Social vulnerability to phosphoethanolamine based on the principlist theory

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Abstract

In Brazil, the dissemination of information regarding the promise of a cancer cure using phosphoethanolamine, observed in some in experimental model studies, has contributed to ill individuals seeking treatment with this drug, even without human clinical trials. This work aims to analyze the use of phosphoethanolamine as a therapeutic approach for the treatment of cancer in the Brazilian population, based on a systematic review of the literature and according to the parameters of the principlist theory and the concept of social vulnerability.
Keywords: Principle-based ethics. Social vulnerability. Neoplasms. Phosphoethanolamine. Bioethics.

Resumo

Vulnerabilidade social diante da fosfoetanolamina a partir da teoria principialista

No Brasil, a difusão de informações acerca da promessa de cura do câncer com fosfoetanolamina, observada em alguns estudos em modelos experimentais, contribuiu para que indivíduos enfermos procurassem tratamento com essa droga, mesmo sem a realização de ensaios clínicos em humanos. Este trabalho tem por objetivo analisar, a partir de revisão sistemática da literatura e segundo os parâmetros da teoria principialista e a concepção de vulnerabilidade social, o uso da fosfoetanolamina como abordagem terapêutica para o tratamento do câncer na população brasileira.
Palavras-chave: Ética baseada em princípios. Vulnerabilidade social. Neoplasias. Fosfoetanolamina. Bioética.

Resumen

Vulnerabilidad social frente a la fosfoetanolamina a partir de la teoría principialista

En Brasil, la difusión de informaciones acerca de la promesa de cura del cáncer con fosfoetanolamina, observada en algunos estudios en modelos experimentales, contribuyó a que los individuos enfermos buscaran tratamiento con esta droga, incluso sin la realización de ensayos clínicos en humanos. Este trabajo tiene por objetivo analizar, a partir de una revisión sistemática de la literatura y según los parámetros de la teoría principialista y la concepción de vulnerabilidad social, el uso de la fosfoetanolamina como abordaje terapéutico para el tratamiento del cáncer en la población brasileña.
Palabras clave: Ética basada en principios. Vulnerabilidad social. Neoplasias. Fosfoetanolamina. Bioética.

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The concept of social vulnerability refers to the context of fragility, disadvantage, helplessness or abandonment, and encompasses various forms of social exclusion or isolation of population groups in relation to advances, discoveries or benefits provided by technological development [1]. In the context of research ethics, social vulnerability is understood as the circumstances of life capable of affecting individuals or groups regarding inclusion, exclusion and/or the choice to participate in the protocols. In addition, lack of access to medical treatment can be considered a social vulnerability, since public health systems have difficulties in distributing medicines to the entire population due to the high prices charged by pharmaceutical companies [2].

Social exclusion in developing countries makes them extremely vulnerable. This is the case of Brazil, a country with great social inequalities where one third of the population lives in conditions of extreme poverty [3]. In this context, social exclusion is a limiting factor of the right to autonomy [4], which can be considered more as a concept of the ethical and individual. In turn, social vulnerability refers to objective inequality between individuals or groups, and recognizing it is essential to guide projects to protect and respect the autonomy of individuals, especially when it comes to health research [5].

Principlism has been widely diffused in the area of health by its objectivity in dealing with moral conflicts and by facilitating the understanding of principles that can guide health professionals [6]. Beauchamp and Childress were responsible for reformulating the ethical principles described in the Belmont Report (1978) - autonomy, beneficence and justice - and defined four basic principles: respect for autonomy, non-maleficence, beneficence and justice [7].

Autonomy, literally the right to be governed according to one's own rules, refers to the person's self-determination to make decisions that affect their life, their physical and mental integrity and their social relations, that is, it is each individual's ability to decide and act freely and independently. Therefore, respect for autonomy is a moral duty and it recognizes personal values and points of view so that individual autonomy is effective [7,8].

Non-maleficence focuses on the idea that one must avoid harm to individuals according to the basic ethical duty of medical practice. Harm, in this case, can be physical (death, pain and disability) or mental, that is, what prevents the fulfillment of the patients' interests [7,8].

Beneficence is the obligation to do good to others, which can be physical, emotional or mental. In the area of health, it refers to ethics in medical conduct and seeks the ideal procedure for the patient, aiming for their well-being by minimizing risks and maximizing benefits [7,8].

Lastly, the principle of justice refers to equal access to health services and the distribution of benefits and resources. Thus, individuals undergoing medical experiments should be treated equally and impartially by the researcher. Beauchamp and Childress define this principle as an expression of distributive justice, that is, fair, equitable and appropriate distribution in society [7,8].

