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Short Communication

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Evaluating bioethical issues on clinical phosphoethanolamine supplementation

Abstract

The amount of patients which develop chronic irreversible illness rises as the life expectancy grows among countries. When cancer patients step into final stages of their illness the complexity of questions and situations is evident. Frequently, terminally ill cancer patients choose to use unprescribed therapies at their own risk to alleviate suffering. When a generalist doctor comes across these situations, bioethical questions tend to raise among physician's minds when assisting the patient and family. In this paper we argue about phosphoethanolamine supplement scenario: the different points of view of regulatory agencies; bioethical considerations; theoretical aspects of the molecule as phospholipid precursor; the biological importance the relation to others systems in different levels; pre-clinical and clinical safety data;

Keywords: bioethics, terminally cancer patients, patients rights, phospholipid metabolism, phosphoethanolamine, PCYT2

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Abbreviations: IUPAC, international union of pure and applied chemistry; calcium-EAP, calcium conjugated with ethanolamine phosphate (phosphoethanolamine); pETN, phosphoethanolamine; PE, phosphatidylethanolamine; PS, phosphatidylserine; ANVISA, national agency of sanitary vigilance; FDA, food and drug administration; MCTI, ministry of science and technology; ICESP, sao paulo cancer institute; OECD, organization for economic cooperation and development; US, united state of america

Main body

Phosphoethanolamine belongs to the class of organic compounds containing a phosphate linked to the second carbon of an ethanolamine (Figure 1A). The chemical formula is C2H8NO4P. The IUPAC name is (2-aminoethoxy)phosphoric acid, and it is known by several other names such as: phosphorylethanolamine, ethanolamine phosphoric acid, phosphoric acid 2-aminoethyl phenyl ester, ethanolamine phosphate, calcium-EAP, etc. In addition, pETN is a compound naturally produced by eukaryotic and prokaryotic organisms and the main function is to serve as building blocks for phospholipid membrane synthesis, specifically phosphatidylethanolamine (PE), which not only serves as building blocks on membrane composition but also is important in metabolic reactions and others biological functions as well (Figure 2A). PE is synthesized not only in the endoplasmic reticulum but also in mitochondria. PE is classified as zwitterionic phospholipid and is produced by The Kennedy Pathway (Figure 2B)[1] or from decarboxylation of phosphatidylserine (PS) in the mitochondria (Figure 2B). These monophosphoesthers take part in the lipid signaling pathways and may include its effects either by direct stimulation of membrane receptors or through the generation of second messengers. Because of the relatively small structure of pETN in the head polar region of PE, results in a conical shaped phospholipid structure that helps to modulate membrane curvature and protein anchoring in the inner leaf of plasma membrane, providing optimal conditions for cellular functions.[2] PE triggers cell death by apoptosis through the mitochondrial-dependent pathway. The apoptotic effect of PE most likely involve the disruption of mitochondrial membrane potential combined with a increase of mitochondrial permeability transition (MPT) and the release of pro-apoptotic members from mitochondria, which includes an increase in caspase-3 activity leading to phosphatidylserine externalization.

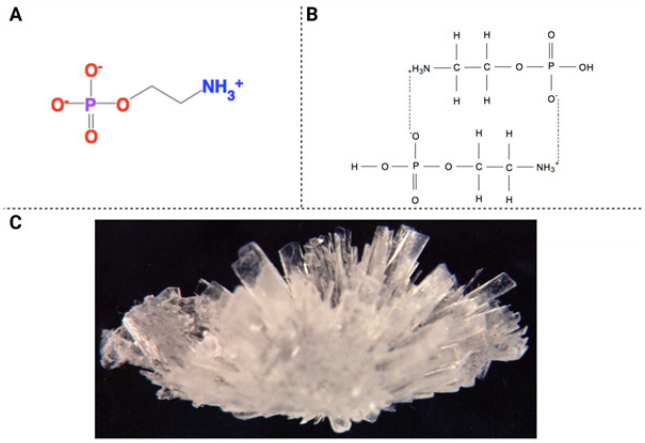

Figure 1 A: pETN chemical formula, on the left is evident the phosphate group and on the right the amino positively charged group. B: The ionic representation of pETN-pETN interaction. C: Crystal salt structure of pETN supplement.[18]

The importance of PE in cancer and others incurable diseases has been reviewed[3] and the amount of laboratories around the world dedicating time to study phospholipid metabolism link to diseases is growing.[4–7] Aberrant phospholipid metabolism has recently been established as a universal metabolic hallmark of cancer, and the phospholipid content seems to increase with cell transformation and tumor progression.

