Written Consent to Use the Drug in Children: The Problem of Off-Label Drugs

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Abstract: Cardiac arrhythmias in pediatric patients have different mechanisms and frequencies compared to adult patients. There are many physiological differences between children and adults that may affect the pharmacodynamic and pharmacokinetic of the antiarrhythmic drugs in pediatric population. Children, and specially breast feeding children, cannot be considered low weighted adults to select antiarrhythmic drug doses.

Although radiofrequency ablation has experienced great technological advances, it is performed in selected pediatric patients. Therefore, the main therapeutic strategy is the use of antiarrhythmic drugs in children. The medical management of arrhythmias in pediatric patients is challenging and complex. There are few clinical guidelines. There is scarce and incomplete information about the efficacy and safety of antiarrhythmic drugs in pediatric population. Most of the doses and drug administration intervals are extrapolated from adult population and applied to children. Antiarrhythmic drug doses have been extensively studied in adult population. However, in pediatric population, there are very few clinical trials and the safety of these drugs is not well known. In general, dose regimens are based on small uncontrolled studies, extrapolation of drug doses from studies performed in the adult population or physician experience. As a consequence, there is a need for further studies to assess the most effective antiarrhythmic drug regimens in children reducing the risk of side effects.

Evidence suggests that medical research in pediatric population is necessary and morally valuable. But investigators involved must take care of moral and ethical values, including the respect for the child-subject and his parents or legal representatives, and this respect compels them to consider the patient and family in the decision making process. The participation request and the informed consent must be obtained according to the competitions the patient exhibits, trying to anticipate information about benefits and possible damages derived from the investigation in an understandable language for him.

In our opinion the pharmacologic clinical investigation of antiarrhythmic treatments in pediatrics is necessary. More clinical studies must be carried out under rigorous scientific rules that contemplate the particular ethical dilemmas this population faces.

Key Words: Antiarrhythmic, pediatric patients, arrhythmias, clinical studies, informed consent.

INTRODUCTION

The cardiac arrhythmias in pediatric patients have different mechanisms and frequencies compared to adult patients. In neonates there are mechanisms that are related with the development of cardiac system such as the incessant tachycardia. The normal range of heart rate depends on the age. The heart rate in neonates is faster compared to older children. A heart rate could be considered normal in neonates but the same heart rate in older children might produce symptoms, require medical treatment and produce in the long term tachycardiomyopathy. The arrhythmias can occur in patients in the absence of heart disease or can be the first manifestation of a cardiomyopathy, metabolic or genetic syndrome. There are some mechanisms that are exclusive of the pediatric population and may be related with a conduction system that is still under development. The incidence of arrhythmias in children is estimated in 55 per 100,000 patients seen in the pediatric emergency department [1].

The clinical presentation depends on the age groups. In neonates and suckling babies, symptoms are not very specific such as low appetite, persistent weeping, sweating and vomits. In children and adolescent, symptoms are frequently palpitations and chest pain, however syncope and sudden death can be the initial presentation of cardiac rhythm disorders [2]. Other patients remain asymptomatic. Beyond the clinical presentation, it is important to identify subjects who have a life threatening arrhythmia and those who have a benign rhythm disturbance.

Rhythm disturbances are the first cause of morbidity and mortality after surgical treatment of congenital cardiomyopathies. The progress in surgical techniques and post-surgical care allow an increasing number of children with complex congenital disease to have longer live expectancy and survive to adult age. This patient population has different mechanisms of arrhythmia and provides a different challenge for management compared to patient with absence of heart disease [3].

For long time, it is known that some types of arrhythmias follow a familiar pattern. In recent years the molecular biology have identified genetic mutations that are associated with life threatening arrhythmias [4-6]. Most of the genetic disorders affect proteins of ionic channels that are related with the generation of the action potential in cells [6,7]. In the future, it may be possible to change the clinical course of these disorders with genetic therapy [7].

In fetus, the supraventricular tachycardia sustained for long time produces heart failure and hydrops [8]. The decision to begin the medical treatment depends on the ventricular function of the fetus. Digitalis, flecainide and sotalol are commonly used to treat these arrhythmias. More recently, amiodarone has shown to be safe and useful in fetus without significant adverse event.