According to the World Health Organization (WHO), cancer is responsible for the deaths of 8.2 million people each year (about 13% of deaths worldwide) [9]. It is a disease characterized by the uncontrolled growth of cells, which can invade tissues and spread to distinct locations of the body. In Brazil, for the year 2016 596 thousand new cases were estimated [10].

Recent experimental studies have investigated the use of phosphoethanolamine to treat cancer [11-14], according to the National Sanitary Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA, the Brazilian regulatory agency) [15], there are still insufficient clinical trials for the free marketing of the substance. Even so, the government approved Law 13,269 of April 13, 2016 authorizing the use and manufacture of the synthetic phosphoethanolamine, allowing the use for patients diagnosed with neoplasias [16].

Phosphoethanolamine, a substance constituent of organic tissues of malignant tumors of cattle, was first isolated in 1936 by Edgar Laurence Outhouse, proving its existence in free state in nature [17]. Later, other researchers found it in the intestines of rats and in bovine brain tissues [18,19].

This substance, present in all animal tissues and organs, is a precursor of phosphatidylethanolamine, one of the main components of membranes and the second most abundant lipid in mammals, with several important functions in cell physiology [20].

Material and methods

The aim of this study was to analyze the use of phosphoethanolamine, according to the parameters of the principlist theory, as a therapeutic approach for the treatment of cancer in a population under

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socially vulnerable conditions, understood as the difficulty to get timely access to health, low schooling level, and individual vulnerability, the case of patients with severe and advanced disease who do not respond to conventional therapies.

This study is a systematic review of the literature with data search in secondary sources (PubMed, Capes Periodicals and SciELO). The descriptors used for the research of articles were "principle based ethics", "social vulnerability", "neoplasias", "phosphoethanolamine", "principlism", "bioethics" and their respective versions in Portuguese.

The survey, systematization, analysis and production of the study took place between March 2016 and March 2017, and the articles surveyed were published between 2000 and 2016 in Portuguese and English. Original articles, theses, literature reviews, systematic reviews, clinical trials and *in vitro* and *in vivo* experimental studies were also included for detailed analysis.

The selected articles were considered valid according to the degree of relevance of the subject under study, considering those that presented in the title or abstract some of the descriptors used in the search.

Discussion

According to the international ethical guidelines for research reviewed by the Conselho para Organizações Internacionais de Ciências Médicas - Cioms (Council for International Organizations of Medical Sciences), vulnerability is linked to the relative or substantial inability to protect one's own interests when individuals or populations reduce or for some reason lose autonomy, and may be due to deficits in education, health, finances, psychological deficits, among others [21-24].

Social vulnerability may be related to low income, but it does not necessarily affect only the population of underdeveloped and emerging countries [4], since there are several forms of social exclusion [1,2] which may involve family income, access to information, resources and health care and socioeconomic situation [1,2].

The brazilian pharmaceutical industry handled about R$ 85 billion in 2016, according to a survey performed by Interfarma [25]. This figure reveals the great commercial power of the pharmaceutical market and, therefore, its importance for scientific research, since this industry sponsors several academic studies and has great influence on researchers and clinicians, opinion makers and prescribers. Thus, everything that is propagated by this industry quickly becomes claimed by patients in offices and hospitals, which leads to the judicialization of health.

A recent study used synthetic phosphoethanolamine in mice with melanoma, in search of new therapeutic strategies, due to the low response to traditional treatments. This research contributed to a better understanding of the substance and its antitumor activity, and evidence was found to inhibit tumor growth and/or proliferation [20]. These results have led oncology patients with the disease at an advanced stage and with no therapeutic perspectives to believe that phosphoethanolamine could increase their time and quality of life, since the substance was associated with the promise of cure [2,25].

Other studies with experimental models support the hypothesis that phosphoethanolamine has antiproliferative action, stimulating the apoptosis of cancer cells and, in this way, would be an alternative to treat cancer [11-14]. But the correlation of data obtained in studies with other species for the application in humans did not present safe results. This tends to occur mainly in the area of oncogenesis, whose studies often reveal discrepancies in responses obtained in the clinical phases [26-32].

