

## MANAGEMENT OF CONVULSIONS IN NERVE AGENT ACUTE POISONING: A POLISH PERSPECTIVE

Slawomir Rump and Marek Kowalczyk\*

Department of Pharmacology and Toxicology, Military Institute of Hygiene and Epidemiology  
Kozielska 4, 01-163 Warszawa, Poland  
Telephone: +48 22 6108459  
Fax: +48 22 6108459  
Email: m.kowalczyk@wihe.waw.pl

### ABSTRACT

Symptoms of acute poisoning with nerve agents such as organophosphorus (OP) compounds include general convulsions that could lead to brain damage if uncontrolled. Seizures are believed to be due to hyperactivity of the cholinergic system as a result of inhibition of acetylcholinesterase (AChE). Evidence suggests that the seizure process could also be the result of activation of the N-methyl-D-aspartate (NMDA) system. Effects of various anticonvulsant drugs, such as classic antiepileptic drugs (barbiturates and phenytoin), agonists of the GABA inhibitory system (full and partial agonists of benzodiazepine [BDZ] receptors), antagonists of excitatory amino acid receptors (competitive and non-competitive NMDA receptor antagonists, aminomethylphosphonic acid [AMPA] receptor antagonists) are presented and discussed. Special attention is given to partial agonists of the BDZ recognition site, which produce high anticonvulsant activity with minor myorelaxant and sedative action. Of special interest is imidazenil, an imidazobenzodiazepine derivative, which may become the drug of choice in the management of convulsions in acute OP poisonings.

### INTRODUCTION

Nerve agents or nerve gases are very toxic organophosphorus (OP) compounds. Tabun (ethyl *N*-dimethylphosphor-amidocyanidate; GA), Sarin (isopropyl methylphosphonofluoridate; GB), Soman (pinacolyl methylphosphonofluoridate; GD) and VX (*O*-ethyl-*S*- [2(diisopropylamino) ethyl] methylphosphonothioate) are nerve agents. OPs with lower toxicity to mammals are used as pesticides and tools in basic research. The nerve agents and many other OPs are very strong inhibitors of hydrolases, especially cholinesterases. Their main toxic effect is due to phosphorylation of the active site serine in acetylcholinesterase (AChE), which in mammals produces hyperactivity of the whole cholinergic nervous system due to the increase of endogenous acetylcholine (ACh) levels at neuronal synapses.

Symptoms of acute poisoning with OP include limbic seizures followed by general convulsions. This convulsive activity creates a problem for medical management and, if uncontrolled, can lead to brain damage. Shih et al. (1991) have investigated the mechanisms involved in the initiation and maintenance of convulsions caused by OP. They proposed a four-stage sequence of events: inhibitions of brain AChE leading to a rapid increase in brain ACh levels; interaction of excess ACh with cholinergic receptors (primarily muscarinic) to initiate cholinergic crisis; release of excitatory

neurotransmitters and loss of inhibitory transmission, triggered by a certain threshold of excess of ACh, and resulting in seizure activity in susceptible brain areas; and release of an excess amount of an endogenous substance (probably glutamate) such that it builds up to toxic concentrations and produces the consequent neuropathology.

The first two stages are relatively clear-cut, but the next two stages, involving excitatory and inhibitory neurotransmitters, are relatively uncertain. Effective management of OP-induced seizures is critical for both minimization of brain damage and full recovery from the central effects of exposure. Some studies (McDonough and Shih, 1993; Bodjarian et al., 1993) have demonstrated that antimuscarinic drugs can block the onset of OP-induced seizures or terminate them when they are administered just after intoxication. These observations suggested that the cholinergic muscarinic mechanism predominated the initiation and early phase of OP-induced seizures. On the other hand, research has established that excitatory amino acids (EAA), such as glutamate, are released under some OP intoxications (e.g., Soman) and probably play a prominent role during seizures (Wade et al., 1987; Lallement et al., 1991).

Acute intoxications with OPs usually have been treated with repeated doses of cholinolytics (mostly atropine) along with repeated doses of an oxime to reactivate the AChE from the phosphorylated AChE (Gall, 1981). This combined regimen, at present, also includes a prophylactic pretreatment with pyridostigmine (Moore et al., 1995). Carbamates, such as pyridostigmine, carbamylate the active site serine in the same way as OPs, but the rate of spontaneous reactivation of the carbamylated AChE is faster than phosphorylated AChE. In that sense, pretreating with a carbamate can protect the AChE from inhibition by OP compounds. In many cases of poisoning with OP, this therapeutic regimen is insufficient and does not prevent or block seizure activity and convulsions (Lallement et al., 1997). Therefore, there is a need for more effective anticonvulsant therapy.

Classic anticonvulsant drugs, such as barbiturates or phenytoin, are not able to block the seizures or increase significantly the antilethal effectiveness of atropine in poisonings with OP (Wills, 1963). Diazepam can be given to mitigate the seizures in OP poisoning, but its sedative properties make it a less-than-optimal drug for use on the battlefield.

