DERLEME / *REVIEW*

Drug Research with Children and Responsibilities for Nurses

ÇOCUKLARI KAPSAYAN İLAÇ ARAŞTIRMALARI VE HEMŞİRELERİN SORUMLULUKLARI

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Abstract

Conducting adult drug researches on children is necessary for improvement of children's treatment and healthcare. Because infant and child physiology is different from that of adults and certain disorders are observed only in the childhood period.

Due to their being dependent, defenseless and weak, and not capable of making legal decisions, the children are a vulnerable group. Vulnerable groups cannot give informed consent by themselves. The children on whom the drug research will be conducted must be sufficiently informed about the research and their consent must be taken. Children who are seven years old or above can be included in the consent process. If the child's legal guardians accept the participation in research but the child does not, even though legally the consent is obtained, ethically it is not obtained.

In the drug researches planned to be conducted at a clinic, like all healtcare providers, nurses also have many responsibilities. First of all, the child's/family's decision to participate in research must be evaluated from an ethical viewpoint. Parents are usually concerned that their decision may influence the care given to their children. For this reason, they must be adequately informed on this subject.

Nurses are responsible for assessment and evaluation of side effects of the researched drug. Nurses must also know the hospital rules pertaining to control, labeling, storage and distribution of the researched drug.One of the most important responsibilities of nurses is to know that drug research is being conducted at the clinic, and to be included in this research. The nurses must be included in drug researches and in this way adhere to rules of professionalism required by their profession, such as those pertaining to care of the sick and defending patients' rights.

Key Words: Ethics, nurses

Özet

Yetişkinler üzerinde yapılan ilaç araştırmalarının çocuklar üzerinde de yapılması, çocuklardaki tedavi ve bakımın ilerlemesi için gereklidir. Çünkü bebek ve çocukların fizyolojisi yetişkinlerden farklıdır ve bazı hastalıklar sadece çocukluk çağında görülmektedir.

Çocuklar; bağımlı, savunmasız, güçsüz ve yasal açıdan karar verme yetisine sahip olmamaları gibi nedenlerle incinebilir bir gruptur. İncinebilir gruplar kendi başlarına aydınlatılmış onam veremezler. İlaç araştırması yapılması düşünülen çocuklar, araştırma hakkında yeterince aydınlatılıp onayları alınmalıdır. 7 yaş ve üzerindeki çocuklar onam sürecine katılabilir. Araştırmaya katılmayı yasal vasileri kabul edip, çocuk kabul etmezse, yasal açıdan onay alınmışsa da etik açıdan çocuğun onayı alınmamış olur.

Klinikte yürütülmesi planlanan ilaç araştırmalarında tüm sağlık çalışanları gibi hemşirelere de çok iş düşmektedir. Öncelikle çocuğun / ailenin araştırmaya katılma kararı etik açıdan değerlendirilmelidir. Ebeveynler, genellikle verdikleri kararın çocuklarına verilen bakımı etkileyeceğinden endişe duyarlar. Bu nedenle bu konuda yeterince bilgilendirilmelidirler.

Hemşireler, araştırma ilacının yan etkilerinin belirlenmesi ve değerlendirilmesinden sorumludur. Hemşireler ayrıca araştırma ilacının kontrolü, etiketlenmesi, depolanması, dağıtımı ile ilgili hastane kurallarını bilmelidir. Hemşirelerin en önemli sorumluluklarından biri klinikte ilaç araştırması yapıldığını bilmek ve bu araştırmanın kapsamı içinde bulunmaktır. Hemşireler, ilaç araştırması içinde yer almalı ve bu şekilde hasta bakımı, hasta haklarını koruma gibi mesleğin gerektirdiği profesyonelliği sürdürmelidir.

