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Amlodipine Reduce Pyrethroid Neurotoxicity in Mice

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Abstract: Permethrin a synthetic pyrethroid poisons are used as insecticide. These toxins can be used insecticides in agriculture and medicine for destruction and/or eradication of ectoparasites of animals. Studies have shown that Permethrin creation seizure effects in different animals. Amlodipine, calcium channel blocker, widely used for treatment of cardiovascular diseases. Studies have shown that the calcium channel blockers are anti-convulsant effects in different animal models. The aim of this study was to determine the effect of Amlodipine on Permethrin-induced seizures in mice. In this experiment, the animals were received different doses of Amlodipine (2.5, 5, 10, 20 and 40 mg kg^{-1} b.wt.) intraperitoneally 30 min before intraperitoneal injection of Permethrin (200 mg kg^{-1} b.wt). After Permethrin injection, clonic and tonic seizures and finally, death was the fate was investigated. Results showed that Amlodipine dose dependently reduced the severity of Permethrin-induced seizures so that Amlodipine at dose of 10 mg kg^{-1} (the lowest, $p<0.05$) and 40 mg kg^{-1} b.wt. (the highest, $p<0.001$) which had anti-convulsant effects. The anti-convulsant activity of Amlodipine suggests that possibly due to antagonistic effect on voltage-dependent calcium channel.

Key words: Amlodipine, pyrethroid, neurotoxicity, seizure, mice, Iran

INTRODUCTION

Epilepsy is one of the major neurological diseases in humans and about 1% of the population is involved. It has been shown that epileptic seizure occurs due to occasional discharges in nerve tissue. It is recognized that occasional changes in reversible neuronal function, causing brain electrical activity. In some cases, the seizure occurs due to the entry of calcium ions into nerve cells and reducing intracellular calcium concentration in some epileptic animal models has inhibitory effect on seizures. During seizures increased intracellular calcium ion concentration while extra cellular calcium concentration decreases (Khanna *et al*., 2000; Van Luijtelaar *et al*., 1995). Calcium channel antagonists for the treatment of hypertension were produced in the year 1980. Use of these drugs over time to treat other diseases was developed such as treatment of angina, supraventricular tachycardia attack, hypertrophic cardiomyopathy, pulmonary hypertension and migraine. It has been shown that calcium channel blockers may have anti-convulsant effects in some animal models. Calcium channel blockers inhibit calcium ion flow through L-type calcium channels sensitive to voltage (Kulak *et al*., 2004). It has been shown that calcium channel inhibitors in models of nerve tissue in a large protective effect (Mikati *et al*., 2004). They also reported that calcium channel inhibitors on the anti-convulsant effects of some models (Chakrabarti *et al*., 1998; Marinho *et al*., 1997) but in all animal models of seizures did not show has not demonstrated these effects (Gasior *et al*., 1996; Khosla and Pandhi, 2000). Also in rats anti-convulsant effects of calcium channel inhibitors shown but seizure agent has not Permethrin. Some medications such as anti-convulsants phenytoin and carbamazepine inducing their effect by inhibiting sodium channels directly and indirectly through preventing the flow of calcium from the membranes of neurons and reduction of excessive concentration of intracellular calcium. Specific drugs used to treat epilepsy are absence seizure kind of like channels as T-type calcium in thalamic neurons are blocked.

Reduction of calcium ion concentration of an important goal in development of neuroprotective and anti-epileptic drugs (Van Luijtelaar *et al*., 1995; Kulak *et al*., 2004). Calcium entry into neurons play an important role in creating the seizures and calcium channel inhibitors have different effects on health including cardiovascular diseases, migraine and headaches caused by vascular changes, nerve regeneration and neuronal regenerative processes (Khanna *et al*., 2000), so it seems calcium channel inhibitors used to treat seizures can be useful. Results of these studies for the anti-convulsant effects of calcium channel inhibitors suggests, therefore likely to Amlodipine reduce Permethrin-induced seizures. Since, no research based on the combined effect of these seizures from Permethrin there, in this case study seems necessary. Insecticide use in agriculture and veterinary medicine as strange since world war II and grew

during the past 20 years until reached its highest rate. While the main consumers of agricultural insecticide industry its uses and application for other industries. Most of insecticide residues on the remaining products and people exposed to low doses of chemicals through the foods. Numerous accidents of acute insecticide poisoning caused by eating food that mainly followed during storage or transportation had been infected was created (Goodman *et al*., 2001). Including the insecticide which are potential toxicity are Pyrethroid. One of the Pyrethroid is Permethrin. The aim of this study was to determine the effect of Amlodipine (calcium channel antagonist) on Permethrin-induced seizures.

