Indian J Physiol Pharmacol 1993; 37(3) : 255-256

LETTER TO THE EDITOR

EFFICACY OF CALCIUM CHANNEL BLOCKER AS AN ADJUNCT IN THERAPY OF ORGANOPHOSPHATE POISONING

Sir,

(Received on July 2, 1992)

Organophosphate (OP) are reported to stimulate the release of intracellular calcium, followed by alterations in neuronal function or release of vasoactive substances that would exacerbate the toxicity of OP (1). Beneficial effects of nimodipine and diltiazem, the two calcium channel blockers against OP and cyanide toxicity respectively have been established (2,3). The present study was planned to evaluate the efficacy of nifedipine, a potent and specific calcium channel blocker as an adjunct to conventional atropine + oxime (obidoxime) therapy against highly toxic OP agents like diisorpropylphosphorofluoridate (DFP) and isoropylmethylphosphonofluoridate (sarin) in male mice (20-22 g).

Preparation of all injectable solutions and their route of administration are reported elsewhere (4). Nifedipine (1mg/kg) was injected intramuscularly 30 sec after oxime therapy. Acute (24h) LD_{50} was determined by Dixon's up and down method (5). The protection index (PI) was calculated as the LD_{50} of OP in animals receiving therapy/LD_{50} of OP in animals receiving normal saline.

Table I indicates that nifedipine did not produce any additional beneficial effect over atropine or oxime alone. The conventional atropine + obidoxime therapy conspicuously enhanced the PI against DFP poisoning, while against sarin poisoning only an additive effect (PI 3.3) was observed.

TABLE I : Efficacy of nifedipine as an adjunct in the therapy of DFP and sarin poisoning in mice.

Therapeutic regimens	*LD_{50} of DFP (mg/kg) (95% confidence limits)*	*PI*	*LD_{50} of sarin (µg/kg) (95% confidence limits)*	*PI*
Saline	4.5 (3.8-5.3)	-	170 (143-202)	-
Atropine	6.4 (5.5-7.4)	1.4	301 (253-357)	1.8
Obidoxime	13.0 (11.6-15.1)	2.9	320 (270-380)	1.9
Nifedipine	6.2 (5.2-7.5)	1.4	266 (229-310)	1.6
Atropine + nifedipine	8.7 (7.7-9.9)	1.9	356 (300-423)	2.1
Obidoxime + nifedipine	15.1 (13.4-16.9)	3.3	287 (255-324)	1.7
Atropine + obidoxime	93.7 (80.6-109.0)	20.6	562 (483-654)	3.3
Atropine + obidoxime nifedipine	167.0 (143.3-194.0)	36.9	750 (645-873)	4.4

Adjunction of nifedipine to atropine + obidoxime potentiated PI to 36.9 against DFP while only marginal effects against sarin was noticed. Therapy of OP poisoning include co-administration of a cholinolytic, usually atropine and a cholinesterase reactivator like pralidoxime, obidoxime and trimedoxime (6) and to further potentiate these effects adjuncts like diazepam (7) and salbutamol or terbutaline (4) alongwith the conventional therapy are tried. In the present study nifedipine augmented the protection offered by atropine + obidoxime alone against DFP poisoning. The toxic manifestations of OPs with regard to release of intracellular calcium requires a high concentration of the OP, which is usually greater than the dose required to inhibit acetylcholinesterase (1). This could perhaps be the reason of enhanced protection offered by nifedipine when challenged with high dose of DFP. Ineffectiveness against sarin could be attributed to rapid onset of poisoning as compared to DFP. However, a marginal increase in PI over atropine + obidoxime combination against sarin intoxication requires further exploration.

S. ROHATGI *, R. BHATTACHARYA** AND S. DAS GUPTA
Division of Pharmacology & Toxicology,
Defence R & D Establishment, Tansen Road,
Gwalior - 474 002

REFERENCES

1. Kauffman FC, Davis LH, Whittaker M. Release of Intracellular calcium: A novel action of organophosphates. *Proc Sixth Med Chem Def Biosc Rev* 1987; 115-122.
2. Trouve R, Nahas G. Nimodipine in combination with atropine and diazepam as an antidote to lethal organophosphorus intoxication. *British J Pharmacol* (Suppl.) 1989; 96: 19P.
3. Johnson JD, Meisenheimer TL, Isom GE. Cyanide induced neurotoxicity: Role of neuronal calcium. *Toxicol Appl Pharmacol* 1986; 84: 464-469.
4. Bhattacharya R, Kumar P, Jeevaratnam K, Pandey KS, Das Gupta S. Therapeutic evaluation of bronchodilators as an adjunct against organophosphorus intoxication in mice. *Asia Pacific J Pharmacol* 1981; 6: 75-80.
5. Dixon WJ. The up and down method for small samples. *Am Statist Assoc* 1965; 60: 967-978.
6. Das Gupta S, Ghosh AK, Moorthy MV, Jaiswal DK, Pant BP. Comparative studies of pralidoxime, trimedoxime, obidoxime and diethyxime in acute fluostigmine poisoning in rats. *Pharmazie* 1982; 37: 605.
7. Grudzinska E, Gidynska T, Rump S. Therapeutic value of anticonvulsant drugs in poisoning with an organophosphate. *Arch Intr Pharmacodyn* 1979; 238: 344-350.

*Present address: Department of Neurology, Sir Sunderlal Hospital, Institute of Medical Sciences, Benaras Hindu University, Varanasi - 221 005
**Corresponding Author