## **REVIEW OF ANTICONVULSANT RESEARCH**

The first successful attempt to stop seizure activity and convulsions in OP poisonings was observed 30 years ago where the effects of diazepam were described (Lipp, 1972; Rump et al., 1972). Diazepam quickly abolished seizure bioelectrical activity in the rabbit's brain induced by fluostigmine (diisopropyl fluorophosphate [DFP]) (Rump et al., 1973) or Soman (Johnson and Lowndess, 1974). When given together with atropine and obidoxime (an AChE reactivator), diazepam increased the effectiveness of that standard therapy in DFP intoxication two-fold (Rump et al., 1974).

In addition, diazepam has been shown to be efficacious not only against OP-induced convulsions, but also against subsequent neuropathological lesions (Martin et al., 1985). However, only administration of diazepam before the onset of convulsions completely prevented expression of pathology. If diazepam is administered at the start of, or at various times after the initiation of convulsions, the therapeutic benefit is

quickly lost (Clement and Broxup, 1993). These observations suggested that diazepam must be administered shortly after exposure to OP. Moreover, it was reported that seizure activity could redevelop within a few hours after diazepam administration when diazepam was given after the onset of seizures (McDonough and Shih, 1993). In our experiments, the subsequent administration of diazepam 90 min after the first dose was without effect on the LD<sub>50</sub> of DFP (Rump et al., 1976).

In addition, diazepam, as with other benzodiazepines (BDZ), has the potential to decrease performance when administered in anticonvulsant doses (Capacio et al., 1992). Diazepam also has anxiolytic, sedative, and muscle-relaxant properties. The last two properties are undesirable in nerve agent exposures.

An ideal anticonvulsant compound in OP poisonings should have minimal debilitating side effects and sufficient water solubility for compatibility with current treatment regimens. Commercially available diazepam is formulated in a nonaqueous solvent. This is incompatible with the aqueous solutions of atropine and oximes and therefore presents several logistical complications. This technical inconvenience could now be overcome. Avizafone (a peptidoaminobenzophenone pro-drug of diazepam) is soluble in water (Upshall et al., 1990; Clement and Broxup, 1993) and could be used in a multiple aqueous drug mixture of atropine and oxime. Avizafone undergoes hydrolysis in the body by aminopeptidase to give lysine and diazepam (Maidment and Upshall, 1990). Effects of other BDZs were also studied. Some experiments suggested a higher efficacy of clonazepam (Lipp, 1974) compared to diazepam. In fact, the effectiveness of all anticonvulsant BDZs are very similar (McDonough et al., 1999).

Despite all these counterindications, the anticonvulsant and antilethal effects and therapeutic value of diazepam in acute OP poisonings are generally accepted and diazepam, alongside with atropine and oxime, is often recommended as the drug of choice for the treatment of OP poisonings (Moore, 1995). As a result, in many countries, diazepam was made available in an automatic injector to counteract OP-induced convulsions. For example, the possibility for nerve agent use on the battlefield during Desert Storm resulted in the US Army providing soldiers with diazepam in auto-injectors.

However, sedation and dependence make diazepam a poor choice for prophylactic treatment, even though this drug is potentially life saving. If diazepam were used in combat conditions, especially in auto-injectors by non-professionals, a performance decrement and a decrease of fighting ability of the soldier, due to sedative and myorelaxant properties of this drug, could be a real consequence. This would occur in the absence of intoxication with OP (e.g., as a result of a false chemical alarm) or nonprescribed use of the injectors. Therefore, further research is needed to find a better antidote against OP-induced convulsions and associated debilitation.

## **ANTAGONISTS OF NMDA RECEPTORS**

Recent evidence suggests that in late stages of intoxication with OP, non-cholinergic EAA receptors may become involved. A non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, dizocilpine (5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate; MK-801) was used

effectively to block seizures induced by Soman in guinea pigs (McDonough and Shih, 1993; Braitman and Sparenborg, 1989; Sparenborg et al., 1992).

In studies of DFP intoxication, a competitive antagonist of NMDA receptors, CGP 39551 (carboxyethylester of *DL*-[E]-2-amino-4-methyl-5-phosphono-3-pentenoic acid), given as an adjunct to atropine and obidoxime, raised the effectiveness of obidoxime three-fold during 2 hours observation but was without effect after 24 hours observation (Galecka et al., 1995).

Lallement et al. (1994) reported that 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide disodium (NBQX), a selective inhibitor of non-NMDA receptors (cocompetitive aminomethylphosphonic acid [AMPA] receptor agonist), can prevent or greatly reduce the epileptic activity resulting from Soman intoxication.

Interestingly, the phencyclidine derivative N-(1-[2-thienyl] cyclohexyl) piperidine (TCP), a NMDA receptor antagonist, was shown to neither prevent nor delay the onset of OP-induced seizures in Soman poisoning but did terminate or reduce these seizures (Carpentier et al., 1994). These observations led to the suggested use of TCP in the treatment of OP poisonings (i.e., co-administration of atropine, NBQX, and TCP) (Lallement et al., 1994a).