MATERIALS AND METHODS

Male mice NMRI, weighing between 25-30 g, maintained at Laboratory Animals Breeding, Center of Tabriz, Islamic Azad University, purchased and were kept under controlled room temperature, light and humidity constant. Animals' were fed food and water *ad libitum*. All tests were performed between 10-16 h. Permethrin and Amlodipine both were solved in Twin 80 (5%). Animals were divided randomly and placed in treatment groups (each group 10 mice).

Amlodipine and Twin 80 were administered intraperitoneally with constant volume and by weight per animal. To remove the effect of injection volume on seizures, all drugs and Twin 80, at 10 mL kg^{-1} was set. First, seizures was assessed in animals receiving Amlodipine and then evaluated the effect of Twin 80 on Permethrin-induced seizures with the above injection, 30 min before the seizure was determined. About 50 mice were given different doses of Amlodipine (2.5, 5, 10, 20 and 40 mg kg^{-1}) 30 min before the intraperitoneal injection of Permethrin. To create seizures, mice received Permethrin (200 mg kg^{-1} b.wt.) intraperitoneally then the animals treated for 120 min were recorded by video camera. Films from the following four behaviors were recorded: starting time of clonic seizures after injection of Permethrin (sec), generation time of death after Permethrin injection (sec), mortality after injection of Permethrin (%) and type of seizures induced by injection of Permethrin (%). After testing data as the mean±SEM expression and to analyze data, ANOVA followed by Tukey multiple comparison tests were used. Value of $p<0.05$ to determine significance between groups was considered.

RESULTS AND DISCUSSION

Effect of Twin 80 as solvent on Permethrin-induced seizures showed that this substance has no significant

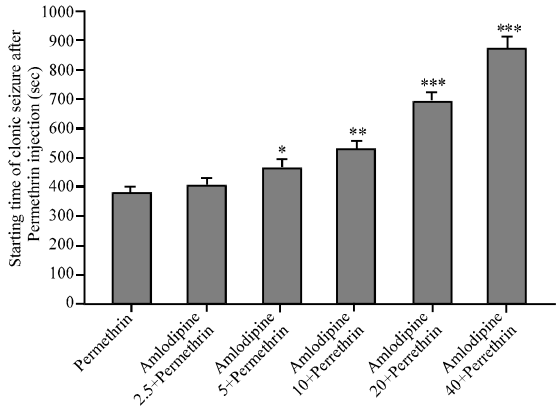

Fig. 1: Effect of different doses of Amlodipine on the starting time of clonic seizures after injection of Permethrin (sec); (Mean±SEM); *p<0.05, **p<0.01 and ***p<0.001 compared with Permethrin group

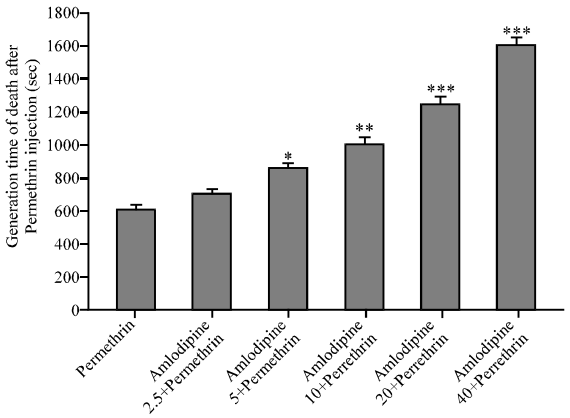

Fig. 2: Effect of different doses of Amlodipine on generation time of death after Permethrin injection (sec); (Mean±SEM); *p<0.05, **p<0.01 and ***p<0.001 compared with Permethrin group

effect on seizures. Therefore, the results had not shown in Fig. 1 and 2 and Table 1 have been avoided. Effect of different doses of Amlodipine (2.5, 5, 10, 20 and 40 mg kg^{-1} b.wt.) on Permethrin-induced seizures showed that this drug dose-dependently reduced the Permethrin-induced seizures (Fig. 1 and 2). Most anti-convulsant effect of Amlodipine on the mortality and severity of seizures with a dose of 40 mg kg^{-1} were observed (Fig. 3 and Table 1).