Great amount of terminally ill patients ends up under the generalist or family physician care, the doctor has to deal not only with the patient emotional suffering but also with the whole complexity of palliative and cancer terminally ill care,[8] in a survey runned by the Brazilian

Oncology Society, 95% of oncologist stated they had patients who wanted to take pETN supplement as adjuvant treatment,[9] the respect of patient's autonomy in the end of life helps in the engagement of the daily preparation for the time of death.[10] Patient rights is a subject of concern among society.[11] The majority of terminally ill cancer patients have reached a stage of disease called metastasis, in the molecular level, tumor metabolism, oxygen reactive species and tumor microenvironment inflammation leads to pain symptoms and organ dysfunction. At a psychological level, depression, anxiety can be present and, frequently, it aggravates the suffering. Doctor's figure can be decisive to alleviate patient and family emotions that emerge from difficult experiences.[12] In the real world there is no general protocol that works for every patient in this scenario and doctors need to be creative to assist the patients at the time of death in a patient-centered fashion.

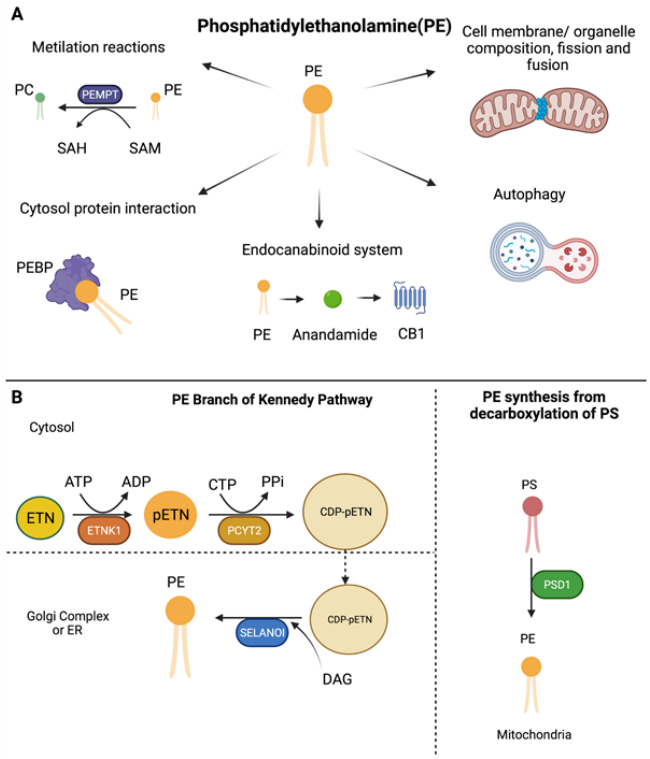

Figure 2 A: Multifunctionality of PE acting as substrate for methylation reactions on the top left;[19] cell membrane and organelle building blocks on the top right;[2] cell death programs on the bottom right;[3] Cytosolic binding protein non-covalent interaction;[21] metabolic precursor in the endocannabinoid system on the bottom center;[20] Abbreviations: PE, phosphatidylethanolamine; DAG, diacylglycerol; ETN, ethanolamine; ETNK1, ethanolamine-kinase 1; ER, endoplasmic reticulum; PCYT2, citidyl-phosphoethanolamine transferase-2; PPi, pyrophosphate; CTP, cytidine triphosphate; ATP, adenosine triphosphate; PS, phosphatidylserine; PC, phosphatidylcholine; PSD1, phosphatidylserine decarboxylase 1; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; PEMPT, Phosphatidylethanolamine N-Methyltransferase; PEBP, phosphatidylethanolamine binding protein; SELENOI, selenoprotein 1; CB1, cannabinoid receptor 1

Forbid the terminally ill cancer patient to choose, have desires and preferences goes against the patient's legal rights and freedom to choose a known safe compound. In pETN supplementation issue, once there is lack of clinical trials on efficacy, is important to draw reflections from bioethics and constitutional rights to garantie cancer terminally ill patients access to pETN through experimental program such as clinical trials or compassive humanized programs until all clinical tests be concluded.

