LECTURE

The Joseph J. Hoet Lecture on Ethics in Paediatric Research given at the European Conference on Clinical Research in Children, 24–25 January 2002, Brussels Putting the child first: research as a part of paediatric care

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The main ethical task of all paediatric activities is to act in the best interests of the child. Even if we can never be absolutely certain as to what are the best interests of children, we must try to get as close as possible by focusing our empathy on the needs of children by means of scrupulously scrutinizing our experiences and observations.

Today's basis of considerations concerning the best interests of children, and how their development is protected and promoted in the best way possible, is the fundamental right of all human beings to be free and equal in dignity and rights – article one of the General Declarations of Human Rights, accepted by most countries in the world. Accordingly, there is no doubt that children are entitled to full human rights and to the right of full identity. This means that in medicine, doctors must show fundamental respect for the unique and sacred life of children as their most valuable possession, as well as for their adequate personal needs at each stage of development. A child does not have to become a human being: he or she is a human being right from the beginning, a person with special needs. Because children and adolescents are greatly dependent on the protection and support of adults, the ethical attitude of doctors is especially significant in saving and promoting children.

In medicine, each ethic must start from a definition of the essence of a human being, uninfluenced as far as possible by ideologies, opportunism and utilitarianism. However, we are not free from egoism and ideologies, and even if we postulate constant and unchangeable elements of ethics, we will find changing elements depending on society, and we cannot find answers to all questions. Therefore, we have to reflect the best interests of the individual child as sincerely as possible, and also the medical and social concerns defining the needs of children for a healthy development.

If we really want to establish the fundamental rights of children in paediatric medicine, we must also read the Convention on the Rights of Children approved by the General Assembly of the United Nations Organization (UNO) in 1989, where guidelines supporting paediatricians' approach in order to realize the fundamental needs of children in daily practice do exist.

Four articles seem to be crucial:

- All human rights apply to all children without exception.
- In all actions, children's interests have priority to ensure the protection and care necessary for the wellbeing of children.
- Children have the right to the highest possible level of health.
- Children have the right to obtain information, and their opinion has to be taken into account.

Therefore, any child has the full right to respect of his or her personality, and the protection of his or her life and health by providing the optimum medical care in each phase of his or her development.

However, optimal medical care can only be based on research. Today's requirement is evidence-based medicine obtained by scientific evaluation of preventive, diagnostic and therapeutic measures on the basis of generally accepted scientific methods.

Unfortunately, there are significant deficits in objective knowledge of the quality and efficacy of relevant medical measures. In the EU, about 50% of medicaments used in paediatric hospitals are not officially registered. Conroy and co-workers found that 39% of applied medicaments were off-label and 7% were unlicensed in general paediatric units. 'Off-label' means medicaments that are registered for adults but not licensed for the relevant age or indication. 'Unlicensed' means medicaments that are not licensed for the applied dosage or formula. In paediatric intensive care and neonatal care units, the rate was much higher, and up to 90% of the children received medicaments that had not been registered.

The majority of the relevant data derives from adults. However, there are evident differences in physiology, pathology, pharmacokinetics and pharmacodynamics between children and adults that do not allow the general extrapolation of adult data on medicinal products to children.

In pharmacokinetics, the differences concern the metabolic pathway, organic functions and metabolic rates. In pharmacodynamics, the differences concern the receptor functions, effector systems and homeostatic mechanisms. Growth and development influence side effects and the dependency of dosage of medicaments on body weight and surface. In addition, there are diseases that exist only in children or that are different in comparison with adults regarding their phenomenology, severity and course.

What are the reasons for this deficit of generally valid knowledge of effects, side effects, dosage and application forms of medicinal products and of evidence-based optimal medicine for child patients? Although 100 years ago the famous paediatrician Theodor Escherich stressed the point that a child is not a small adult – and this paradigm could be proved scientifically during the last century – many doctors in the world are still not aware of this fact. Furthermore, because of unethical and cruel trials in fascist societies, one can understand why older ethical declarations exclude the child from research if this research has no immediate benefit for the individual child. However, we know that this strong imperative impedes epidemiological studies and prospective randomized trials with control groups, which form the basics of clinical research. International recommendations for good clinical practice that take the need of responsible and child-specific research into account to an adequate extent are only a few years old, such as the last revision of the Declaration of Helsinki, the Topic E11 of the International Conference on Harmonisation, including the EMEA guidelines, the last EU Directive of the European Parliament and the Council, and the Operational Guidelines of the Confederation of European Specialists of Paediatrics, among others. Moreover, it is not easy for parents to understand why their child should be involved as a participant in a research trial, and pharmaceutical companies that are confronted with greater difficulties in conforming with clinical trials regulations, potentially higher risks and a reduced market are sometimes not very motivated to develop child-specific medicinal products.

The requirement for optimal medical care based solely on scientific evaluation on the one hand, and the banning of biomedical research with generally approved methods on the other hand, would lead to an insoluble dilemma. Nevertheless, if we want to do justice to children and to respect their best interests, we have to follow two ethical demands simultaneously, as the ICH stated: 'The ethical imperative to obtain knowledge of biomedical data and the effects of medicinal products in paediatric patients has to be balanced against the ethical imperative to protect the individual child in clinical studies and respect his or her integrity and personal dignity.'

Therefore methodically sound research must be combined with measures that take the special needs of children into account. We have to protect the personality of children, protect their potential for development, respect their specific vulnerabilities and fears, and consider the biological differences that exist between different ages and between the child and the adult.