Phosphoethanolamine was tested for the first time in research centers in three Brazilian states: the Instituto do Câncer do Estado de São Paulo - Icesp (Center for Translational Research in Oncology of the Cancer Institute of the State of São Paulo), the Núcleo de Pesquisa e Desenvolvimento de Medicamentos, NPDM-UFC (Research and Development Center for Medicines of the Federal University of Ceará), and the Instituto Nacional do Câncer - INCA (National Cancer Institute), in Rio de Janeiro. Human clinical trials were conducted to test the alleged beneficial effects of the substance on healthy volunteers (no cancer) to test their toxicity and groups of patients with 10 different types of cancer to confirm their apparent non-toxicity: head and neck, breast, prostate, cervix, colon and rectum, stomach, liver, lung, pancreas and melanoma. The first phase of the two-month clinical study evaluated the safety of the drug in 10 patients and did not find significant toxicity, allowing for the continuation of the studies [33-36].

However, after this period, ICESP suspended trials with new patients due to the lack of

significant clinical benefit in the research conducted on individuals who took the substance at the dosage used in the study. That is, patients who had abandoned conventional treatment to use phosphoethanolamine would be making use of an ineffective and perhaps harmful substance. So far, 72 patients from 10 different tumor groups were treated, but only one with melanoma had a significant response to treatment, with a 30% reduction in tumor lesions [37].

In addition, phosphoethanolamine would be marketed as a food supplement, but ANVISA stopped advertising, since supplements can not assume therapeutic properties, and stated that it had not received an application for registration of the drug to be sold or manufactured in Brazil [38,39]. Although phosphoethanolamine had an impact as a "cancer pill", more human studies are needed to prove its efficacy, and it will only be distributed after going through the procedures described in Law 6.360/1976, which include evaluation of its efficacy, safety and quality by ANVISA.

Without these assays, the agency can not consider the substance a drug and release its use for the treatment of the disease [15,40]. In the case of phosphoethanolamine, ITS efficacy, side effects, applicability and effective action against the disease have not yet been scientifically proven in humans, which makes its commercial use reckless, at the very least.

However, the Federal Government enacted Law 13,269/2016 authorizing the use and manufacture of phosphoethanolamine in cases of patients with malignant neoplasias [16]. This ruling, which ignored the essential safety measures for good practice in the manufacture and use of drugs, can cause health problems for the Brazilian population. In addition, one must take into account the impact on public health of the fact that the government itself legislates contrary to that determined by the official regulatory agency, that is, disrespecting the right of the population to promote and protect their health.

It can be considered that the decision taken by the government would be beneficial, in view of the studies with phosphoethanolamine for the treatment of cancer, thus meeting the ethical principle of beneficence. Even if his administration were innocuous, one could invoke the "placebo effect," which would bring the sense of well-being to the patient, even if induced by his psyche. However, there is the question of the patient's long-term exposure to this molecule of unknown action, which may have adverse effects on the patient, contrary to the ethical principle of non-maleficence [7,41].

Because of lack of knowledge or hope of advanced disease cure, cancer patients and their families opt for the use of media drugs as "miraculous." However, such unproven disclosure can make them switch conventional treatment for something ineffective or even harmful, leading them to make hasty decisions. This impasse leads to the major ethical consideration of the case - patients who could still enjoy quality survival with conventional treatment, can adopt phosphoethanolamine and take risks.

While it can not be denied that patients exercised their autonomy in using the substance, consideration should be given to the extent to which the ethical principle of respect for that question was actually taken into account in ensuring that therapeutic choice was made by legislative decision without any scientific basis. Law 13.269 / 2016 does not consider the norms for approval of medicines nor the principles for good practices in research, which guide the action of ANVISA. Therefore, even if it were consecrating the right to autonomy as State policy, the law could be considered unconstitutional because it had failed to protect and promote the health of the population, enshrined in Article 196 of the Brazilian Federal Constitution [42].

Finally, considering the principle of justice as fairness, as defined by Beauchamp and Childress, the legislative decision to produce and distribute an innocuous substance may be considered contrary to the best use of health resources, thus being opposed to the elemental idea of managing them wisely to maximize access for the entire population.

Final Considerations

Although phosphoethanolamine has been shown to be effective in the treatment of cancer in rats, tests performed on humans have not yet shown significant results, enough to demonstrate the efficacy and safety of the substance. Thus, it has not yet been established whether it can cause adverse effects in the population. However, the federal government, in authorizing its use, manufacturing and distribution, sought to meet citizens' needs, based on only three of the ethical principles (respect for autonomy, beneficence and justice). However, non-maleficence was ignored, as there were no clinical trials required for its approval.

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Participation of the authors

Edilaine Farias Alves and Marcello Henrique Araújo da Silva wrote the manuscript. Fabiana Araújo de Oliveira collaborated in the bibliographic survey. Tatiana Tavares da Silva contributed to the final review of the text.

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