Anahtar Kelimeler: Etik, hemşireler

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Medical research involving children is an important means of promoting child health and well-being. Such research includes investigation into normal childhood development and the aetiology of disease as well as careful scrutiny of the means of promoting health care and diagnosis, assessing and treating disease in children. It is also important to validate in children the beneficial results of research conducted in adults. Medical research involving children therefore can be regarded as essential for the improvement of care in children.[1]

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Clinical trials, and research studies in general, are often complex and include interventions or tests that possess risks. Therefore, the way in which information is presented is extremely important.[2] Many medications, that are widely used in children, are rarely first tested on children. Without pediatric studies, labeling cannot include guidance about dosage and side effects. Seventy per cent of the current medications lack sufficient data in children.[3]

As advocates for children, nurses must ensure that children's preferences and concerns are recognized in the informed consent process. Too often, because parents have the legal authority for the decisions affecting their child, only the parents are consulted about treatments for their child or their child's participation in research. As a result, the children's fears and concerns may not only be unconsidered , but also unaddressed.[4]

It is clear there is a scientific need to include children in research studies in order to have results relevant to children. In the past few decades, there have been remarkable findings from research based on children. Vaccines have been developed and proved successful in eradicating many previously devastating diseases such as smallpox, polio, and measles.[4]

Research in humans is needed and cannot completely be replaced by animal models or cell cultures.[5] Neither results from animal research nor findings from studies on adults can be generalized to children without further investigation. Therefore, clinical research on children is important and necessary.[6] Helsinki Declaration is acknowledged that children are unique and not just 'small adults', and that research results from an adult population are not necessarily valid for or transferable to a young population.[7]

There are a number of reasons why research conducted in infants and children is necessary. Firstly, physiology and pathophysiology in infants and children is in many respects different from that in adults. Although physiological principles will be the same in children compared to adults, the way they are regulated might be different. Secondly, a number of diseases are unique for children and therefore can not be studied in adults. Thirdly, the infant is in a period of growth and development. Diseases which might not be of any harm to the adult, can have serious consequences for the developing individual. Also pharmacokinetics of drugs can be very different in children compared to adults as well as the reaction of children to drugs. It is often impossible to draw guidelines regarding safe and optimal drug dosages in infants from results obtained in adults. Studies often will have to be performed at all different ages. Not conducting this research in children will be to the disadvantage of them. Not only will insight into their physiology and metabolism , needed for optimal treatment, not be available,but also drugs either can not be prescribed or will be prescribed in incorrect dosages. Research in children is not only necessary, but essential for the improvement of health care in infants and children.[1]

Most drugs are used in children without an adequate profile of toxicities or optimal administration regimens. According to the US FDA, only 33% of new medical entities with potential usefulness in paediatric patients and approved for marketing in 1997 had any labelling for paediatric indications. More generally, 80% of drugs used in children do not have approved labelling for paediatric patients.[8,9] An analysis of data from 1994 assessed the frequency with which drugs are prescribed for children on an outpatient basis despite inadequate paediatric labelling. The 10 most frequently prescribed included asthma drugs, antibacterials and antidepressants, accounting for approximately 5 million paediatric prescriptions in 1 year. Thus, the research imperative in paediatric medicine reflects not merely a set of desirable goals, but a weighty obligation to improve drug therapy for children. At the same time, the endeavour to satisfy this imperative may conflict with obligations to protect the moral interests of this patient group.[8,10]

Short History of Drug Research

In 1789, Jenner inoculated his 10-month-old son with the virus of a pox found on a pig. On the

eight day the baby became sick and several small pustules appeared. It is not known how long Jenner waited, but later he inoculated smallpox matter into the baby's arms five or six times, without producing the slightest inflammation. The infant had appearently become immune to smallpox, Jenner then tested this vaccine on 48 children living in an almshouse to determine whether they also would become immune to smallpox.[4]

In 1915, the U.S. Public Health Service discovered that the incidence of pellagra in children could be reduced by including fresh, milk, eggs, and vegetables in the diet. As a result, the nutrition of the nation's children improved. Unfortunately, not all research was so benign. The germ theory was tested by the intentional infection of children with the herpes virus and in 1920, the health officer at a Hawaiian leprosarium injected six girls with the syphilis virus. A few years later, a New York physician reported he was able to successfully produce gonorrhea in a 4-year-old boy with chronic epilepsy as well as a 16-year-old boy who was mentally retarded.[4]

