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Review Article

Perspectives in pediatric clinical trials: a review

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ABSTRACT

Children are different from adults in many aspects of pharmacotherapy, including capacity to absorb, distribute, metabolize and excrete drugs and have their own taste preferences. International Conference on Harmonisation (ICH) guidelines classify pediatric age groups into five groups namely preterm, term new born infants, infants and toddlers, children and adolescents. United States conducts maximum number of pediatric drug trials as compared to developing countries. Most of the prescribed drugs are either unlicensed or have an off label use. That is these have not been evaluated for their safety and efficacy in children. As children are separate population entity and not mini-adults, these clinical trials with adults cannot be simply generalized or extrapolated to pediatric population. Thus it is mandatory to conduct clinical trials involving pediatric population in order to get full benefits to the children. To study this gap between adults and children for their wellbeing, disease prevention, diagnosis and treatment, high quality clinical trials are required.

Keywords: Review, Child, Pediatrics, Clinical Trials, Informed consent, Pharmacology

INTRODUCTION

Clinical trial means a systematic study of the new drugs in human subjects to generate data for discovering and / or verifying the clinical, pharmacological (pharmacodynamic and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.[1] Pediatric clinical trial refers to clinical research in pediatric population from birth to 18 years of age. According to International Conference on Harmonization (ICH) guidelines, pediatric age groups are classified into five group's namely preterm, term new born infants, infants and toddlers, children and adolescents.[2] A recent review of pediatric clinical trials submitted to the United States Food and Drug Administration (USFDA) between September 28, 2007 and December 21, 2010 revealed that the United States conducts a maximum number of pediatric drug trials. The involvement of developing countries in pediatric drug development is not increasing. These countries however participate significantly in vaccine trials.[3] In India, there are 440 million children and every fifth child in the world is an Indian. Child specific medicines are the most cost effective tool to reduce morbidity and mortality. Most of the prescribed drugs are either unlicensed or off label. That is these have not been evaluated for their safety and efficacy in children.[4] In order to meet children's rights and demands for highest attainable health, the General Assembly of United Nations (Convention on the Right of the Child 1989) has emphasized the need to study new and existing therapies specifically in children.[4]

Historical perspective of pediatric research and pediatric drug tragedies

During World War II, orphan children were easily available for experimentation without taking informed consent. Experiment on children resulted in pain, disability and death so antivivisectionist started protesting against the use of children in experiments. Most of the physicians ignored the Nuremberg code and conducted pediatric clinical research without any regulations till 1960s. After the establishment of World Medical Association in 1964, physicians and researchers started to conduct sound ethical research. In 1902, there were death of children following diphtheria antitoxin vaccination which were contaminated with tetanus spores. In 1905, infant deaths were reported due to the misuse of medications causing coma, addiction and death. In 1936, sulfanilamide dissolved in diethylene glycol used to treat infection, killed 107 children. In 1961, it has been found that use of thalidomide as antiemetic during pregnancy led to limb deformities in infants.[5]

Critical problems associated with pediatric drugs formulations

There are many problems seen with the use of pediatric drug formulations such as inaccurate dosing, bad taste, lack of stability, adherence problems, lack of standardization and environmental safety. An ideal oral pediatric dosage form must be tasteless, easy to swallow, with minimal excipients, and heat, humidity and light stable.[6] There is also inadequate information related to safety and effectiveness of various drugs used in children. Most of the time children are treated in the same way as adults despite having significant differences in physiological, pharmacokinetic and pharmacodynamics profiles. There are also wide differences in metabolic pathways and organ functions in children. Thus, it is very difficult to extrapolate the data from adult studies for use in pediatric population.[7]

Unmet needs of pediatric clinical trials

- To establish the safety and effectiveness of existing drugs.
- To protect the child from harmful adverse drug effects.
- To develop new diagnostic modalities and treatment.
- To prevent unlicensed or off label use