The effectiveness of dizocilpine and NBQX in preventing lethality in Soman poisoning was studied in our laboratory. The antilethal effects of dizocilpine were significantly weaker than those of diazepam; treatment with NBQX was more lethal than treatment without an anticonvulsant, using only atropine and the oxime HI-6 (1-(((4-amino-carbonyl)pyridino)methoxy)methyl)-2-(hydroxyimino)methyl-pyridinium dichloride monohydrate, C<sub>14</sub>-H<sub>16</sub>-N<sub>4</sub>-O<sub>3.2</sub>Cl) in Soman poisonings of mice (table 1) (Kowalczyk et al., 1997).

**Table 1. Increase in LD<sub>50</sub> of Soman with various anticonvulsants in the mouse for 24h observation\***

Treatment	LD <sub>50</sub> (µg/kg) <sup>†</sup>	TI <sup>‡</sup>	TE <sup>§</sup>	Source
Soman	137 (126–150)	1	NA <sup>  </sup>	Rump et al. (2001)
+ atropine + HI-6	856 (609–1204)	6.2	1	Rump et al. (2001)
+ atropine + HI-6 + diazepam (5 mg/kg)	1287 (808–1832)	9.4	1.5	Rump et al. (2001)
+ atropine + HI-6 + CGS 9896 (20 mg/kg)	1848 (1290–2114)	13.5	2.1	Kowalczyk et al. (1997)
+ atropine + HI-6 + imidazenil (2 mg/kg)	2140 (1640–2790)	15.6	2.5	Rump et al. (2001)
+ atropine + HI-6 + MK-801 (1 mg/kg)	1242 (902–1709)	9.1	1.4	Kowalczyk et al. (1997)
+ atropine + HI-6 + CGP 39551 (10 mg/kg)	1090 (674–1207)	7.9	1.3	Kowalczyk et al. (1997)
+ atropine + HI-6 + NBQX (30 mg/kg)	802 (696–923)	5.8	0.9	Kowalczyk et al. (1997)

\* Anticonvulsants were given intraperitoneally (i.p.) together with atropine (10 mg/kg) and HI-6 (70 mg/kg) immediately after the intoxication. Soman was given subcutaneously (s.c.)

<sup>†</sup> LD<sub>50</sub> = Lethal dose; dose that causes death in 50% of the animals tested

<sup>‡</sup> TI = Therapeutic index: LD<sub>50</sub> treated : LD<sub>50</sub> untreated animals

<sup>§</sup> TE = Therapeutic efficacy: LD<sub>50</sub> treated : LD<sub>50</sub> animals treated only with atropine and HI-6

<sup>||</sup> NA = Not applicable

## OTHER ANTICONVULSANTS

McLean et al.(1992) tested the effects of memantine, an aminoadamantane derivative used in therapy of Parkinson's disease and reported to be protective against maximal electroshock (MES) seizures in rats (Meldrum et al., 1986b). McLean et al. found that pretreatment and/or therapeutic administration of memantine with atropine reduced seizure intensity in rats intoxicated with Soman. However, further experiments by Koplovitz et al. (1997) did not confirm that initial positive finding.

Scopolamine also has been found to be efficacious against Soman-induced convulsions (Shih et al., 1991; Capacio and Shih, 1991). Anderson et al. (1994) suggested that scopolamine (at least in guinea pigs) could replace atropine or diazepam or both as therapy against Soman-induced incapacitation.

In another paper, Anderson et al. (1994) studied the efficacy of other anticholinergic drugs against Soman-induced convulsions. They found biperiden, a synthetic tertiary amine with strong atropine-like blocking effects in the CNS, also used for the treatment of Parkinsonian syndrome, to be of special interest. Biperiden has been reported to have anti-NMDA activity (Olney et al., 1987). In guinea pigs, biperiden and scopolamine were superior to diazepam in their effectiveness against Soman-induced convulsions and lethality (Anderson et al.,1994).

## PREVENTING SEIZURES BY PRETREATMENT

Research has also been done on prophylactic measures against OP-induced seizures (i.e., on drugs that may be administered before OP intoxication). Reversible AChE inhibitors, mainly carbamates, have been used as a pretreatment for OP poisonings. These include pyridostigmine and physostigmine. Pyridostigmine, a quaternary ammonium carbamate derivative, does not cross the blood-brain barrier and therefore cannot protect against seizures and subsequent neuropathology (Grunwald et al., 1994). Physostigmine does cross the blood-brain barrier but has a very short half-life (Aquilonius and Hartvig, 1986) and high degree of individual variation in its bioavailability (Whelpton and Hurst, 1985). These characteristics make physostigmine unacceptable for pretreatment in OP intoxications.