Research with both adults and children continued well into the 20th century without any protection of human rights. The Nuremberg trials in 1949 prompted the development of the Universal Code of Ethics, including refining the doctrine of informed consent. It is believed that once competent adults are properly informed about the risks, benefits, and alternatives to their partipication in a research project, they can make an informed decision about their participation. Children may lack the cognitive and / or moral development to be able to make such an informed decision. As a result, in 1964 the World Medical Association's Declaration of Helsinki acknowledged children as appropriate research participants but in need of special protection and adequate surrogate decision to be made on their behalf.[4]

In 1972 the accounts of the Tuskegee Syphilis Study sparked public outrage and an examination of the ethics of clinical trials. The purpose of the study, started in 1932 by the Public Health Service in Tuskegee, Alabama, was to determine the naturel course of syphilis in adult black men. The study group included 400 men with untreated syphilis, and the control group consisted of 200 men without syphilis. Although penicillin was known to be an effective treatment for syphilis, the men were not treated. In fact, steps were taken to prevent the subjects from receiving treatment. Upon investigation, it became clear that information was withheld from study subjects. Many of them did not understand the purpose study, and some did not realize they were partipicating in research. Reports from study were published as early as 1936, but no action was taken to stop the study. As late as 1969, the Centers for Disease Control indicated the study should continue. After the public became enraged in 1972, the Department of Health, Education and Welfare halted the study.[2]

Because of the Tuskegee Study and other ethically questionable situations, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974. This commission examined the ethical and human rights issues of experimentation with humans. The findings from the commission were published in 1978 in "The Belmont Report", which established stricter guidelines concerning information provided to research subjects. The Belmont Report required that risks versus benefits of a clinical trial be documented in the consent form, and guidelines were established for special protection of children and the mentally ill.[2]

In a Turkish university hospital, the effects of surfactan alternative healing methods on 57 prematurely infants with Respiratory Distress Syndrome is performed. Subjects are partitioned into 4 groups. The first group of 15 subjects are not given any medicine, the second group of 14 subjects are given aminofilin, the third group of 13 subjects are given deksametazon and fourth group of 15 subjects are given both aminofilin and deksametazon. 5 infants out of 1. group, 1 infant out of 2. group and 1 infant out of 3. group has died while there were no people dead in 4. group. In this study where the death probability is high, a control group was used such that 5 infants are not given any medication leaving them to death.[11]

All clinical trials must be conducted within Good Clinical Practice (GCP) guidelines, which is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials that involve human subjects. The origin of the GCP guidelines was the Declaration of Helsinki in 1961. These guidelines provide public assurance that the rights, safety, and well-being of research participants are protected.[2]

Children as Vulnerable People

Vulnerable populations are groups of people who can be harmed, manipulated, coerced, or deceived by researchers because of their diminished competence, powerlessness, or disadvantaged status. Thus, the vulnerable are those who are unable to protect themselves by valid informed consent. These persons may include those with acute, chronic, and terminal illnesses; prisoners ; racial and ethnic minorities; the elderly; the poor; women; children; and those with diminished cognitive functioning. Because of their unique health care needs, members of these vulnerable populations are often the focus of many studies.[12]

Children are a vulnerable population. Two main ethical and legal issues pertain to children's vulnerability in clinical research : the risk benefit ratio, and the question as to whether or when children can decide on their own if they want to participate in a clinical study. Both issues have been poorly defined and are difficult to measure.[6]

Current acceptance of potentially beneficial research has concealed a lack of clarity over which benefits justify the risks of pediatric research. This issue was highlighted by an Office for Human Research Protections ruling that psychological benefits from donating bone marrow to a sick sibling can justify the risks of pediatric research. Do psychological or altruistic benefits justify research risks only when the recipient is a first-degree relative?[13] The treshold for harm in children uses the standard of minimal risk beyond which specific justification for such risk exposure must be present. By minimal risk it is meant thet the magnitude of har mor discomfort to be experienced or expected is not gretaer than the risks thet the child may encounter in daily life.[14]

