American-Eurasian Journal of Toxicological Sciences 3 (3): 204-207, 2011
ISSN 2079-2050

Effect of Nimodipine on Dichlorvos-Induced Seizure in Mice

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Abstract: Dichlorvos a synthetic organophosphate 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 Dichlorvos creation seizure effects in different animals. Nimodipine, dihydropyridine calcium channel blockers, widely used for treatment of cardiovascular diseases. Studies have shown that the calcium channel blockers are anticonvulsant effects in different animal models. The aim of this study was to determine the effect of Nimodipine on Dichlorvos-induced seizures in mice. In this experiment, the animals were received different doses of Nimodipine (2.5, 5, 10, 20 and 40 mg/ kg b.wt.) intraperitoneally 30 min before intraperitoneal injection of Dichlorvos (50 mg/kg b.wt). After Dichlorvos injection, clonic and tonic seizures, and finally death was the fate was investigated. Results showed that Nimodipine dose dependently reduced the severity of Dichlorvos-induced seizures, so that Nimodipine at dose of 5mg (The lowest, $p<0.05$) and 40 mg/kg b.wt. (The highest, $p<0.001$) which had anticonvulsant effects. The anticonvulsant activity of Nimodipine suggests that possibly due to antagonistic effect on voltage-dependent calcium channel.

Key words: Dichlorvos · Nimodipine · Seizures · Mice

INTRODUCTION

Epilepsy is one of the major neurological diseases in humans and about one percent 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 [1, 2]. 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. Recently have shown that calcium channel blockers may have anticonvulsant effects in some animal models. Calcium channel blockers inhibit calcium ion flow through L-type calcium channels sensitive to voltage [3]. It has been shown that calcium channel inhibitors in models of nerve tissue in a large protective effect [4]. They also reported that calcium channel inhibitors on the anticonvulsant effects of some models [5, 6], but in all animal models of seizures did not show has not demonstrated these effects [7, 8]. Also in rats anticonvulsant effects of calcium channel inhibitors shown but seizure agent has not Dichlorvos. Some medications such as anticonvulsants 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 antiepileptic drugs [2, 3]. 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 [1], So it seems calcium channel inhibitors used to treat seizures can be useful. Results of these studies for the

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anticonvulsant effects of calcium channel inhibitors suggests, therefore likely to Nimodipine reduce Dichlorvos-induced seizures. Since no research based on the combined effect of these seizures from Dichlorvos 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 [9]. Including the insecticide, which are potential toxicity, are organophosphate. One of the organophosphate is Dichlorvos. The aim of this study was to determine the effect of nimodipine (calcium channel antagonist) on Dichlorvos-induced seizures.

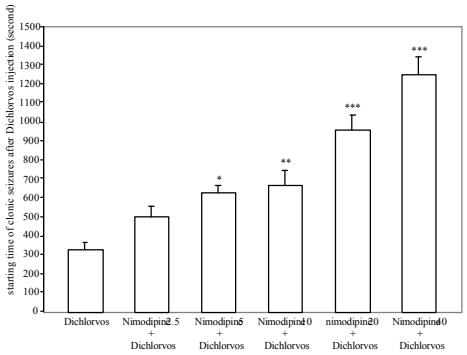
MATERIALS AND METHODS

Male mice NMRI, weighing between 25-30 grams, 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 hours. Dichlorvos and Nimodipine, both were solved in Twin 80 (5%). Animals were divided randomly and placed in treatment groups (each group 10 mice). Nimodipine 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 was set. First, seizures was assessed in animals receiving Dichlorvos and then evaluated the effect of Twin 80 on Dichlorvos-induced seizures with the above injection, 30 minutes before the seizure was determined. 50 mice were given different doses of nimodipine (2.5, 5, 10, 20 and 40 mg/kg) 30 min before the intraperitoneal injection of Dichlorvos. To create seizures, mice received Dichlorvos (50 mg/kg b. wt.) intraperitoneally, and then the animals treated for 120 minutes were recorded by video camera. Films from the following four behaviors were recorded: starting time of clonic seizures after injection of Dichlorvos (second), Generation time of death after Dichlorvos injection (second), mortality after injection of Dichlorvos (percentage) and type of seizures induced by injection of Dichlorvos (percentage).

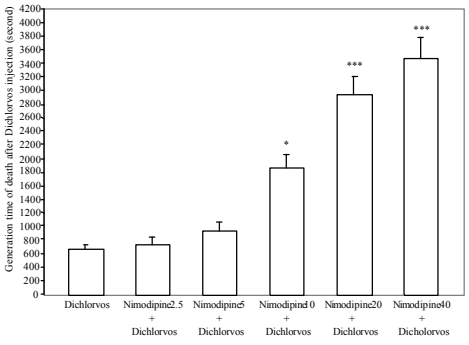
Statistical Analysis: After testing data as the mean±SEM expression and to analyze data, ANOVA followed by Tukey multiple comparison tests were used. Value of $p<0.05$ to determine significance between groups was considered.