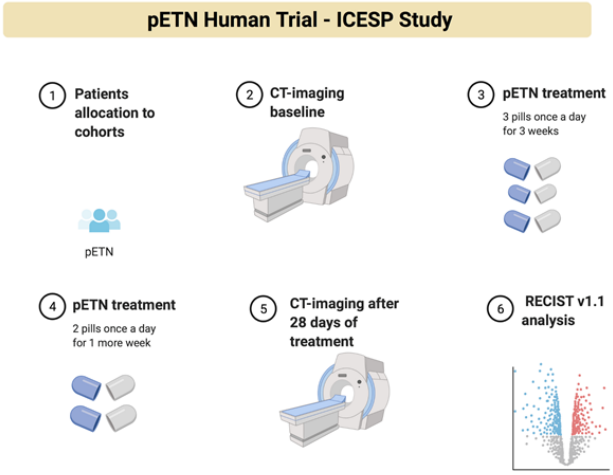

Figure 3 After patients sign the informed consent term they were allocated into a specific cohort based on type of tumor, inclusion and exclusion criteria (1); after the enrollment a CT-imaging was performed as baseline (2); after treatment was initiated, patients were seen weekly by the doctor for 4 weeks (3) and (4); a new CT-imaging scan was performed (5) and RECIST v1.1 criteria was used to classify tumor response or disease progression (6). Abbreviations: pETN, phosphoethanolamine; CT, Computer Tomography; ICESP, State of São Paulo Cancer Institute.[16]

In Brazil, the National Health Surveillance Agency of Federative Republic of Brazil(ANVISA) states that substances without registry are considered experimental. Promissory experimental drugs can be prescribed exclusively in the context of clinical trials, under medical supervision and amplified assistance to patients.[13] In addition, patients can be included in the compassive (by compassion) program, when there is no therapeutic alternative specific for inevitable mortal conditions and the patients benefits justify over the risks of taking experimental substante.[14] On the other hand, in the United States, the regulatory agency (FDA) views the pETN supplementation differently, and access to pETN supplements is easier. Is commercialized as Phosphopure□, the legislation permits the commercialization of supplements with suggested dosage for orally take and caution signs such as "not be evaluated by FDA", "not recommended for pregnant or nursing mothers and children under 18" and others similar informations.

In 2015, the Brazilian Ministry of Science and Technology (MCTI) invested around $2 million US dollars on pETN supplementation pre-clinical studies. In vitro genotoxicity evaluated with *Salmonella tryphimiurium* showed mutagenic index less than 2(not-mutagenic), micronucleus genotoxicity tests in accordance with OECD 471 guidelines did not observe genotoxicity at 8, 50, 320 and 2.000 mg/kg dosage, absence of toxic action on stem cells from medula was also observed. The in vivo evaluation of cardio and neuro toxicity of pETN orally supplemented showed neurologic and cardiologic safety. On the maximum dosage tolerated test, all dosages tested were safe and the animals showed no weight or nourish pattern alteration, in addition, no significant hematological and biochemical alteration were noted. Overall, pETN orally supplementation is safe in pre-clinical assays.[15]

A phase 1 clinical study with 10 metastatic cancer patients was done by São Paulo Cancer State Institute (ICESP), they only evaluated the safety of pETN supplementation when orally taken, and was considered safe. The study moved to a phase 2 designed to enroll 210 patients in 10 different metastatic solid tumor cohorts; patients

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enrolled had already failed to respond in previous clinical trials [16]. RECIST v1.1 criteria was chosen to evaluate the treatment response, patients were treated with 1500mg/day (3 pETN 500mg capsules) for 3 weeks(first cycle) and adjusted for 1000mg (2 capsules) for one more 1 week (second cycle), during the total 28 days of treatment none adverse events were attributed to pETN supplementation in the 73 patients enrolled, one patient in the melanoma cohort presented tomography significant response(tumor shrink) to the treatment. The trial was interrupted to draw a new strategy based on therapeutic dosage and other important information on pharmacokinetics and pharmacodynamics. Even with safety evidence, be aware about the lack of evidence and be realistic to our patients and their families, avoiding false hopes is reasonable. Inform and consent for patients and family about possibilities of drug interactions and unexpected phenomena that might emerge.

Hopefully, in the near future, Medical Schools, Hospitals and other Health Institutions will engage themselves in the study of pETN supplementation. If they don't, what might happen? Comparing the phenomena with melatonin supplementation in the US, where more than 3 million people used melatonin supplementation by 2012, and only in 2021 ANVISA registered the supplement. Now melatonin is commercialized in Brazil as a dietary supplement,[17] if pETN supplementation follows the same path, the tendency is to raise the usage of pETN as a supplement, even without all scientific questions answered.

Conclusion

The absence of evidence about pETN supplementation is not equal to absence of efficacy, in fact, it can be viewed as a scientific opportunity to develop projects on the subject. Pre clinical and clinical data suggest for security when orally taken, while scientific evidence about efficacy is being produced, doctors have to deal with bioethical issues while assisting terminally ill cancer patients with pETN supplementation, to not abandon our patients in difficult times taking unprescribed supplements, informed consent should be offered about the uncertainty that surrounds the subject.

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All the figures were made using BioRender.com platform

Conflicts of interest

The authors have no conflict of interest to declare.

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