More vulnerable children include those who are younger, psychologically immature, suffering from serious disease, or institutionalised. For example, safety testing of a new paediatric drug formulation should not occur in institutionalised children when the research question can be adequately answered using children in the general population. Because their social situation poses greater burdens in achieving a good life, institutionalised children should bear an additional burden only if the research problem has special relevance to their status as institutionalised.[8]

Therapeutic-Nontherapeutic Research

Clinical research has been categorized as "therapeutic" and "nontherapeutic" research.[6] In therapeutic research, the direct aim of the study is to improve the case and treatment of the group involved in the study. The ethical dilemma in this type of studies lies with the control group. Whenever possible these studies should be placebo-controlled double-blind studies. This involves a group that might benefit from the new intervention, but also a group which will not receive the new treatment or drug. This group therefore has no direct benefit. As results of these studies will benefit ultimately children with the diseases at stake, it is acceptable to include a group without the new treatment, although the infants can not have given their consent for the studies. Not involving a proper control group will make the study useless.[1]

In nontherapeutic research, the investigator intervenes within the normal situation without the aim to improve the situation of the patient. The following example is the early phase of studies with drugs. For instance, a new and promising antibiotic might be important for use in children in infants, but data on pharmacokinetics are completely lacking. Then it will be not appropriate to give this drug as treatment in a child with an infection. Therefore one dose might be given to a healthy child or to a child with an infection in addition to regular antibiotic therapy and blood samples are taken.[1] Nontherapeutic research, on the

other hand, will not directly benefit that particular patient, although the results may be very useful in benefiting future patients. It serves as a learning mechanism for future patients.[15]

Assent-Consent (Informed Consent)

From a legal point of view, children cannot consent and the consent of the parents or a legal representative is necessary. 'Assent' is sometimes used to define the agreement that can be given by a legally non-competent child. The youngest children, i.e. neonates and infants, cannot even assent; no guidance can set, with absolute clarity, the age at which a child is able to assent.[3,16]

Assent refers to helping the patient achieve a developmentally appropriate awareness of the nature of the condition. As children develop, they gradually should become the primary guardians of medical decision making, assuming responsibility from their parents. Informed consent, in contrast to assent, requires a relatively advanced level of cognition. Informed consent refers to competency standards that require abstract appreciation and reasoning of the information involved in the informed consent document. The individual must be able to understand factors not immediately present, as well as multiple complex elements within a situation. Douglas referred to Piaget, Kohlberg, and others to support his belief that "the moral and intellectual maturity of the 14-year-old approaches that of an adult.[4]

Decision-making involving the health care of older children and adolescents should include, to the greatest extent feasible, the assent of the patient as well as the participation of the parents and the physician.[17]

The concept of consent is based on the principle of autonomy, but how are we to judge when a particular child has the level of competence to make an informed decision about participation in research? Akers and Bell believe assent should be obtained from children aged 7 or over, alongside the consent of their parents or guardians, but age does not necessarily reflect a child's level of competence, as the rate of maturity differs with individuals.[18,19]

Research suggests that the capacity of children for autonomous decision-making is usefully conceptualised as involving three categories of competency. Children 14 years of age and older exhibit decision-making capacities similar to those of adults. For example,Weithorn and Campbell compared the decision-making competence of 4 groups of healthy individuals aged 9, 14, 18 and 21 years, using 4 hypothetical treatment decisions. The investigators found that 14-year-olds did not differ significantly from 18- and 21-year-olds in their understanding of key facts, the reasoning for their deliberation or the treatment option selected.[8,20]

Lewis et al. studied the decision-making process of school-age children, ages 6 to 9 years, who were given the opportunity to participate in an experimental influenza vaccine trial. The children were able to freely decide whether to participate in the research stusy. The researchers concluded, based on analysis of the questions posed in the classrooms and the decisions reached by the children, that children age 7 or older should be included in the informed consent process. The few focused attempts by cognitive psychologists to apply Piaget's theory to the analysis of a child's ability to consent to participation in research have reached conclusions supporting the notion that school-age children age 7 and older can understand the informed consent process and are capable of making a decision on their own behalf. The findings support the idea that children are able to comprehend the notion of research and should be allowed to participate in the informed consent process.[4] Children and adolescents under 18 years of age do not have the legal right to provide independent consent to participate in clinical research.[21]