There is controversy about the more appropriate antiarrhythm drug scheme and the adequate doses to be given to the mother to reach adequate levels in the fetus through the placenta. The pharmacokinetik of the drug can be affected by the increased plasmatic volume during pregnancy. The need of lyposoluble drugs to pass through the placenta is an additional challenge to select the adequate drug. In some cases, serious adverse effects in the mother or fetus have been described.

In the 80’s, the introduction of radiofrequency ablation (RFA) modified the management of cardiac arrhythmias in adults. However the success reported in the adult population might not necessary apply to the pediatric patients [9]. Many of the arrhythmias that occur in the first year of life in the absence of heart disease may spontaneously disappear and may have a high rate of response with conventional medical treatment. Radiofrequency ablation (RFA) is an invasive treatment that is performed under anesthetics agents. Some of them may have electrophysiological effects. The electrophysiological conditions of the children during the RFA may change by the anesthetic agent or due to changes in the conscience.
status. Therefore the investigation of the electrophysiological properties during an electrophysiological study may produce less reliable and reproducible results in children.

RFA may be associated with complication related with the procedure such as auriculo-ventricular block, valve or coronary artery damage. It is also important to consider the risk of ionizing radiation exposure during the RFA. After RFA in fetus, abortion have been reported in 0.3% of cases [10]. Therefore RFA is reserved for selected pediatric cases with severe arrhythmias that do not respond to medical treatments in small children or symptomatic supraventricular paroxysmal tachycardia in older children.

Although radiofrequency ablation has experienced great technological advances, it is performed in selected pediatric patients. Therefore, the main therapeutic strategy is the use of antiarrhythmic drugs in small children. The medical management of arrhythmias in pediatric patients is challenging and complex. There are few clinical guidelines. There is scarce and incomplete information about the efficacy and safety of anti-arrhythmic drugs in pediatric population. Most of the doses and drug administration intervals are extrapolated from adult population and applied to children. There are many physiological differences between children and adults that may affect the pharmacodynamic and pharmacokinetic of the antiarrhythmic drugs in pediatric population. Children, and especially breast feeding children, cannot be considered low weighted adults to select anti-arrhythmic drug doses. The distribution volume of most of the antiarrhythmic drugs is increased in breast feeding children. Breast feeding children have higher percentage of corporal water compared to older children. Breast feeding children have lower albumin concentration compared to older children reducing plasmatic drug levels of drugs that are binding with plasmatic proteins. In the neonates, the immature kidney and liver might reduce the elimination of anti-arrhythmic drugs [11,12]. In contrast, children between 7 to 12 years have a higher proportion of fast acetylators explaining the fast metabolisms of some drugs and the need of higher doses or shorter intervals [13].

Oral administration is the route of choice to give anti-arrhythmic drugs in children that are clinically stable or seen in the outpatient facilities. In children, the gastrointestinal absorption of anti-arrhythmic drugs may differ from adults. The commercially available pills for adults have larger doses for children that require to be fractionated or diluted into water to achieve an adequate dose. This manipulation of the pills may affect the absorption in the gastrointestinal tube [14]. In neonates and breast feeding children, the metabolism of drugs in the gastrointestinal tube and in the immature liver may result in a lower plasmatic concentration compared to older children [15]. In patient with heart failure, the gastrointestinal mucosa edema, the reduced perfusion of kidney and concomitant use of anti-acid may further reduce the drug absorption [16]. Monitoring plasmatic levels of anti-arrhythmic drugs may be misleading. In some children, the arrhythmia control can be achieved with lower plasmatic levels than levels that are assumed to be therapeutic. In contrast, other children may require higher doses for arrhythmia control and plasmatic drug levels can achieve values that are considered to be toxic [17]. Side effects of anti-arrhythmic drugs have been reported to occur below or above therapeutic levels in children [18]. Anti-arrhythmic drug doses have been extensively studied in adult population. However, in pediatric population, there are very few clinical trials and the safety of these drugs is not well known. In general, the dose regimens are based on small uncontrolled studies, or an extrapolation of drug doses from studies performed in the adult population or physician experience.

