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SERIES: ETHICS IN PAEDIATRIC RESPIRATORY MEDICINE

Development of medicines for children in Europe: ethical implications

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Summary Ethics of clinical trials in children have been a longstanding topic for debate. Children are vulnerable, unable to consent to participation in trials from a legal perspective and deserve to be protected. Ethical principles and the European legal framework define the safeguards that need to be put in place in any paediatric trial, be it performed in developed or in developing countries. It was considered that children should not be included in trials for ethical reasons. However, there is an ethical need to study medicines as data obtained in adults cannot be extrapolated to children. It is our collective responsibility to obtain sufficient information to be able to prescribe medicines safely whilst protecting children who are exposed in the trials. Future European paediatric regulations should encourage the development of medicines in high-quality ethical research and ensure availability of information to the public.

INTRODUCTION

The ethics of clinical trials in children have been a longstanding topic for debate. Children are vulnerable, unable to consent to participation in trials from a legal perspective and deserve to be protected. Ethics principles, such as those expressed in the Declaration of Helsinki[1] and the Convention on Human Rights and Biomedicine (Council of Europe),[2] have been established to protect trial subjects. It has been considered that paediatric clinical trials were unethical. Simultaneously, very little protection against unsupported use of medicines has been established for this vulnerable population. Off-label use is still the main basis for prescription of medicines to children, who are denied access to well-studied and assessed treatments and diagnoses.

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THE CURRENT SITUATION IS NOT ETHICALLY ACCEPTABLE

Medicines used in children have not been studied properly

Most of the medicines used to treat children in Europe have not been fully developed and assessed. Recent surveys have confirmed that the European situation[3–9] is no different from that of the USA or other regions. Providing a full range of both old and recent medicines that are fully developed and assessed to cover the therapeutic needs of children in Europe is a major ethical and practical challenge.

Most medicines used in children have not been studied specifically for this population.[10] In some cases, only the older subgroups were studied. In some therapeutic areas, such as oncology where many trials have been performed and published by academic centres independently of pharmaceutical sponsors, no application for marketing authorisation was made to the authorities.[8] Therefore, no

assessment was made to provide reliable information and guidance to prescribers and the public.

Paradoxically, most of the catastrophies observed with medicines in the 20th century happened in children (to cite only the toxic effects in children of antifreeze, chloramphenicol, thalidomide and Jesse Gelsinger's case with gene therapy).[11–13] Many other less publicised findings were also made in children, such as renal tubulopathy due to tetracyclines. These dramatic findings triggered major steps forward in regulatory processes to protect the public, but did not result in requirements to study medicines adequately in the paediatric population. The literature repeatedly shows that off -label use of medicines is associated with increased risk of adverse drug reactions, prescription errors and significant quantitative and qualitative under-reporting.[3,5] Europe is lagging behind the USA in establishing proper requirements to study medicines in children,[14] as it has been lagging behind to stimulate the development of orphan medicines for patients affected by rare diseases.

The use of medicines in children is based on conviction rather than evidence

Using medicines that have not been properly studied and assessed is based on conviction, word of mouth and experience rather than on verified evidence.[15,16] Each child becomes the single participant of an uncontrolled trial. The dose used in such a trial is based on an extrapolation of adult doses based on weight, body surface area or, worst of all, age. This type of extrapolation has been shown to be inaccurate in many situations. Additionally, the adult dose may even have been originally established for another disease. Adverse reactions may occur without detection. In addition, missed opportunities for successful treatment due to underdosing are probably frequent but more difficult to detect. No information resulting from the trial can be used for the individual child or the group, as the methodology prevents drawing any conclusion. Even a success could be classified as a chance finding. Doing 'anything' rather than abstaining is a frequent temptation for the physicians, convinced (and therefore biased in the methodological meaning of the word) by a sincere intention of improving the child's health.

It is not our intention to defend systematic therapeutic abstention when information is lacking. Instead, we wish to promote ethical action in research to develop high-quality trials where needed and whenever possible. All the requirements that make clinical research ethical need to be present.[17,18]

CHILDREN NEED MEDICINES THAT HAVE BEEN STUDIED

Differences between adults and children justify paediatric trials

Children are not small adults and weight difference is not the only difference of relevance for the use of medicines. On the basis of what we know of paediatric pharmacology in different groups of children, it is not possible to extrapolate findings and results from adults to children.[18,19] Differences can be found in disease patho(physio)logy and expression, in the influence of maturation and growth, in pharmacokinetics, pharmacodynamics and adverse drug reaction types, and in severity, timing and consequences.[20]

Some conditions are specific to, or mostly observed in, children; for example, meconial inhalation, some forms of pulmonary hypertension, asthma or cystic fibrosis. Children are not small adults in respect of pharmacokinetics. Differences in absorption, distribution, metabolism and/or elimination of drugs have been well demonstrated in children compared with adults; for example, ibuprofen in children with cystic fibrosis.[21–24] Other aspects may add to these differences; for example, the use of nebulisers requires hand/breathing co-ordination. Drug pharmacodynamics may also vary; diazepam may produce sedation in adults and agitation in children. The effects of steroids on growth are observed in children. Maturation may influence drug response or metabolism; for example, some receptors only appear after some months or years of life.[25] The closure (or persistance) of a patent ductus arteriosus is another process related to maturation. Apart from situations where differences have been established, there is a wide gap in our knowledge of maturation, which makes it impossible to assume similar pharmacodynamics. Finally, we also lack the tools to assess pharmacodynamic effects, particularly in very young children; for example, full evaluation of respiratory function requires co-operation and can only be assessed on limited parameters in infants and even more so in newborns.

Differences within the paediatric population add to the complexity

Children cannot be considered as a single homogenous population when it comes to studying medicines. The International Conference on Harmonisation (ICH) guideline, adopted by the European authorities,[26] distinguishes at least four subgroups: neonates including preterm and term from birth to 28 days of life; infants from 1 to 23 months of age; children from 2 to 11 years of age; and young people from 12 to 18 years of age. Each of these subgroups has its own characteristics, which may require separate trials. In addition, these conventional subgroups do not fully coincide with maturation of some organs. Liver maturation mainly occurs in infants and is probably achieved by 3–4 years of age, whilst, conventionally, the infant subgroup does not go beyond 23 months of age. Including infants in a trial will therefore lead to having a study population with different levels of hepatic maturation, drug metabolism and different risks of adverse drug reactions, whilst it is likely that the trial will lack the power to analyse each subgroup fully.

Differences within the paediatric population justify the need for multiple subgroups or multiple studies, or for