Preliminary results of our experiments on the protective effects against OP-induced seizures with another reversible AChE inhibitor, donepezil, used in the treatment of Alzheimer's disease (Thomas et al., 2001), suggested that this drug could be of practical value in the prophylaxis of OP poisonings. Donepezil, given prophylactically, decreased the intensity of bioelectrical seizure activity subsequently induced by Soman in the rat brain. Donepezil, given together with pyridostigmine, significantly reduced the lethal effects in mice poisoned with DFP or Soman (Rump et al., unpublished data).

Huperzine, an alkaloid isolated from the Chinese club moss *Huperzia serrata*, has been established as a slow, reversible inhibitor of AChE (Ashani et al., 1992). It was reported that huperzine gives some protection against OP-induced seizures and subsequent neuropathology (Lallement et al., 1997).

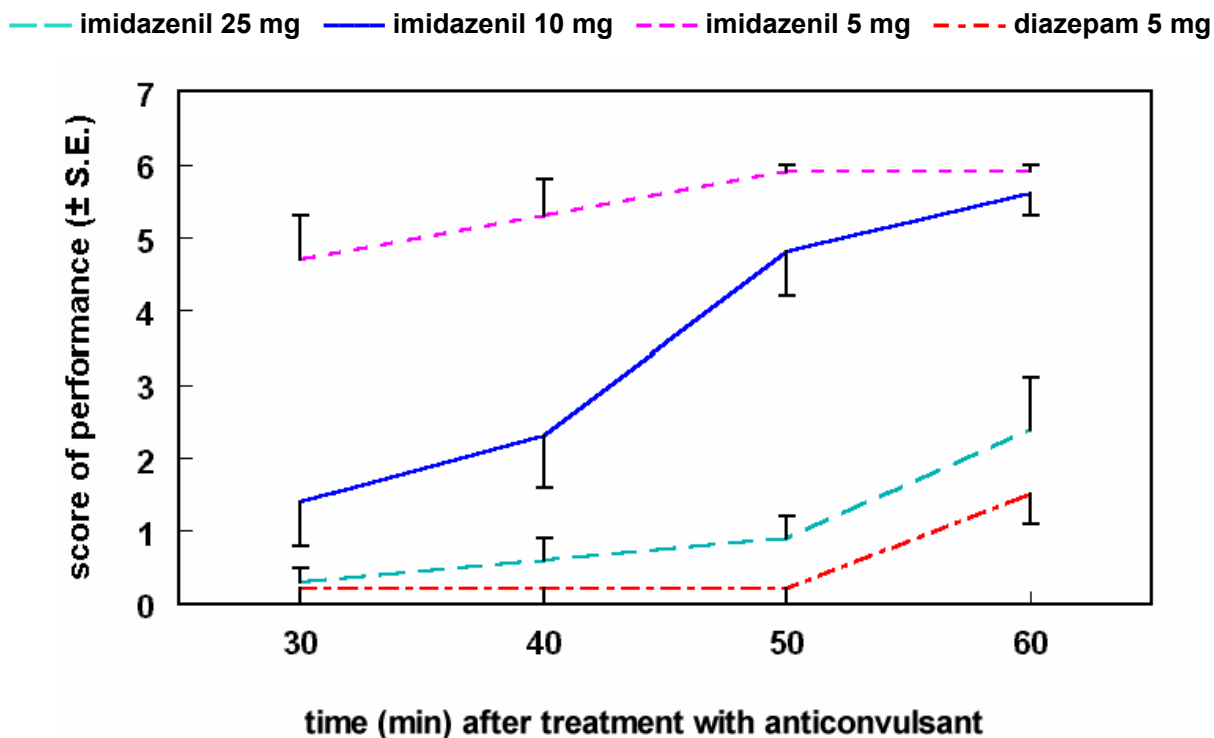
## PARTIAL AGONISTS OF BDZ RECOGNITION SITES

Despite the progress in assessing the protective functions of these anticonvulsant drugs, it is not obvious which of these drugs are best to include in the treatment for OP-induced seizures. For that reason, we continued our research on possible anticonvulsants. We were especially interested in partial agonists of BDZ recognition sites. These drugs have anxiolytic effects, high anticonvulsant activity, and minor myorelaxant and sedative actions (Bernard et al., 1985; Meldrum and Chapman, 1986a).

A pyrazoloquinoline derivative, 2-p-chlorophenyl-pyrazolo 4,3-c-quinolin-3[5H]-one (CGS 9896), was studied as an anticonvulsant drug in OP poisonings. CGS 9896, given together with standard therapy consisting of atropine and obidoxime, was twice as effective as diazepam in mice poisoned with DFP during 24 hours observation (Rump et al., 1990). Similar effects for CGS 9896 were observed in Soman poisonings, where standard therapy consisted of atropine and HI-6 (table 1) (Kowalczyk et al., 1997). These observations, as well as lack of sedative and myorelaxant activity, suggested that CGS 9896 could be of value as an adjunct to cholinolytic drugs and AChE reactivators in the treatment of OP poisonings. Unfortunately, CGS 9896 has not been approved as a drug in any country.