In pediatric population, there is a need for further studies to assess the best anti-arrhythmic drug regimens to control arrhythmias and reduce the risk of side effects. The document elaborated by the Health Canada 1997 Therapeutic Products Directorate Guidelines for Inclusion of Pediatric Subjects in Clinical Trials recognizes the need for progressively including pediatric population in clinical research studies since age, grow and development of children may affect the dose, pharmacokinetic, interactions and beneficial or deleterious effects of the drugs.

The lack of clinical research studies in pediatric population may lead to error when data from adult population is applied to children. In contrast with data from clinical trials in adults, Shaddy et al. reported a randomized controlled trial that carvedilol did not improve survival compared to placebo in children [19]. Therefore, new medical treatments for children have to be based on clinical evidence. There is a need to perform randomized clinical trials in children to identify effective treatments and to develop clinical guidelines for children care [20].

Children have different metabolism and drug pharmacokinetic and different natural history of disease compared to adults. Children are considered a specific and particular population when a randomized controlled trial is planned. Clinical investigators have to take into account these differences when clinical trials are designed to avoid damage to children after the enrollment in clinical studies. Children with arrhythmias disorder are a small study population and pharmaceutical companies have little incentive and interest to performed randomized controlled trials. Therefore, the scientific community has the duty to stimulate clinical trials in children to identify new effective treatments. However, performing randomized clinical trials in children has major ethical challenges [21]. For long time, clinical trials have been avoided in children to protect them [22]. The protection of the children has its roots in the Nuremberg code that allows clinical investigations only in subjects that are competent to provide consent [23]. Some people have the feeling that clinical investigations use patients like experimental rats and children cannot be used for clinical experimentation. Sometimes, parents may have this negative view about clinical research making clinical investigation challenging. It is possible that some investigators have abused of the good faith of patients. However, fraud is less common since the local ethical committees review the studies, the sponsor and regulatory agency requirements control investigators that perform clinical trials, and the ethical requirements of journal to publish data from clinical trials.

There are some features that make clinical research ethically adequate. Clinical research has to have a clear hypothesis and have to be conducted in order to obtain measurable answers, and objective results. It is discussed that clinical trials have to have an adequate design to be ethically adequate. Some investigators promote phase I/II clinical trials in parallel for adults and children and highlighted the need of intermediate reports of clinical trials in adults to led changes to improve clinical studies in children. These studies will reduce the time to obtain useful and valid data of treatment in children and protect children of exposition to inefficacious and harmful treatments.

Clinical research in children has to be view from broad perspectives. First, it is a right of the children to secure efficient treatments and evidence based treatments. Second, it is an obligation and responsibility of health authorities and regulatory agencies to offer medical care of high quality based on clinical research evidence.

The Nuremberg code constitutes international clinical standard for research and has been adopted by the United Nations to guide clinical research practice. Subsequently, the Helsinki declaration was established in 1948 during de 18th World Medical Association Assembly and has been reviewed and updated several times [23]. Both declarations constitute the most important references to guide ethical principles of clinical research. In 1979 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research formulated a code called the ‘Belmont Report’ [24] that mentioned the need of special guidelines to perform clinical research in vulnerable subjects such as patient with mental disorders or children. This reports established three principles to
guide clinical research: respect for the subject, beneficence, and justice.

The World Health Organization and the UNESCO have published International Ethical Guidelines for Biomedical Research in human subjects. In 1996, the European Union, the United States and Japan generated a consensus for pharmacological clinical research studies called International Conference of Harmonization E6 (ICH): Good Clinical Practice of the International Conference of Harmonization [25,26]. These guidelines explain how to investigate a new drug, new dose regimen or new drug indication. In addition many countries have developed its ethical recommendations and regulatory guidelines for clinical research. For example, the European Parliament released the recommendation 2001/20/EC that established the special conditions of clinical research with children or disabled [27].