Pediatric studies

There are several approaches for the extrapolation of efficacy of drugs from adult to the pediatric population. If the disease progression, response to intervention and exposure response relationship in children are similar to adults, then only pharmacokinetic and safety studies are needed which is termed as full extrapolation. If the disease progression and response to intervention in children are similar to adults but exposure response relationship is different, then pharmacodynamic measurements are done to predict the efficacy. In this case, if it is possible to measure pharmacodynamic parameter to predict efficacy then single adequate pharmacokinetic, efficacy and safety studies are needed termed as partial extrapolation. If the disease progression and response to intervention in children are not similar to adults and pharmacodynamic measurements are not also possible to predict efficacy, then two adequate pharmacokinetic, efficacy and safety studies are needed which is termed as No Extrapolation. Multiple failed trials for similar condition as in adults, known differences in mechanism of action, site of effect or other physiological parameters and novel indication in pediatric patients such as tinea capitis are some important reasons for no extrapolation.[8]

Challenges in pediatric clinical trials

The number of clinical trials carried worldwide in children are relatively few. There are many reasons for nonparticipation of children in clinical trials. The high developmental costs involved and limited expected gain of new pediatric drugs usually do not attract the pharmaceutical industry to invest in these areas. The recruitment issues such as lack of suitable trial subjects and limited number of children with specific diseases due to the heterogeneity of the pediatric population affects pediatric clinical trials. There is fear and inconvenience among parents to let their children participate in clinical trials. Ethical concerns about the strict inclusion criteria of children in clinical trials have been disproportionately high, resulting in strict laws and ethical guidelines and phobia for clinical trials in children. [9,10]

Pediatric study design considerations

While designing a pediatric study, many things have to be taken into consideration. Pediatric patients are usually susceptible to unique disease states such as respiratory distress, seizures and rickets, so there is a need of an expert pediatrician for the diagnosis of such disease states. Children have more body water as compared to fats, so the volume of distribution of drugs are different. Liver and kidneys are not developed requiring dose adjustments over a time. There is also wide variation in growth and development status among children. Study end points such as physical activity score, number of days missed at school and scholastic performance are taken into consideration. Sometime, question arises while designing a pediatric trial regarding the comparator. Pharmacokinetic data can be extrapolated in children more than 12 years of age because they have similar pharmacokinetics as adults. Many diseases in adolescents such as seizures, diabetes and migraine are influenced by

hormonal changes around puberty that may interfere with the results of pediatric clinical trials.[2]

Ethical considerations

Before conducting a pediatric clinical trial, it is mandatory to take informed consent from their parents or assent should be taken if the child age is more than seven years. It is difficult to take consent of a diseased, underage and poor parents or legally accepted representatives. In emergency situations such as eclampsia, predelivery consent is taken. Sometimes ethical question may arise in clinical trial of very sick children, whether to put them on standard clinical care or clinical trial. Taking an appropriate decision is worthwhile. There is also a question regarding the use of contraceptives and history of illicit drug intake in adolescent children.[2]

Practical considerations in pediatric clinical trials

It is necessary to ensure that the participant's experiences in clinical trials are positive with less discomfort and distress. Pediatric clinical trials should always be carried out in a well-planned manner with complete information given to the parents. Trials should be conducted in a familiar environment such as hospital or clinic, where the pediatric study participants normally receive their medical care. Topical anaesthesia should be used whenever needed and indwelling catheters placed to avoid repeated venepuncture for blood sampling. Frequency and volume of blood sampling must be prespecified in the clinical study protocol. The study should be planned in such a way so that it may not interfere with the child's routine activities such as sleep and feeding. Adolescent children should feel free to ask any question with respect to the conduct of the study as sometimes they may not agree with their parents and would not participate in the pediatric clinical trial.[2]

CONCLUSION

Pediatric clinical trials are vital for studying new drugs as well as designing rational and effective therapeutic regimens in children. Children should be viewed as a separate population entity and not as mini-adults. The unique pathophysiology and pharmacology of pediatric population should be considered while designing pediatric clinical trials. There are multiple ethical and practical challenges of carrying out clinical trials in pediatrics. Understanding these needs, concerns and addressing these challenges will pave the way for more clinical research in some key therapeutic areas for children.

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