Another partial agonist of the BDZ receptor, imidazenil (6-(2-bromophenyl)-8-fluoro-4H-imidazo[1,5-a]benzodiazepine-3-carboxamide), may be of interest. Imidazenil is

now extensively studied in many laboratories and clinics as a potential new-generation anti-epileptic drug (Costa and Guidotti, 1996). Recently we reported the effects of imidazenil in acute poisonings with DFP (Rump et al., 2000). This drug significantly decreased convulsion intensity and seizure patterns in bioelectrical activity of the brain and increased antilethal effectiveness of the standard therapy. These effects were comparable to those of diazepam but had fewer side effects. Motor coordination effects were noted in imidazenil at doses 5–10 times higher than therapeutic doses, but these effects were noted in diazepam at therapeutic doses (figure 1).

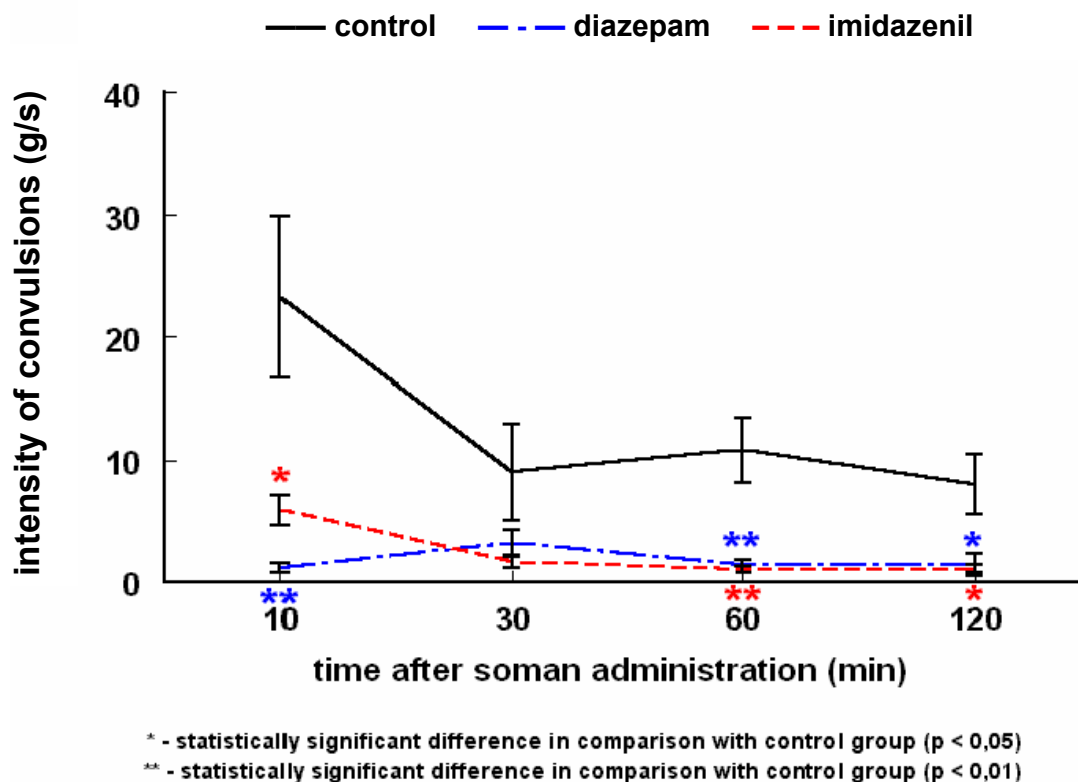


**Notes:**

- Results were expressed as ability of performance (time to remain on the rod) according to Kuribara et al. (1977).
- Proposed scores were defined as follows: 0: 0–4 s; 1: 5–9 s; 2: 10–14 s; 3: 15–19 s; 4: 20–24 s; 5: 25–29 s; 6: > 30 s. (Rump et al., 2000).
- There was no DFP exposure.

