PHARMACOLOGICAL PROFILE OF FLUNARIZINE: A CALCIUM CHANNEL BLOCKER

Shilpi Chauhan*, Parveena Devi, Nidhi

1 College of Pharmacy, Pt. B.D. Sharma University of Health Sciences, Rohtak, Haryana, INDIA
2 P.D.M. College of Pharmacy, Bahadurgarh, Haryana, INDIA
3 Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, INDIA

Abstract
Flunarizine is a non selective calcium channel antagonist. It is highly lipophilic compound which distributes preferentially in adipose tissue and passes the blood brain barrier readily. Numerous preclinical and controlled clinical studies, including double blind clinical studies in which the drug was compared with placebo or standard drugs in particular disease showing efficacy in migraine, vestibular vertigo, reading epilepsy, generalised epilepsy and Landau-Kleffner syndrome. This review highlights the pharmacodynamics, pharmacokinetics, therapeutic indications, dose and side effects of flunarizine. Although flunarizine is well tolerable drug, some side effects appears which can be avoided by following a special schedule or administration.

Key words: Migraine, flunarizine, vestibular vertigo, reading epilepsy, generalised epilepsy, Landau-Kleffner syndrome

Corresponding Author:
Shilpi Chauhan
Assistant Professor,
College of Pharmacy,
Pt. B.D. Sharma University of Health Sciences,
Rohtak, Haryana, INDIA
Email: shilpivats23@gmail.com
Phone: +91-8930097365
INTRODUCTION

Calcium ion is an important signal transduction molecule in body which acts as a secondary messenger that regulates vital functions in almost all mammalian cells [1]. Ca\(^{2+}\) and maintenance of the cellular calcium level is necessary for the proper functioning of the nervous system, growth and development [2-5], essential component for neurotransmission [6,4] and contributes to the various gene expression in neurons [7-9]. All mammalian cells have developed several homeostatic mechanisms to maintain the intracellular level of Ca\(^{2+}\) through either from intracellular pools or enter from the exterior. These mechanisms include entry of Ca\(^{2+}\) through voltage operated and receptor operated channels (ROCs), Ca\(^{2+}\) buffering by plasma membrane and cytosolic proteins, storage of calcium in intracellular organelles and calcium efflux [10-12]. Receptor operated channels or “fast” channels are activated by binding of a specific ligand on receptor or the formation of ligand receptor complex at the external surface of the cell membrane. Voltage operated channels or “slow” channels are activated by the changes in the membrane potential of the cell. These channels are of three kinds: transient (T) type, long lasting (L) and neuronal (N) type. Calcium channel antagonists exert their therapeutic and pharmacological action through voltage operated channels [13]. When a certain changes occur in the membrane potential of a cell, the slow channels or VOCs open to allow the influx of calcium. Ca\(^{2+}\) is responsible for the plateau phase of action potential and allows the cell to their normal functioning [14]. Intracellular calcium homeostasis is essential for the normal functioning of all cells but the overloading of calcium inside the cells leads to disturbances in the vital functioning and produces various pathological conditions in the body. Therefore, intracellular balance of Ca\(^{2+}\) is necessary to allow the cell do work in a normal way. Calcium channel antagonists acts on the voltage operated channels by binding to specific sites on the exterior facing surfaces and modulate the functional states of VOCs and helps in the reduction of the overloading of intracellular Ca\(^{2+}\) [15]. Calcium channel blockers are heterogenous groups of compounds and employed in various pathological conditions. The World Health Organisation (WHO) classified them onto two types: (i) those selectively acts on slow channels, (ii) those non-selectively acts on slow channels. These main groups are again sub-divided on the basis of the clinical and detailed pharmacological properties of the individual compounds [14]. The compound flunarizine is a non-selective calcium antagonist with a similar chemical structure and pharmacological profile to the related compound “cinnarizine”. However, in contrast to cinnarizine, it has a long plasma
half-life and need only be given once a day [16]. Flunarizine possess diphenylpiperazine moiety and highly selective for cerebral blood vessels [17].