In Canada Tri-Council Policy Statement was created (TCPS), an organism destined to control the ethical aspects of the clinical studies applied in humans. This organism has established that pediatric patients only can be included in clinical tests when the objective of the study cannot be evaluated in other way, when an informed consent is obtained from parents or legal representatives and when the investigation does not expose them to more than a minimum risk [28].

In the United States of America the National Institute of Health (NIH) contemplates under a law, that the inclusion of children in clinical tests can be made unless exist “scientific or ethical reasons to be excluded”. In addition the Food and Drug Administration (FDA) approved in 1998 that new drugs to be introduced in the market to be used in children must have been previously evaluated on “clinical tests in pediatric population to determine their security, effectiveness and correct dose” [29,30].

Also the American Academy of Pediatrics through its Ethic Committee participates actively in the supervision of the design of clinical studies made in children and emits its recommendations. Afshar et al. mention seven items to be considered during the process of investigation in pediatric population: 1) abuse of the autonomy of the children in previous clinical studies, 2) restrictions imposed by the different control organisms, 3) the problem of the investigation “in itself” and “the sate of equipoise”, 4) risks-benefits balance, 5) the consent and assent process, 6) preoccupations about confidentiality and 7) restlessness about the economic allowances offered to participants or their legal representatives [31].

All clinical test must include the certainty that the medical community does not know if the drug at issue is superior or not to the conventional treatment. This principle of “honest uncertainty” not only is vital for the ethical validation of the investigation itself but also for achieving its success. It has been demonstrated that part of the failure on the recruitment of patients in clinical studies relied upon the absence of conviction from treating professionals about the validity of the hypothesis. The concept of “pursue and protect” [28] is essential to carry out any investigation in pediatric populations. But it is extremely difficult to define in each case what means a risk and a benefit. The Belmont Report defines as “minimum risk to the probability and magnitude of physical and psychological damage that is normally in the daily life or on a routine medical and psychological examination on a healthy child”, nevertheless the evaluation of the risk of a clinical test can imply so much in the physical, psychic or economic aspects that it’s not always possible to carry out on impartial evaluation, so the independent ethics committees must act in an active form to defend the rights of the child and their family.

It is also important to recognize the benefits of participating in the investigation.

The economic compensation towards the child and his family from the sponsor is a controverted and delicate matter. In clinical studies that imply the mobilization of the family, it is acceptable that expenses from transfers are covered by the sponsor. But when the reward offered is “disproportionately” elevated, it should not be proposed until the child and his family have evaluated and decided to participate in the study [21].

The money can influence the decision making, especially in low income families, thus it is essential that the independent ethics committee involved, recognizes this situation and always intervenes protecting patients and their families.

The participant must know who will cover expenses in case an injury or complication related to the study should happen; and also has to have direct contact to a responsible person in case some damage or doubts appear.

The “process” of consent-assent occupies a special and fundamental place during the course of a clinical trial. The act of obtaining the consent from the patient to participate is an ethical, medical and legal act. Conceptually the Informed Consent can be defined as the conformity or assent of the patient (and/or parents or legal representatives) to receive a medical procedure or operation after having received and understood all the information necessary to make a free and intelligent decision. The legal foundation in which this medical tool is sustained is the respect for the personal rights, since each patient has the right to know everything necessary to make a free decision to accept or not the proposed study. In case of children, the informed consent relies on a legal representative (parents or tutors), who must know as much as necessary of the characteristics of the procedure, alternative treatments and potential complications that could happen. This information must be provided by a person completely informed about the intention of the study, and impartial and honest in the transmission process.

Some people argue that if the doctor-investigator had previous relation with the patient, he should inform the patient the recommended treatment in his opinion [32,33].

Sometimes, the participation of an independent defender could be of aid at the time of making the decision with respect to the possible participation or nonparticipation in the investigation.

Phase I/II tests suppose additional preoccupations in ethical terms. The object of phase I test is to define the toxicity and the pharmacokinetics of a new agent but not determining its effectiveness. Generally they are carried out in patients who no longer respond to conventional therapy. It is a common practice to determine the maximum tolerated doses by adult subject and then to try them in children with initial more elevated doses. This avoids the exposition to lower and non effective doses in the child-subject of the investigation and accelerates the process to introduce a new clinical therapy.