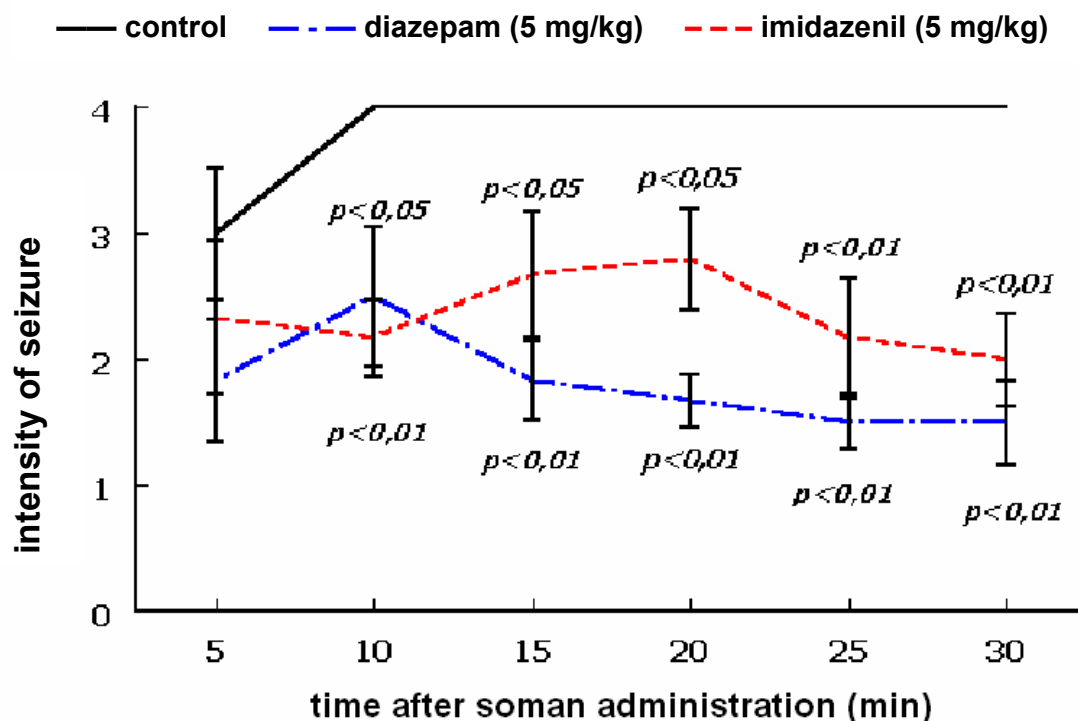
**Figure 1. Effects of imidazenil and diazepam in rota-rod test in the mouse**

More recently we confirmed the efficacy of imidazenil in Soman intoxication (Rump et al., 2001). The effectiveness of imidazenil, given together with atropine and HI-6, was even higher than that of diazepam (table 1) for preventing death in mice. The effects of imidazenil in the management of Soman-induced convulsions (figure 2) and seizure bioelectrical activity in the brain (figure 3) were also very close to the effects of diazepam.

**Notes:**

- To increase the survival rate, all animals received HI-6 (75 mg/kg i.p.) 15 min before the experiment.
- Intensity of convulsions was determined on Convulsometer (Columbus Instruments, USA) and expressed in g/sec (Rump et al., 2001).
- Imidazenil was given at 2 mg/kg i.p.
- Diazepam was given at 5 mg/kg i.p.
- Soman was given at 200  $\mu$ g/kg s.c.

**Figure 2. Effects of imidazenil or diazepam on convulsions induced by Soman in the mouse**

**Notes:**

- To increase the survival rate, all animals received HI-6 (80 mg/kg i.p.) and methylatropine (10 mg/kg i.p.) 15 min before the experiment.
- Four stages of intensity of seizure were determined according to Lallement et al. (1994): stage 1 – absence of spikes and sharp waves; stage 2 – discrete spikes and sharp waves on normal background; stage 3 – high voltage spikes and sharp waves on a suppressed background; stage 4 – continuous or bursting high voltage spiking (Rump et al., 2001).
- Imidazentil was given intraperitoneally at 5 mg/kg
- Diazepam was given intraperitoneally at 5 mg/kg
- Soman was given subcutaneously at 180  $\mu$ g/kg

**Figure 3. Effects of imidazenil or diazepam on seizure bioelectrical activity of the rat brain induced by Soman**

However, imidazenil is still not approved and registered as a drug. But if the clinical studies conducted at present, especially those concerning the chronic toxicity, confirm the initial positive finding and if imidazenil becomes registered, it could become a drug of choice for the management of convulsions in OP poisonings.

**CONCLUSIONS**

Controlling the seizures induced by OP poisoning is an essential part of medical treatment. It is critical to give the anticonvulsant drug as soon as possible after OP exposure. For this reason, it is important to have the drug available in the field for soldiers to administer to themselves, along with atropine and a cholinesterase regenerator, such as HI-6. Diazepam is currently either fielded or suggested for use in many countries. Administration of this drug in the absence of OP exposure can cause

the degradation of the soldier's motor coordination and other effects; in addition, there have been documented risks of abuse of the diazepam. Consequently, based on our experiments using imidazenil, we are suggesting that imidazenil is of similar effectiveness to diazepam but has fewer unwanted side effects. This may permit the use of this drug in combat conditions without decreasing the fighting ability of the soldier.

***Acknowledgement.*** This work was supported in part by the grant No 1486/C-TOO/95 from the State Committee for Scientific Research (KBN), Poland.