To realize these objectives, we must first observe the general principles of medical ethics:

- Respect for human dignity, life and – in children as far as possible – autonomy
- Beneficence (doing good)
- Non-maleficence (not doing any harm)
- Distributive justice
- Community spirit and solidarity

However, good clinical practice in children involved in clinical trials also includes the following concerns:

- Trials should focus only on the knowledge, cure, relief or prevention of the diseases of children.
- Efficacy, pharmacokinetic and safety studies must be performed first in animals, and then in adults if the disease is not confined to childhood.
- In clinical studies, the search for the superiority of a substance by using controls or placebos may also be necessary in children. Not using a proper control can make a study worthless and therefore unethical. Finally, a benefit for the child should be expected when participating in a study.
- Adequate evaluation of medicinal products for use in children means observing physiological, pathological and pharmacokinetic differences at different ages. Therefore, homogeneous age-specific groups are suggested: premature newborns, term newborns, infants and toddlers, preschool and school children, and adolescents.

The preconditions for a clinical study involving children are that the investigation intends to reduce harm and poor outcome, that the benefit should outweigh known risks, and that there are no foreseeable serious risks. Because the vulnerability of children can be different, the individual situation must be evaluated for each child.

Different degrees of risk have to be considered in paediatric research. Minimal risk stands for procedures such as questioning, observing and measuring carried out in a sensitive way. Greater than minimal risk means invasive procedures or therapies that should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned.

Only well-designed studies are ethically justified. This means that in addition to the well-known general guidelines for good clinical practice, specific items have to be observed in paediatric research, such as:

- justifying the necessity of the research concerned;
- elaborating the study design by competent researchers experienced with paediatric concerns;
- performing the study in an institution where a child-specific atmosphere and infrastructure is provided, and competent personnel familiar with the good clinical practice guidelines and capable of empathic and trustworthy communication with children and parents are working in the best interests of the children, allowing the adequate performance of the study by preventing risks and somatic and psychomental burdens as far as possible.

How do we observe special aspects to minimize risks? First of all, by knowing all safety data obtained during preclinical and adult studies; by recruiting as few child participants as possible, but a number that is high enough for adequate statistical evaluation; and furthermore by limiting the number and the extent of examinations, especially invasive interventions, to the minimum necessary for the study by applying adequate methods for laboratory tests, using small blood sample volumes, and adapting population-kinetic methods to reduce the number of blood samples per subject.

Principles for minimizing discomfort and preventing predominantly pain and fear should be observed by the following measures:

- Personal knowledge and skills to deal with child patients and understand their age-specific needs.
- Familiar environment with adequate furniture, toys, availability of activities, school attendance and rooming-in of parents.
- Use of measures that minimize the inconvenience of interventions, e.g. local anaesthetics before injections or insertion of catheters or tubes and blood sampling when routine clinical blood samples are obtained.

A very important and challenging topic is obtaining informed consent or assent of child participants and their legal representatives in accordance with national legislation before the beginning of the study. Informed consent means the approval of the parents or guardians for the participation of their child in a research study, or also the approval of the legally competent minor following appropriate information. Informed assent means the additional acquiescence of the legally non-competent child to participate in research following information that should be adapted to the mental capability of the child. The information should contain standardized items. Separate written information sheets as well as consent or assent forms should be provided for the legal representatives and competent children. The child's or parents' decision as to the participation of the child patient must not be obtained by force or improper influence. Parents and competent children should also be made aware of their rights to decline to participate, and the refusal of an informed child should be accepted without disadvantage for the child. However, it is our experience that the more suitable the information process in a comprehensive trustworthy and empathic atmosphere is, the rarer the refusal of participation will be.

Today, it is generally required and accepted that a biomedical research project has to be evaluated in all details by an ethics committee or review board. The approval of the committee is a precondition for the beginning of the study. Competent medical experts and other people who are well acquainted with the needs of children involved in research should be represented in ethics committees evaluating paediatric research. They have to review the projects not only according to internationally accepted general recommendations, but also with regard to all of the child-specific concerns mentioned above. In particular, the informed consent/assent sheets have to be evaluated carefully concerning their compliance and clarity in respect to the mental capability of the children to be included into research trials. Because a survey of CESP published in 1999 demonstrated that paediatric projects are usually reviewed by local ethics committees, but that there are only a few national committees or committees of paediatric societies concerned with research in children, CESP recommended that all national societies should establish ethics committees and that the interests of children should always be represented in ethics committees. Their aim is also to create an attitude of respect towards the dignity and integrity of the life and personality of children, and to enforce the measures for the protection of rights and needs of children in the medical field, especially in paediatric research.

Summarizing the concerns of children who need medical care, we can say that a child does not have to develop to become a human being, but is a human being with full identity and equal values at each stage of development. Therefore, the child is entitled to full human rights, which include the right to the protection of his or her life and health by providing the optimum medical care that is based on scientifically valid methods. Because there is a lack of generally valid knowledge of effects and side effects of medicinal products in paediatrics, and medical measures are widely based on empirical medicine and not on standardized and evidence-based medicine, research should be improved as an essential part of paediatric care. However, children need special support to be able to protect their personality and development potential because of their vulnerability. Therefore, child-specific guidelines for good clinical practice have to be respected and followed in paediatric research, and each ethics committee should include experts who are highly experienced in the biomedical peculiarities and age-specific needs of children involved in research.

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