Recognizing that children and adolescents may have limited capacity and decision-making abilities, some have suggested that the standard for anyone under the age of majority should be assent, not consent. Discussions of assent have arisen from the recognition of an ethical requirement to acknowledge the rights and responsibilities of children. Assent is a concept that addresses the need for a middle ground between autonomous consent

and no involvement in a consent process. It has been defined as the process of concurring with someone to agree to treatment or involvement in research, but it does not entail a demonstration of understanding or reasoning ability. Assent is usually used when referring to minor children and, while consent as a term has legal status, assent does not.[22]

To secure the rights of human subjects, investigators are required to have research participants sign an informed consent. The Declaration of Helsinki stated that in any research on human begins, each participant must be adequately informed about the aims, methods, anticipated benefits, potential hazards of the study, and any probable discomfort. Informed consents are to be dotained from legal guardians of minors, but whenever the minor child is competent to give his or her own consent, it must be obtained in addition to the guardian's.[6]

With rare exceptions, consent is now ethically required for healthcare research. Such consent is viewed as valid, informed consent only if it meets three criteria:

-The consent should be given by someone competent to do so

-The person giving consent should be adequately informed

-The consent is given voluntarily.[23]

Competence : Normally, consent is viewed as being there in order to respect the autonomy of the person consenting; clearly, this does not apply to proxy consent. Parental consent may function to protect the child's welfare. However, if the proper mechanisms of ethical review are in place, then no child's welfare should be at risk from research.[23]

Information : This criterion presents no special ethical problems in relation to the consent of chlildren or their proxies: The information that either of these groups requires will be the same as that required by adults in order to give an informed consent. There are, however, practical problems to do with how one should best present information to children in a form they can understand.[23] Sufficient information is the basis for children's autonomous decisions about participation in research. By framing the information with wording familiar to the children, the chance that they receive and understand the information about the study increases.[7]

Voluntariness: This criterion presents a number of ethical problems. Younger children can not consent, but some can assent or dissent. One danger here is that adults who are in the habit of overruling the protests of young children against healthcare interventions may too easily overrule their protests where the interventions are to do with research. Parents can not be expected to be the gatekeepers here as, having given their proxy consent, they may feel some obligation to help the researcher. Thus, it is up to the researchers to bear in mind that the significant dissent of a child should be heeded.[23]

Dissent is defined as the actual objection of the child to research. Most children with cancer are involved in research that presents more than minimal risk but "holds out the prospect of direct benefit for the individual subject " and is considered somewhat differently. Even in therapeutic research the child should understand clearly the purpose of the research, what is expected, and the risks and benefits. Interestingly, the child's dissent is not generally considered to be binding in therapeutic research, in which direct benefit is expected for the individual child and is available only in the context of the research, 1° as it is in nontherapeutic research. Instead, the parent may override the child's objections, especially that of school-aged children.[24]

Responsibilities for Nurses

Parents are especially vulnerable when their child is ill, and this may be intensified by the vulnerability caused by hospitalization. Their autonomy and independence may be threatened by lack of knowledge, fear of the outcome of illness and the unfamiliar environment. As with hospitalized patients., parents may have difficulty understanding explanations of their child's treatment and be unable to make rational and objective decisions about their care. This extreme vulnerability may mean that parents will not always make decisions

in the best interests of their child., making them very dependent on ethical standards of practitioners and researchers.[19]

Clark suggests that patients may believe that partipication in research will allow them the greatest care and attention, a belief that has been substantiated in studies looking at aspects of care, where groups of patients under investigation have often received better care than the non-study group. The pediatric nurse must ensure that parents are not consenting to their child's partipication in research in the belief that the child will receive better care. It is important that parents are assured that their child's care will not be affected if their consent is withheld.[19]