## References

- Anderson, D.R., Gennings, C., Cater, W.H., Harris, W., Lennox, W.J., Bowersox, S.L., Solana, R.P. (1994) Efficacy comparison of scopolamine and diazepam against soman-induced debilitation in guinea-pig. *Fundam Appl Toxicol.* **22**, 588–593.
- Anderson, D.R., Harris, L.W., Bowersox, S.L., Lennox, W.J., Anders, J.C. (1994) Efficacy of injectable anticholinergic drugs against soman-induced convulsive/subconvulsive activity. *Drug Chem Toxicol.* **17**, 139–148.
- Aquilonius, S.M. and Hartvig, P. (1986) Clinical pharmacokinetics of cholinesterase inhibitors. *Clin Pharmacokinet.* **11**, 236–249.
- Ashani, Y., Peggins, J.O., Doctor B.P. (1992) Mechanism of inhibition of cholinesterase by huperzine. *Biochem Biophys Res Comm.* **30**, 719–726.
- Bernard, P.S., Bennett, D.A., Pastor, B., Yokoyama, N., Liebman, J.M. (1985) CGS 9896: agonist-antagonist benzodiazepine receptor activity revealed by anxiolytic, anticonvulsant and muscle relaxation assessment in rodents. *J Pharmacol Exp Ther.* **235**, 98–105.
- Bodjarian, N., Carpentier, P., Blanchet, G., Baubichon, D. Lallement, G. (1993) Cholinergic activation of phosphoinositide metabolism during soman-induced seizures. *NeuroReport.* **4**, 1191–1193.
- Braitman, D.J. and Sparenborg, S.P. (1989) MK-801 protects against seizures induced by the cholinesterase inhibitor soman. *Brain Res Bull.* **23**, 145–148.
- Capacio, B.R., Harris, L.W., Anderson, D.R., Lennox, W.J., Gales, V., Dawson, J.S. (1992) Use of the accelerating rotarod for assessment of motor performance decrement induced by potential anticonvulsant compounds in nerve agents poisoning. *Drug Chem Toxicol.* **15**, 177–201.
- Capacio, B.R. and Shih, T.M. (1991) Anticonvulsant actions of anticholinergic drugs in soman poisoning. *Epilepsia.* **32**, 604–615.
- Carpentier, P., Foquin-Tarricone, A., Bodjarian, N., Rondouin, G., Lerner-Natoli, M., Kamenka, J-M., Blanchet, G., Denoyer, M., Lallement, G. (1994) Anticonvulsant and antilethal effects of the phencyclidine derivative TCP in soman poisoning. *Neurotoxicology.* **15**, 837–852.
- Clement, J.G. and Broxup, B. (1993) Efficacy of diazepam and avizafone against soman-induced neuropathology in brain of rats. *Neurotoxicology.* **14**, 485–504.
- Costa, E. and Guidotti, A. (1996) Benzodiazepines on trial: a research strategy for their rehabilitation. *TIPS.* **17**, 192–200.
- Galecka, E., Gidynska, T, Jakowicz, I., Rump, S. (1995) Effects of CGP 39551 in acute experimental intoxication with fluostigmine. *Acta Pol Toxicol.* **3**, 58–61.

Gall, D. (1981) The use of therapeutic mixture in the treatment of cholinesterase inhibition. *Fundam Appl Toxicol.* **1**, S14.

Grunwald, J., Raveh, L., Doctor, B.P., Ashani, Y. (1994) Huperzine A as a pre-treatment candidate drug against nerve agent toxicity. *Life Sci.* **54**, 991–997.

Johnson, D.D. and Lowndess, H.E. (1974) Reduction by diazepam of repetitive electrical activity and toxicity resulting from soman. *Eur J Pharmacol.* **28**, 245–250

Koplovitz, I., Schulz, S., Shutz, M., Railer, R., Smith, F., Okerberg, C., Filbert, M. (1997) Memantine effects on soman-induced seizures and seizure-related brain damage. *Toxicol Methods.* **7**, 227–239.

Kowalczyk, M., Rump, S., Antkowiak, O., Gidynska, T., Galecka, E. (1997) Efficacy of anticonvulsive therapy in the treatment of intoxications with soman: a comparative study. Presented at The Chemical and Biological Medical Treatment Symposium. Middle East I. Cairo, 7–10.12.1997.

Kuribara, H., Higuchi, Y., Tadokoro, S. (1977) Effects of central depressants on rotarod and traction performance in mice. *Japan J Pharmacol.* **27**, 117–126.

Lallement, G., Carpentier, P., Collet, A., Pernot-Marino, I., Baubichon, D., Blanchet, G. (1991) Effects of soman-induced seizures on different extracellular amino acid levels and on glutamate uptake in rat hippocampus. *Brain Res.* **563**, 234–240.

Lallement, G., Pernot-Marino, I., Foquin-Tarricone, A., Baubichon, D., Piras, A., Blanchet, G., Carpentier, P. (1994) Antiepileptic effects of NBQX against soman-induced seizures. *NeuroReport.* **5**, 425–428.

