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Clinical commentary

Influence of perfluorocarbons on Carbamazepine and Benzodiazepine for a neuro-lung protective strategy

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ABSTRACT

Lennox-Gastaut syndrome (LGS) is commonly characterized by a triad of features including multiple seizure types, intellectual disability or regression. LGS type of seizures is epilepsy which is due to abnormal vibrations occurring in seizures. During the time of such abnormal vibrations, both the seizures and the lungs suffer a lack in oxygen content to a considerable extent. This results in prolonged vibrations and loses of nervous control. As a neuro-lung protective strategy, a novel attempt has been made to enrich both seizures and lungs with oxygen content through the support of Perfluorodecalin (an excellent oxygen carrier) $C_{10}F_{18}$ (PFD) and Perfluorohexane C_6F_{14} (PFH) along with an enhancement in the antiepileptic activity by the two chosen antiepileptic drugs (AEDs) Carbamazepine (CBZ) and Benzodiazepine (BDZ). Perfluorodecalin $C_{10}F_{18}$ (PFD) and Perfluorohexane C_6F_{14} (PFH) emulsions were prepared by sonication process with combination of nonionic emulsifier, Lecithin (L-α-phosphatidylcholine) as a surfactant in Aqueous phase medium. These emulsions were mixed with Carbamazepine (CBZ) and Benzodiazepine (BDZ) drugs maintained at a temperature of about −20 °C to 20 °C and were set to slow evaporation process. The products are subjected to Optical microscope, Transmission electron microscopy (TEM) and Scanning Electron Microscope (SEM) – Energy dispersive X-ray Spectroscopy (EDS). Study reveals the co-existence of fluorine and drug ensuring the oxygen uptake by the drug. Morphology of TEM, Optical microscopic images and the particle diameter estimated through Image_J confirms this analysis.

1. Introduction

Lennox-Gastaut type of syndrome is complex epilepsy occurring due to abnormality in seizures. Lennox-Gastaut type of seizures that affects the Central Nervous System (CNS), are facing drug administration problems. Control of seizures is difficult [1–5]. An unexpected disharmony in seizures results in epilepsy. Drugs that are most preferred and prescribed for such kind of disease causes adverse side effects [6]. Further any new drug for that matter faces such problems and their effectiveness on the affected seizures is still an unsolved problem [7–13].

Though the valid reasons for the abnormal behavior of seizures, at any particular time, are still a mystery, there seems to be an in adequacy in the supply of oxygen content to both the seizures and lungs. Patients affected by such problems, happens to find it difficult to breath freely, tends to lose the nervous balance. Seizures, at the time of abnormal vibrations, too lack in oxygen content and hence the abnormal vibrations prolongs for a longer period of time [14–18]. In our previous study Natchimuthu et al. [19] we tried to establish the self-supporting transporter by oxygen enrichment mechanism. This had been achieved by addition of fluorine atom to Benzodiazepine.

In the present research work, we have tried to come out with a Neuro-Lung protective strategy. A novel attempt has been made through the phenomenon of oxygen enrichment to both seizures (brain) and lungs simultaneously with the support of Perfluorodecalin $C_{10}F_{18}$ (PFD) and Perfluorohexane C_6F_{14} (PFH). At the same time the antiepileptic activity is expected to enhance through the chosen antiepileptic drugs (AEDs) like Carbamazepine (CBZ) and Benzodiazepine (BDZ). CBZ and BDZ are chosen for this study because of their simple chemical structure Fig. 1(a) and (b) respectively and could be more adoptive to accommodate such fluorinated compounds.

The properties of fluorine such as its small size, combined with the high electronegativity may modulate electronic, lipophilic and

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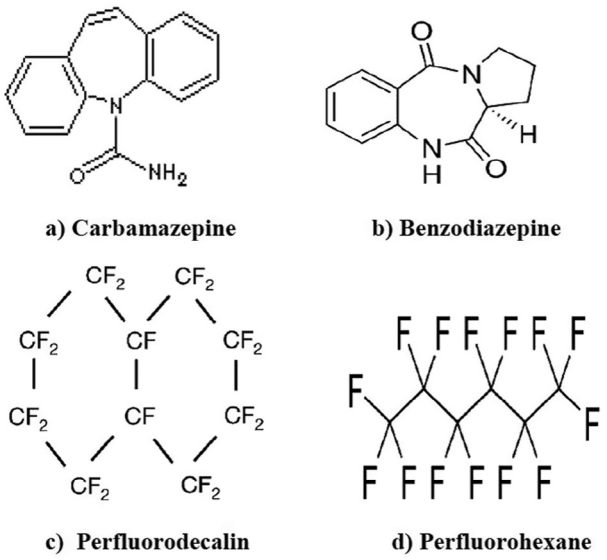

Fig. 1. (a–d) Chemical structure of (a) Carbamazepine, (b) Benzodiazepine, (c) Perfluorodecalin and (d) Perfluorohexane.

steric parameters crucial for biological activity [20]. Additionally, an excellent oxygen carrying capacity, decrease of toxicity and side effects has been reported in many cases of fluorine containing derivatives [21,22]. Thus, fluorinated compounds are the focus of much interest in modern pharmaceutical chemistry, and the incorporation of fluorine content plays a significant role in development of drugs, including anticonvulsant active molecules [23]. However, the synthesis of these significant molecules is fundamentally difficult due to the high reactivity of fluorinating agents.