An important preoccupation to include children in this type of studies is that, like in adult patients, the understanding of the object and aims of phase I test is frequently erroneous, since it is biased by the motivation of the patient to participate, motivation that is based on a desire, sometimes too much optimist, to obtain a direct benefit, and not in the true intention of the study: the valuation of the toxicity of a new drug. Very few adults indicate that their participation in phase I studies are just motivated by altruistic attitudes. Equally, sometimes doctors recruit patients for phase I tests suggesting they can obtain a direct benefit and not informing them into the true object of study.

About antiarrhythmic drugs, most of the initial security and tolerance studies are carried out in adults and the possible benefits in pediatric population are extrapolated, diminishing the potentially risks of exposing children to phase 1 and 2 studies.

The decision to participate in a study must be free, and the patient should know he/she can retire as soon as feels it necessary, and
also that will be provided with all the information as far as partial results can affect their disposition to continue in the study. Harth et al. reported that near 20 to 35% of the parents whose children were participating in different clinical tests did not know that they could retire the child of the investigation when they considered it. It is important as well that parents or tutors know that if they decide not to let the kid participate, this does not imply losing the possibility of continuing the medical attention in the same hospital or any other

It must be specified that investigators can decide to retire a participant if he/she does not obey the rules or if they consider that the permanence can be dangerous for the patient or his family.

In addition, it must be informed that the collected data will be protected respecting the confidentiality of the investigation and the person. At the International Conference of Harmonization (ICH) E6 [26] in its Guidelines for Good Clinical Practice, it is specified that: Monitors, auditors, Independent Ethics Committee and the regulatory authorities will be allowed to access to registries or original medical archives for verification of the procedures or data of the clinical tests, respecting the confidentiality and that, when signing a form written of informed consent, the participant or his legal representative is authorized to such access. That the registries that identify the patient will be confidential and, in the measurement that the laws or applicable regulations allow it, they will not be available publicly. If the results of the test are published their identity will be kept in secret.

If the patient accepts to participate must register this consent writing, signing and dating his consent. If the person does not know or cannot write, the Rule 2001/20/EC of the European Union specifies that the person will be able to give consent in oral form in the presence of at least a witness, as stipulates the legislation of each country.

According to the Guidelines for Good Clinical Practice (GCP) of the ICH E6 [26] “in emergency situations, when it is not possible to obtain informed consent, the consent of its legal representative must be asked for, if he/she is present. When the informed consent is not possible and his legal representative is not available, to include the patient requires descriptive guidelines in the protocol and/or on the other hand, the favorable opinion or approval of the Independent Ethics Committee, to protect rights, security and well-being of the participant and to assure the adjustment to the applicable regulatory requirements. The participant or his legal representative must be informed about the test as soon as it is possible to give the consent to continue, which requires an appropriate informed consent”.

The United States Department of Health and Human Services interprets that if it is considered that the study implies more than a minimum risk without a direct benefit for the child, each father must separately give consent.

In case of adolescents, when the participation of the parents or legal tutors is not possible or it is denied by the patient, the Society for Adolescent Medicine generated the Guideline for Adolescent Health Research, which establishes that in these cases a third independent person must be present to protect the interests of the adolescent [35].

In case of smaller children, the Committee of Bioethics of the American Academy of Pediatrics (AAP) includes the child in the decision making process and some call to this “dyad of consent”, since it includes the informed consent of parents and the kid. The AAP bases this, arguing that the power the parents exert on the child not always express their desires and can commit errors influenced by different external or internal circumstances. Motivations of the parents to grant the informed consent are complex and non uniform. For example, Zupancic et al. [36] found that near 32% of the parents wanted that doctors decided if their children should participate or not in the clinical study. In an article recently published by Simon et al, it is discussed if altruism concepts would have or not to be included in the informed consent, since many authors think this can exert a pressure to parents in their decision to include their child in the investigation [37]. The Declaration of Helsinki establishes that “when a diminished or legally incompetent subject, as pediatric patient, is able to give his assent about participating or not in a clinical study, the investigator must altogether obtain this assent from him and his legal parents or representatives”.