In this study, Permethrin cause clonic and tonic seizures ultimately death. After the mice received intraperitoneal Permethrin, some degree of tremor and excessive activity showed that over time the symptoms became more severe and cause death. In this study, Amlodipine dose dependently reduced clonic and tonic seizures and deaths from Permethrin. The results showed

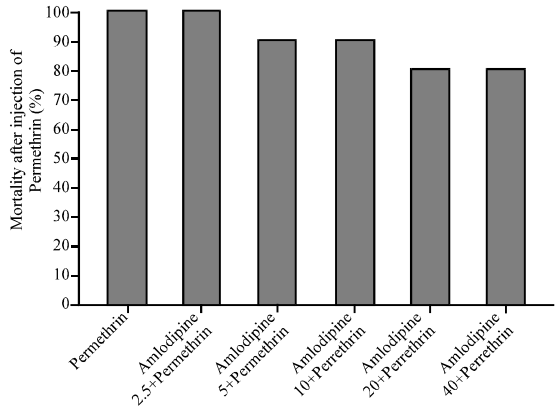

Fig. 3: Effect of different doses of Amlodipine on the mortality after injection of Permethrin (%)

Table 1: Effect of different doses of Amlodipine on the type of seizures induced by Permethrin injection (%)

	Type of seizures (%)		
Groups	Low	Moderate	Severe
Permethrin	0	0	100
Amlodipine 2.5+Permethrin	0	0	100
Amlodipine 5+Permethrin	0	30	70
Amlodipine 10+Permethrin	10	20	70
Amlodipine 20+Permethrin	20	30	50
Amlodipine 40+Permethrin	20	40	40

that the results of different researchers before treatment with calcium channel antagonists, seizure activity in preventing tonic convulsions caused by PTZ (Khanna *et al*., 2000), Aminophyline (Chakrabarti *et al*., 1998) and pilocarpine (Marinho *et al*., 1997) have a protective effect but unlike the above models in all tests anti-convulsant effect has been observed. For example Kainic acid induced seizures, administration of nimodipine before this material could not reduce seizures (Mikati *et al*., 2004).

In another study showed that nimodipine with values >80 mg kg^{-1} could inhibit tonic seizures from chemicals including PTZ in mice and rats (Gasior *et al*., 1996; Wurpel and Iyer, 1994) but later showed that high doses of calcium channels blockers cause systemic and cardiac disorders, such as a sharp reduction in coronary blood pressure, decreased movements, imbalance headache relief (Van Luijtelaar *et al*., 1995; Kulak *et al*., 2004). Epilepsy in patients who were resistant to treatment have reported that nimodipine in an uncontrolled study, seizure frequency is reduced (De Falco *et al*., 1992) but in another study that two strains were unaware controls, no anti-convulsant effects was observed by nimodipine (Larkin *et al*., 1991). Other problems prescription drug, long-term administration of drugs with low prescribed intervals (3-4 times a day to several weeks) and side effects include headache and hypotension, pronounced the man was from animal models. However, after 24 and 72 h of administration of nimodipine, percent of alpha (α) and theta (θ) waves was increased and vice versa percent in delta waves electroencephalogram was reduced (Kulak *et al*., 2004; Larkin *et al*., 1991). Other studies have shown that the anti-convulsant effects of calcium channel blockers, especially nimodipine with other anti-epileptic drugs, increases. For example, in mice and rats with concurrent administration of nimodipine with other drugs can be decreased PTZ-induced tonic seizures, seizures resulting from sound and relieve the electroshock (Mikati *et al*., 2004; Gasior *et al*., 1996; Khosla and Pandhi, 2000). Dihydropyridine calcium channels blockers in experimental seizures by ischemia, bicuculine, electrical cortical shocks, nitrous oxide and alcohol withdrawal syndrome is caused due have anti-convulsant effects (Kriz *et al*., 2003).

In another study, calcium channel blockers such as verapamil, nifedipine and Flunarizine to prevent of penicillin-induced seizures and electroencephalogram range have changed (Kriz *et al*., 2003). Calcium channel inhibitors on seizures induced by N-Methyl-D, L-Aspartate (NMDLA) and dihydropyridine calcium channel agonist BAY K 8644 have been effective (Van Luijtelaar *et al*., 1995; Palmer *et al*., 1993). In another study on rats have shown that nimodipine in animal models of seizures, nerve discharge from BAY K 8644 and reduced the decrease in spike wave EEG (Van Luijtelaar *et al*., 1995). Also have shown that this drug is ischemic brain damage has protective effects (Kriz *et al*., 2003).