**Pharmacodynamics**

Flunarizine decreases the transmembrane fluxes of calcium in case where calcium is stimulated to enter the cell in excess, thus preventing the deleterious consequences of “calcium overload” within the cell. It does not cause any interference when the concentration of calcium is present at normal level [16]. It causes significant and long lasting inhibition of calcium related contraction of vascular smooth muscles. The degree of inhibition depends on the origin of blood vessels, the species and the nature of stimulus. It showed protection of endothelial cells against damage from calcium overload. It has been dose dependently reduces echinocyte formation and concomitant membrane rigidity induced by calcium overloading in red blood cells. It also showed the survival of brain cells after hypoxia or anoxia after acute as well as chronic treatment. Various studies revealed vestibular depressive effect, antihistaminic, anticonvulsant and antiserotonin actions both in animals and humans studies. It has little negative inotropic effect on heart muscle and possesses no action on the myogenic tone of blood vessels [16].

**Pharmacokinetics**

Flunarizine is a highly lipophilic and poorly water soluble compound. It distributes preferentially in adipose tissues, tightly to plasma and tissue proteins and readily crosses the blood brain barrier. The blood level of the drug is low whereas tissues level is much higher. It is readily absorbed in gastrointestinal tract and having high first pass metabolism [14]. Peak plasma concentration achieved 2-4 hours after oral administration in healthy volunteers. With repeated administration of 10 mg daily, plasma concentration increases very gradually reaching a steady state concentration after about 5-6 weeks of drug administration. It has large volume of distribution i.e. 43.2 L/kg [16]. Its half life is 7-10 days and metabolic degradation occurs by aromatic hydroxylation and oxidative dealkylation [14].

**Therapeutic implications**

**Migraine**

Migraine is the most common and major headache diagnosis in neurological disorders in Asia and is among the top ten most disabling disorders worldwide [18]. Migraine prophylactic treatment involves avoidance of trigger factors, lifestyle advice followed by considerations of
medications. Calcium channel antagonists are one of the classes used in the treatment of migraine. Flunarizine is regarded as one of the most important prophylactic therapies for migraine. Initially, it has been shown that flunarizine reduces the influx of Ca\textsuperscript{2+} ions in vascular smooth muscles and may stabilise vasomotoricity and thus avoiding or reducing pain. But continuing research demonstrated that flunarizine possessed additional properties which might explain the drug’s activity in migraine. It was discovered that flunarizine able to protect brain cells against hypoxic damage [19] and positing neuronal genesis for migraine. Flunarizine had no myogenic action on vessels and in fact caused neither vasodilation nor arterial pressure changes [20]. Flunarizine was found to be able to raise the excitability threshold in spreading depression and to reduce recovery time from that condition. Flunarizine can also affect the release of neurotransmitters such as dopamine and met-enkephalin [21] which could be involved in the pathogenesis of migraine. Flunarizine can cause inhibition of transmission along the trigemino-vascular system. These all mechanism of actions of flunarizine may be responsible for its antimigraine activity.

Dose: 5-10 mg/day has been found to be effective in migraine prophylaxis [22].

Vestibular Vertigo

Vertigo is defined as the illusion of the being subject to an involuntary motion pattern. Vertigo can occur from lesions in the central nervous system, especially in the nuclei of the vestibular nerve, the cerebellum and the connections between cerebellar and vestibular nuclei. Vertigo is labyrinthine disorder, caused by disturbances of the vestibular end organ in the inner ear [23]. Vertigo can exists in various forms like benign paroxysmal positional vertigo, vestibular neuritis and menière’s disease but actual etiologic diagnosis remains unknown. Vertigo continually changes its character as well as its intensity with time which further complicates its diagnosis and treatment. Therefore, vertigo having the impact on the patient’s quality of life. Thus, its treatment is essential. The drugs that are commonly used in maintenance therapy (antihistaminics, neuroleptics and β-histidine) are moderately effective against intermittent and continuous vertigo, which indicates the need for other drugs. Flunarizine was found to effective in vertigo both in animals and human studies. These studies demonstrated that flunarizine reduces vestibular receptor excitability, and direct inhibition of vestibular cells, through activation of the cerebellar cortex. These effects of flunarizine are related to the calcium entry blocking properties at vestibular and sensory cell sites [23].
Dose: 10 mg/day has been found to be effective for the maintenance therapy of vertigo [23].