To achieve this, either one has to come out with a novel drug containing fluorine compounds and the suitable AEDs, both as single organized structure (in the form of a single crystal) or try to convert both the drug and the perfluorocarbons (PFCs) into an emulsified mixture through ultrasound and study their predominant contents and asses the particle diameter.

The above said first notion is purely optional because, Perfluorodecalin (PFD) and Perfluorohexane (PFH) are absolutely neutral by structure Fig. 1(c) and (d) respectively. It is quite difficult to break any of its bonds and to make it reactive with either CBZ or BDZ. Though the neutral structure of PFC is not so conducive for perfect chemical reactions, the basic reason for choosing $C_{10}F_{18}$ and C_6F_{14} is due to the fact that it is an excellent oxygen carrier. The role of PFD in Cardiopulmonary by-pass, lung ventilation, ventilation fluids, cell-culture supplement, diagnostic imaging agents, magnetic resonance imaging, oxygen – carrying agents, drug formulation and delivery were extensively proved [24–28]. Marsh et al. [29–31] has made quite a good number of studies on perfluorocarbons to prove it to be an excellent targeting agent.

In spite of all these applications their perfect neutral chemical structure is not supportive for any chemical reaction with any compounds. The only effective way to use them is to convert them into an emulsion. The most common implementation of PFCs to enhance oxygen transfer is in the form of nanoscale emulsion and micelle emulsion. PFCs are immiscible in aqueous systems, including biological fluids; they must be converted to an emulsified form to be safely injected into the blood vasculature. There are decent numbers of studies substantiating the excellent oxygen carrying capacity of PFD in emulsified form [32–38]. Based on the above said facts the second idea is more vulnerable.

Table 1
Composition of the emulsion studied.

Emulsion	Perfluorocarbons (50%(w/v))	Surfactant (5%(w/v))	Aqueous Phase	Antiepileptic drugs (100 mg)
1.	$C_{10}F_{18}$	Lecithin	Water	Carbamazepine
2.	$C_{10}F_{18}$	Lecithin	Water	Benzodiazepine
3.	C_6F_{14}	Lecithin	Water	Carbamazepine
4	C_6F_{14}	Lecithin	Water	Benzodiazepine

2. Experimental

2.1. Materials and methods

Carbamazepine (CBZ), Benzodiazepine (BDZ), Perfluorodecalin (PFD) and Perfluorohexane (PFH) used were generic 99% pure from Sigma–Aldrich. The surfactant used as Lecithin (l-α-phosphatidylcholine) from egg yolk with purity of 99% (lyophilized powder) from sigma–Aldrich. They were utilized as received without any further purification. Deionized and double-distilled water prepared from reverse osmosis and filtered through Millipore milli-Q plus system used as the only solvent.

The study involves three steps. In the first step, emulsions of 50% (w/v) of each perfluocarbon in aqueous phases using 5% (w/v) of Lecithin as surfactant were prepared by sonication, using a probe sonicator. The sonication was performed with 5 kHz sweep

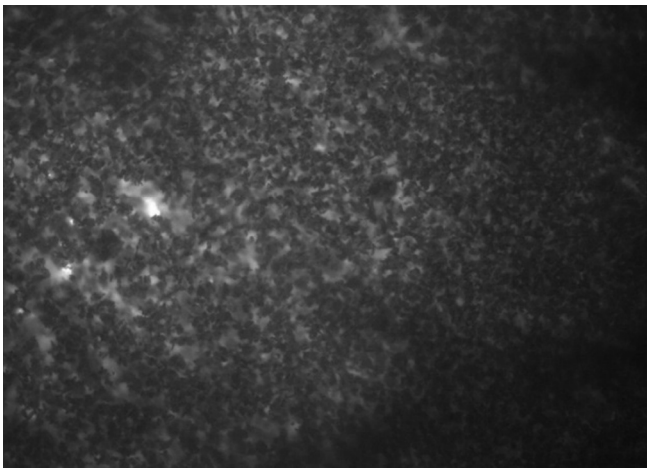

Fig. 2. Optical microscopic images for CBZ + PFD emulsion.

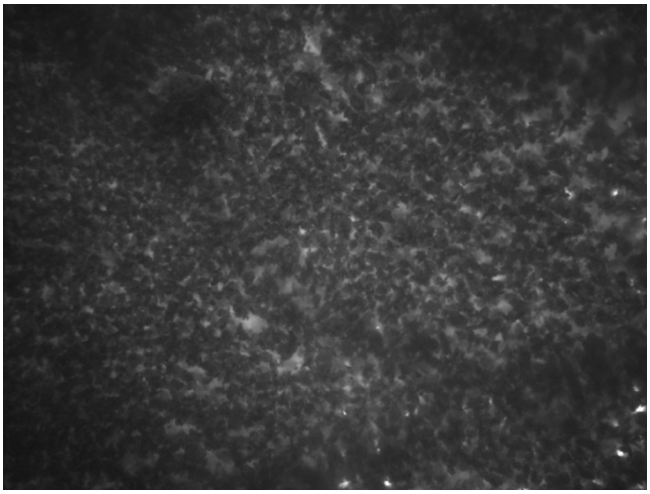

Fig. 3. Optical microscopic images for BDZ + PFD emulsion.