such trials.

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Abbreviations: ADR, adverse drug reaction; RCT, randomized controlled trial

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PLoS Medicine makes an important contribution to the question of whether there are differences in treatments effects between children and adults [12]. In an effort to investigate whether children and adults with drug-resistant partial epilepsy respond differently to active treatment versus placebo, these authors performed a comprehensive search for methodologically rigorous RCTs evaluating antiepileptic drugs as add-on treatment for both children and adults. Overall, the treatment effect for their primary outcome (i.e., 50% responder rate) was significantly lower for children with a relative risk ratio of 0.67 (95% confidence interval 0.51–0.89), explained by the higher rate of response in the placebo arms of the pediatric trials (19% versus 9.9%, $p < 0.001$) [12].

Unfortunately, this study by Ryvlin and colleagues is limited by the relative paucity of pediatric data, with only five of the 32 trials having been performed on children and only one pediatric trial for each of the five agents examined. This study again underscores the relatively weak evidence base informing medical care in children compared with adults. Further, the comparison of treatment effects between adults and children was across and not within trials. Therefore the results could be explained by residual confounding, despite the meta-regression done by the authors, arising from differences in disease severity, drug dosages, outcome measures, and diagnostic categories.

Where to Go from Here

We know that the lack of trial evidence goes beyond neurological diseases to other childhood areas, such as pediatric cardiology, neonatology, pediatric intensive care, and oncology [2,13]. If we use publication of RCTs in general medical journals as a marker, it would appear the gap is widening between the annual number of published pediatric trials and adult trials [14]. Furthermore, a recent review of studies published in six leading medical journals showed that "studies involving adults were significantly more likely than child studies to be randomized, controlled trials, systematic reviews, or studies of therapies" [15].

The future agenda is 2-fold: while more research is required, careful attention must be paid to design and reporting. In terms of design, attention needs to be given to:

- Ensuring adequate sample sizes that consider the potential placebo response and that are derived from calculations based on pediatric data, or taking into account relevant considerations when only adult data are available.
- Choice of objective, clinically relevant endpoints that can be measured in a valid and reliable manner.
- Choice of clinically appropriate comparator (i.e., placebo versus other active agent).
- Identification of a priori subgroups within the pediatric population that may show differential responses to treatment (e.g., infants, preschoolers, school-aged children, adolescents) and adequate power to avoid type II errors in such subgroup analyses.
- Child-focused attention to the evaluation of adverse effects. Careful consideration in terms of sample size and length of follow-up is needed in order to avoid claims of safety when in fact the studies were underpowered to detect rare events. The role of (prospective) meta-analysis to this end should be exploited.
- Predefined tasks for committees that monitor safety and adverse drug reactions. A recent literature review of therapeutic clinical trials involving oral and intravenous medicines in children from 1996 to 2002 showed that only 13 (2%) of 739 trials had safety monitoring committees [16]. Of the 739 trials, 523 (71%) trials reported adverse drug reactions (ADRs), and 151 (20%) of these trials reported a serious ADR. About 11% of trials have a moderate or severe ADR. All pediatric clinical trials should have a safety monitoring committee.

The above design considerations need to be balanced with the ethical requirements for conducting research. However, where true equipoise exists, sufficient numbers of children need to be studied in order to provide valid estimates of treatment effects. Moreover, inadequately powered studies should themselves be considered a breach of ethical standards [17]. Recently, the creation of specialty-specific pediatric research networks in the United States, Canada, and Europe (The International Forum of Standards for Research with Children lists some of them at http://www.ifsrc.org/) was in part motivated by the need for multi-centered trials in order to ensure adequate and timely recruitment into trials.

Conclusion

While more empirical evidence is needed to guide clinical practice for children, further research, such as the study by Ryvlin and colleagues, is important to inform the design and reporting of pediatric trials. Standards for the design and reporting of pediatric trials would contribute to the development of a methodologically strong and relevant evidence base for pediatric care. Moreover, adequate reporting will assist end-users in assessing the relevance and applicability of a study's findings (http://www.equator-network.org/).

Looking to the future, the evidence is mounting that there is an urgent need for high-quality RCTs in children, to ensure the medication we use is both safe and effective. To facilitate this development, an international group of clinical and methodological experts, of which the co-authors are members, have launched a forum around an international project to develop standards for research with children (http://www.ifsrc.org/). Membership of this forum is open to all who wish to contribute to the development of these standards, whether they are clinical researchers, basic researchers, regulators, patients, or parents. ■

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