Nurses play an important role in ensuring that the patient understands and remembers that the drug is experimental, and that the benefits for the condition under study are not known. If a nurse hears any comments from the patient that indicates that the patient isunclear about this issue,she or he should report this to the investigator in charge of the study, the primary physician, or the research nurse for this study. The patient should clearly understand thet there may be no personal benefit for participation in the research study. The patient should be clear that no claims are being made that this investigational new drug is more reliable, safer, more effective, or in any way superior to another drug on the market.[25]

In one study, researchers noted that parents who volunteer their children for clinical trials are less educated and from lower socio-economic groups, have less social support, consume more habit-forming substances, and display greater health-seeking behaviour than do parents who decline to have their children take part.[26]

This is possibly related with the research payments that could occasionally result in a number of ethical problems. Even though a child refuses to participate in a research, the approval of the legal guardian is valid legally. However, it is ethically important for the nurses to be careful; as such an approval might have been obtained against research payment.[27,28]

The copy of the informed consent for the study should be in the patient's medical record as well as documentation that the patient is participating in a drug study. Nurses must make sure that the patient has not been pressured to make a hurried decision to participate or that there are questions remaining regarding participation. Beyond nurses' responsibility for assessment and identification of adverse events to study medication, nurses need to know their hospital's guidelines for the proper labeling, storage, distribution, and control of investigational drugs.[25]

It is of primary importance that the nurse involved with research patients understands that one of the underlying premises of research is voluntary participation. Subjects who refuse, have a change of mind, or are unsure of their desire to participate need to be supported in their decision. The principal investigator or research nurse should be notified if a study patient no longer wishes to participate, so that the patient can be officially withdrawn from the study. Patients are never to be made to feel that the care that they are receiving or their relationship with the healthcare system will be adversely effected by their decision to withdraw. Nurses need to immediately report any occurrence of undue pressure on a patient to participate in a research study.[25]

A nurse, acting as a patient advocate, should ensure that the patient children clearly comprehend, and are well informed of, the research purposes, potential risks and inconveniences, any advantages and disadvantages, and the possibility to withdraw from the research, and it is necessary for a nurse to examine the approval form to understand if the child consciously and voluntarily participate in the research.

Nurses must also be aware of the federal guidelines related to patient compensation and incentives in research. Patient appreciation programs for participation must be consistent with the level of participation required and never should be significant enough to influence a patient's decision to participate or continue in a research study. When discussing a research study with a patient, the nurse must be careful to not infer any promise

of special consideration, compensation, or advantage for participation. Likewise, the nurse should report any incidence of preferential treatment of patients for study participation.[25]

Nurses need to serve as patient advocates if there is reason to believe that study patients are not being given similar appropriate medical attention by the principal investigator; examples might include careless physical examinations, inattention to abnormal laboratory values, or inattention to inclusion/exclusion criteria. Many people who have no access to healthcare services currently volunteer for participation in a research study. Therefore, patients should never be led to believe that they are receiving free medical care; rather, a distinction is made that the care they will receive will be consistent with the study protocol and may include components of routine health screening for which there is no charge.[25]

The nurses might sometimes not be aware of, or interested in a drug research implemented in their clinic. However, it is the nurse who administers the research drug, and first meets its positive/negative effects on the patient, and renders a continuous patient care. When a nurse is not aware even of a research implemented on the patient, how could he/she act as a patient advocate? The nurses should not only know if a drug research is conducted in the clinic, they should also be involved in such researches to maintain their professional roles as the patient care and advocacy.

The nurses are the health workers who spend the longest time with the patients, and have the possibility to firstly evaluate the symptoms observed in the patients, and therefore they have a great responsibility. Hence, the patients undergoing a drug research should be closely monitored for any possible symptoms and complications that are to be reported to the research group. A careful monitoring of the patients by the nurses is very important to determine at an early stage any advantages and disadvantages of the research drug, and if the patient's health is jeopardized.

If a research excludes the nurses, who administer the research drug, or the nurses do not know that they administer a research drug, they would likely omit potential symptoms induced by the administered drug, or ignore minor changes in the symptoms. However, when a nurse is involved in a drug research, he/she would be fully aware of such developments, and make considerable contributions to the implementation and conclusion of the research. If a drug research is teamwork, the nurses should be a part of such a team to administer drug and observe any possible symptoms.

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