RESULTS

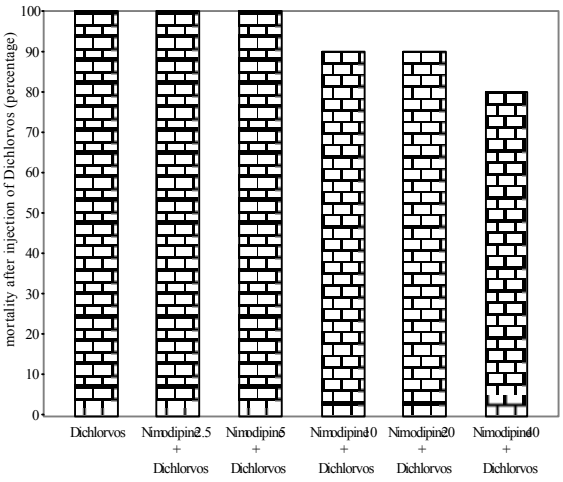
Effect of Twin 80 as solvent, on Dichlorvos-induced seizures showed that this substance has no significant effect on seizures. Therefore the results had not presented in graphs and tables have been avoided. Effect of different doses of Nimodipine (2.5, 5, 10, 20 and 40 mg/ kg b.wt.) on Dichlorvos-induced seizures showed that this drug dose-dependently reduced the Dichlorvos-induced seizures (Graphs 1 and 2).Most anticonvulsant effect of Nimodipine on the mortality and severity of seizures with a dose of 40 mg/kg was observed (Graph 3 and Table 1).



Graph 1: Effect of different doses of nimodipine on the starting time of clonic seizures after injection of Dichlorvos (second). (Mean±SEM) any forms of graphs are presented. * P<0.05, ** P<0.01 and *** P<0.001 compared with Dichlorvos group.



Graph 2: Effect of different doses of nimodipine on Generation time of death after Dichlorvos injection (second). (Mean±SEM). any forms of graphs are presented. * P<0.05 and *** P<0.001 compared with Dichlorvos group.



Graph 3: Effect of different doses of nimodipine on the mortality after injection of Dichlorvos (percentage).

Table 1: Effect of different doses of nimodipine on the type of seizures induced by Dichlorvos injection (percentage)

Type of seizures (percentage)			
Group	Low	Moderate	Severe
Dichlorvos	0	0	100
Nimodipine 2.5 + Dichlorvos	0	10	90
Nimodipine 5 + Dichlorvos	0	30	70
Nimodipine 10 + Dichlorvos	10	50	40
Nimodipine 20 + Dichlorvos	20	60	20
Nimodipine 40 + Dichlorvos	40	50	10

DISCUSSION

In this study, Dicholorvos cause clonic and tonic seizures, and ultimately death. After the mice received intraperitoneal dichlorvos, some degree of tremor and excessive activity showed that over time the symptoms became more severe and cause death. In this study, nimodipine dose dependently reduced clonic and tonic seizures and deaths from Dicholorvos. The results showed that the results of different researchers before treatment with calcium channel antagonists, seizure activity creation of different materials down to is in agreement. If nimodipine in preventing tonic convulsions caused by PTZ [1], Aminophyline [5] and pilocarpine [6] have a protective effect, but unlike the above models in all tests anticonvulsant effect has been observed. For example Kainic acid induced seizures, administration of nimodipine before this material could not reduce seizures [4]. In another study showed that nimodipine with values above 80 mg/kg could inhibit tonic seizures from chemicals including PTZ in mice and rats [7, 10], 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, and headache relief [2, 3]. Epilepsy in patients who were resistant to treatment, have reported that nimodipine in an uncontrolled study, seizure frequency is reduced [11], but in another study that two strains were unaware controls, no anticonvulsant effects was observed by nimodipine [12]. Other problems prescription drug, long-term administration of drugs with low prescribed intervals (three to four 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 hours of administration of nimodipine, percent of alpha and theta (θ) waves was increased and vice versa percent in delta waves electroencephalogram was reduced [3, 12]. Other studies have shown that the anticonvulsant effects of calcium channel blockers, especially nimodipine with other antiepileptic 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 [4, 8]. Dihydropyridine calcium channels blockers in experimental seizures by ischemia, bicuculine, electrical cortical shocks, nitrous oxide and alcohol withdrawal syndrome is caused due, have anticonvulsant effects [13]. In another study, calcium channel blockers such as verapamil, nifedipine and Flunarizine to prevent of penicillin-induced seizures and electroencephalogram range have changed [13]. Calcium channel inhibitors on seizures induced by N-methyl-D, L-aspartate (NMDLA) and dihydropyridine calcium channel agonist BAY K 8644 have been effective [2, 14]. 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 [2]. Also have shown that this drug is ischemic brain damage has protective effects [13]. 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 [1], 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 [15]. Some of the other antiepileptic 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 [2, 3]. So it is likely that dihydropyridine calcium channel antagonists to act with similar mechanisms. Also have shown that nimodipine may inhibit calcium, sodium, chloride, potassium and calcium-dependent glutamate channels [2].

CONCLUSION

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

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