These studies suggest that protective effects of calcium channel antagonists probably due to blocking L-type calcium channels during seizures. These drugs inhibit voltage-dependent calcium channels in seizures, the increase in intracellular calcium to prevent. Well marked that increased Ca^{2+} into the cell in the incidence of certain types of seizures plays a role (Khanna *et al*., 2000), also marked the loss of calcium outside the cell with reduced flow of calcium from the membranes of neurons for several seconds the discharge of neurons that causes seizures be prevented and the threshold increases (McNamara, 1992). Some of the other anti-epileptic drugs such as phenytoin and carbamazepine with a direct effect on neuronal sodium channels act directly or indirectly the flow of calcium ions from the membranes of neurons are inhibited (Van Luijtelaar *et al*., 1995; Kulak *et al*., 2004). So it is likely that calcium channel antagonists to act with similar mechanisms. Also have shown that calcium channel antagonists may inhibit calcium, sodium, chloride, potassium and calcium-dependent glutamate channels (Van Luijtelaar *et al*., 1995).

CONCLUSION

This study showed that Amlodipine (voltage-dependent calcium channel antagonist type L) decreased clonic and tonic seizures from Permethrin in mice are probably the main mechanism anti-convulsant related to block calcium channels and reduce calcium flow within neurons. Of course, this could be generalized to humans rather than question and anti-convulsant effects of calcium channel antagonists in humans, further investigation is needed.

REFERENCES

Chakrabarti, A., H.K. Saini and S.K. Garg, 1998. Dose-finding study with nimodipine: A selective central nervous system calcium channel blockers on aminophylline induced seizure model in rats. Brian Res. Bull., 45: 495-499.

De Falco, F.A., U. Bartiromo, L. Majello, G. di Geronimo and P. Mundo, 1992. Calcium antagonist nimodipine in intractable epilepsy. Epilepsia, 33: 343-345.

Gasior, M., R. Kaminski, T. Burdniak, Z. Kleinrok and S.J. Czuczwar, 1996. Influence of nicardipine, nimodipine and flunarizine on the anti-convulsant efficacy of anti-epileptics against pentylenetetrazol in mice. J. Neural Transm., 103: 819-831.

Goodman, L.S., L.E. Limbird, J.G. Hardman and A.G. Gilman, 2001. Insecticides: Goodman and Gilman's the Pharmacological Basis of Therapeutics. 10th Edn., McGraw-Hill, New York, USA.

Khanna, N., S. Bhalla, V. Verma and K.K. Sharma, 2000. Modulatory effects of nifedipine and nimodipine in experimental convulsions. Indian J. Pharmacol., 32: 347-352.

Khosla, P. and P. Pandhi, 2000. Anti-convulsant effect of nimodipine alone and in combination with diazepam and phenytion in a mouse model of status epilepticus. Meth. Find Exp. Clin. Pharmacol., 22: 731-736.

Kriz, J., G. Zupan and A. Simonic, 2003. Differential effects of dihydropyridine calcium channel blockers in kainic acid-induced experimental seizures in rats. Epilepsy Res., 52: 215-225.

Kulak, W., W. Sobaniec, K. Wojtal and S.J. Czuczwar, 2004. Calcium modulation in epilepsy. Pol. J. Pharmacol., 56: 29-41.

Larkin, J.G., P.J. McKee, J. Blacklaw, G.G. Thompson, I.C. Morgan and M.J. Brodie, 1991. Nimodipine in refractory epilepsy: A placebo-controlled, add-on study. Epilepsy Res., 9: 71-77.

Marinho, M.M.F., V.M.S. de Bruin, F.C.F. de Sousa, L.M.V. Aguiar, R.S.N. de Pinho and G.S.B. Viana, 1997. Inhibitory action of a calcium channel blocker (nimodipine) on seizure and brain damage induced by pilocarpine and lithium-pilocarpine in rats. Neurosci. Lett., 235: 13-16.

McNamara, J.O., 1992. The neurobiological basis of epilepsy. Trends Neurosci., 15: 357-359.

Mikati, M.A., G.L. Holmes, S. Werner, N. Bakker, L. Carmant, Z. Liu and C.E. Stafstrom, 2004. Effects of nimodipine on the behavioral sequalae of experimental status epilepticus in prepubescent rats. Epilepsy Behav., 5: 168-174.

Palmer, G.C., M.L. Stagnitto, R.K. Ray, M.A. Knowels, R. Harvey and G.E. Garske, 1993. Anti-convulsant properties of calcium channel blockers in mice: NMDLA and BAYK 8644-induced convulsions are potently blocked by the dihydropyridines. Epilepsia, 34: 372-380.

Van Luijtelaar, E.L.J.M., N. Ales and A.M.L. Coenen, 1995. Role of L-type calcium channel modulation in nonconvulsive epilepsy in rats. Epilepsia, 36: 86-92.

Wurpel, J.N.D. and S.N. Iyer, 1994. Calcium channel blockers verapamil and nimodipine inhibit kindling in adult and immature rats. Epilepsia, 35: 443-449.