The ICH E6 refers that information to the pediatric patients must be offered according to their degree of understanding, and if they are able they should sign and date the informed consent [26]. The minimum age to obtain this assent or dissent should be stipulated by each local country or Independent Ethics Committee. The Committee of the Control and Prevention of Diseases Center of the United States (CDC) considers that the assent can be applied from 7 years old. Nevertheless, several studies demonstrate that just from the 12 years old, the children display a greater degree of understanding of the information.

In spite of all these guides, many problems exist around the informed consent. First of all, it has to be written in a clear and understandable language for parents and children. Information related to health has demonstrated to be more difficult to understand than other types of information. Likewise Snowdon found that 57% of the parents did not understood the meaning of the word “randomization”, in spite of having been explained by a medical professional [38]. Low income social classes present greater probabilities of having difficulties for reading and understanding the objective of the investigation as well as the valuation of the risks it can imply.

It is recommended to use short phrases with intelligible words (to use synonymous), double-spaced, not abusing of capital letters, not to place more than an idea by sentence. Following these guidelines, the informed consent must include all the information related to the study, the intention of the investigation, the design of the study, the characteristics of the disease to treat, the way the study will be driven (frequent extractions of blood, visits, etc) and as already mentioned, all aspects related to risks/benefits, confidentiality, rights and obligations of the participant, investigators and sponsors and finally, the economic compensation.

When the same professional in charge of the health of the child is the one who is in charge to take the informed consent, it can be altered the freedom of parents or the child in the decision making.

The person in charge of this task has an enormous responsibility and besides to be completely enabled to respond all the questions that arise, he/she must dedicate patience to the decision making process. The guidelines of the ICH E6 specify that “it must be given extensive time and opportunity to ask about details of the clinical test and to decide to participate or not. All doubts must be satisfied” [26].

Most clinical trials in children are in populations with some disease, which generates pain and stressful situations that must be respected and considered in the decision making process. The participation and permanence of the children in the clinical studies are reflection of the understanding and seriousness of the object of study, design and attitude of the professionals in charge of the investigation altogether with patients and their families [39].

CONCLUSIONS

The medical research in pediatric is something necessary and morally valuable. It is necessary to allow the medical equipment to evaluate and to deal with the pediatric patient, who frequently has been rejected from the investigation process. The ethical expectations demanded to the clinical investigators include the respect by the child-subject and this respect compels them to consider him in the decision making process. For the investigation to be valid from the ethical point of view, it must be conducted so that all significant
information can be understood and extended in the future, thus obtaining the consent or the disagreement of the minor with total certainty. The participation request and the consent must be obtained according to the recommendations of the pediatric exhibits, trying to anticipate information about benefits and possible damages derived from the investigation in an understandable language for him. The inherent risks will be compensated by the benefits that can be achieved. Benefits can be direct, like in phase III tests; or indirect like those derived from phase I/II studies, in which the possibility of direct benefit is minimum, being the benefit for the pediatric patient to know the result of those tests can help other patients in the future. The determination of risks must recognize that the children are more vulnerable, with greater load of psychological, social and physical stress. It is required; therefore, special attention to the continuous evaluation of the natural evolving their disease and its conditions of life. The special relation that the doctor/investigator maintains with a child, and concretely the obligation to take care of the maximum interests of the child, requires to be considered in the process to obtain the conformity to participate in the investigation. Many ill patients and their families feel impotent to take care of themselves when the disease progresses, and so the dependency to medical aid is intensified. This reduces the capacity to decide freely to a minimum. The doctor-investigator must, then, be very conscious of the coercive influences of their situation as an expert in the handling with the disease and concomitant role of investigator who tries to recruit patients.

In our opinion the pharmacologic clinical investigation of antiarrhythmic treatments in pediatric is necessary. More clinical studies must be carried out under rigorous scientific rules who contemplate the particular ethical dilemmas this population faces.

REFERENCES