**Reading Epilepsy**

Reading epilepsy is a type of reflex epilepsies. Reflex epilepsy is defined as those in which seizures can be precipitated by highly specific stimuli [24]. It accounts about 5% of the seizure disorders [25]. Reading epilepsy can considered as “primary” and in most reported cases no clear underlying abnormality has been identified [26]. In this epilepsy, reading is the primary stimulus to seizures and typically occurs in adolescence [26] and in few patients a genetic factor appears to be present [27]. It is one of the most complexes of the sensory evoked reflex epilepsies [25]. Although the question as to whether the epilepsy is cortical or subcortical in nature is still unresolved [27], evidence is showing that complex cortical mechanism involved in language production are involved in this type of epilepsy because in some cases seizure activity was provoked not only be reading but also by other activities related to the production of language [27]. The epileptic seizure in reading epilepsy is starts by a myoclonic jerking of the jaw musculature and jaw jerking continuously increase in rate and amplitude with time until the generalised seizure begins and consciousness is lost [28]. The treatment of reading epilepsy with either phenytoin or carbamazepine is not successfully [29,30]. Clonazepam [31,32] and valproic acid [33] have been reported moderately effective in treating reading epilepsy. Flunarizine with valproic acid as add on therapy is found to be successful to control seizures in reading epilepsy. Flunarizine reduces seizure intensity, increased percentage survival time in animals with experimentally induced convulsions [34]. Future trials should, therefore, be indicated to determine flunarizine efficacy as monotherapy.

Dose: 10 mg/kg is effectively used as add on therapy with standard anticonvulsant drugs.

**Generalised Epilepsy**

Low voltage activated (t-type) calcium channels play a role in various physiological functions like neuronal burst firing, hormonal secretion and cell growth [35]. Thus, blockade of calcium channels control seizure activity in brain. Flunarizine is a non-selective calcium channel antagonist and blocks the entry of calcium ions into the cells and control the convulsions. It reduces the tonic extensor phase, convulsion and post-ictal phase. It enhanced the latency of onset of seizures and decreased the duration of convulsions. Flunarizine showing the potential as an individual antiepileptic drug as well as in combination with standard antiepileptic drugs like phenytoin and valproate in epilepsy [36].

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Dose: 5-10 mg/day is administered both as add on therapy and individual drug for controlling the convulsions [36].

**Landau-Kleffner Syndrome**

It is also known as acquired epileptic aphasia and was firstly described by Landau and Kleffner in 1957 in children with a history of normal language acquisition but later developed acquired aphasia with convulsive disorder [37]. It is generally occurs at the age of 3-5 yrs and most frequently in males than females [38,39]. Abnormalities in the receptive language are the first clinical manifestation such as omissions and paraphasias that progresses the lack of language [40]. It is often associated by behavioural such as hyperactivity, indifference to the environment and autistic behaviour [41,42]. Electroencephalogram (EEG) abnormalities are also found in this disorders which includes outbreaks of spikes, sharp waves or show spike-wave complexes in temporal and parieto-occipital regions unilaterally and bilaterally [43]. The seizure can be easily treated with standard anticonvulsant drugs but these drugs are not effective in the recovery of the language and behaviour. But if flunarizine is administered with valproic acid, it showed improvement in the receptive language such as increase in the amount of vocabulary, pronunciation of more than 100 words and the ability to initiate a spontaneous conversation and echololia persisted in lower amount. Further studies should be conducted to find out the more mechanism of actions, effectiveness and efficiency of flunarizine in Landau-Kleffner syndrome [43].

Dose: 2.5 mg/kg is administered for the improvement in receptive language [43].

**Adverse Effects**

The main adverse effect of flunarizine is of drowsiness, which can be avoided by taking the dose at night. Weight gain is another side effect which is avoided by reducing the dose of the drug [16]. Other minor effects are gastrointestinal effects, antimuscarinic effects and rarely extrapyramidal symptoms and galactorrhea.

**Future Prospects**

Flunarizine is well established drug in various disorders like migraine, vestibular disorders, epilepsy and Landau-Kleffner syndrome. Due to its calcium channel blocking activity, it may be effective in various neurological diseases. Overloading of calcium is the main phenomenon in various neurological disease which leads to excitotoxicity. Flunarizine may inhibit this
overloading of calcium via blockade of Ca\(^{2+}\) channels as well as highly selectiveness to cerebral blood vessels. Future trials can explore its pharmacological potential in several disorders.

CONCLUSION

The overloading of calcium leads to excitotoxicity and produces various pathological conditions in the body. Flunarizine is a non selective calcium channel blocker and plays a protective role in several disorders such as migraine, vestibular vertigo, reading epilepsy, generalised epilepsy and Landau-Kleffner syndrome etc. Further studies may also evaluate better pharmacological potential of flunarizine.

REFERENCES


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