Lallement, G., Pernot-Marino, I., Foquin-Tarricone, A., Baubichon, D., Piras, A., Blanchet, G., Carpentier, P. (1994a) Coadministration of atropine, NBQX and TCP against soman-induced seizures. *NeuroReport.* **5**, 2265–2268.

Lallement, G., Veyret, J., Masqualiez, C., Aubriot, S., Burckhart, M.F., Baubichon, D. (1997) Efficacy of huperzine in preventing soman-induced seizures, neuropathological changes and lethality. *Fundam Clin Pharmacol.* **11**, 387–394.

Lipp, J.A. (1972) Effects of diazepam upon soman-induced seizure activity and convulsions. *Electroenceph clin Neurophysiol.* **32**, 557–569.

Lipp, J.A. (1974) Effects of small doses of clonazepam upon soman-induced seizure activity and convulsions. *Arch int Pharmacodyn.* **210**, 49–50.

Maidment, M.P. and Upshall, D.G. (1990) Pharmacokinetics of the conversion of a peptido-aminobenzophenone pro-drug of diazepam in guinea-pig and rhesus monkeys. *J Biopharm Sci.* **1**, 19–32.

- Martin, L.J., Doebler, J.A., Shih, T.M., Anthony, A. (1985) Protective effect of diazepam pretreatment on soman-induced brain lesion formation. *Brain Res.* **325**, 287–289.
- McDonough, J.H. Jr., McMonagle, J., Copeland, T., Zoefel, T. (1999) Comparative evaluation of benzodiazepines for control of Soman induced seizures. *Arch Toxicol.* **73**, 473–478.
- McDonough, J.H. and Shih, T.M. (1993) Pharmacological modulation of soman-induced seizures. *Neurosci Biobehav Rev.* **17**, 203–215.
- McLean, M.J., Gupta, R.C., Dettbarn, W-D., Wamil, A.W. (1992) Prophylactic and therapeutic efficacy of memantine against seizures produced by soman in the rat. *Toxicol Appl Pharmacol.* **112**, 95–103.
- Meldrum, B.S. and Chapman, A.G. (1986a) Benzodiazepine receptors and their relationship to the treatment of epilepsy. *Epilepsia.* **27** (suppl.1) S3–13.
- Meldrum, B., Turski, L., Schwarz, M., Czuczwar, S.J., Sontag, K-H. (1986b) Anticonvulsant action of 1,3-dimethyl-5-aminoadamantane. Pharmacological studies in rodents and baboon Papio Papio. *Naunyn Schmiedebergs Arch Pharmacol.* **332**, 93–97.
- Moore, D.H., Clifford, C.B., Crawford, I.T., Cole, G.M., Baggett, J.M. (1995) Review of nerve agent inhibitors and reactivators of acetylcholinesterase. In *Enzymes of Cholinesterase Family.*:(D.M. Quinn, A.S. Balasubramanian, B.P. Doctor and P. Taylor, eds.). New York: Plenum Press, 297–304.
- Olney, J.W., Price, M.T., Labruyere, J., Salles, K.S., Friedrich, G., Mueller, M., Silverman, E. (1987) Anti-parkinsonian agents are phencyclidine agonists and N-methyl-aspartate antagonists. *Europ J Pharmacol.* **142**, 319–320.
- Rump, S., Faff, J., Szymanska, T., Bak, W., Borkowska, G. (1976) Efficacy of repeated pharmacotherapy in experimental acute poisonings with fluostigmine. *Arch Toxicol.* **35**, 275–280.
- Rump, S., Gidynska, T., Galecka, E., Antkowiak, O., Nawrocka, M., Kowalczyk, M. (2000) Effects of imidazenil, a new benzodiazepine receptor partial agonist, in the treatment of convulsions in organophosphate intoxications. *Neurotoxicity Res.* **2**, 17–22.
- Rump, S. and Grudzinska, E. (1974) Investigations of the effects of diazepam in acute experimental intoxication with fluostigmine. *Arch Toxicol.* **32**, 223–232.
- Rump, S., Grudzinska, E., Edelwein, Z. (1972) Effects of diazepam on abnormalities of bioelectrical activity of the rabbit's brain due to fluostigmine. *Activ Nerv Sup (Prague).* **14**, 176–177.

Rump, S., Grudzinska, E., Edelwein, Z. (1973) Effects of diazepam on epileptiform patterns of bioelectrical activity of the rabbit's brain induced by fluostigmine. *Neuropharmacology*. **12**, 813–817.

Rump, S., Kowalczyk, M., Antkowiak, O., Gidynska, T., Galecka, E. (2001) Use and risks of anticonvulsant therapy in nerve agents poisonings in combat conditions. *Voj Zdravot Listy*. **70** (suppl), 26–29.

Rump, S., Raszewski, W., Gidynska, T., Galecka, E. (1990) Effects of CGS 9896 in acute experiental intoxication with fluostigmine. *Arch Toxicol*. **64**, 412–413.

Shih, T-M., Koviak, T.A., Capacio, B.R. (1991) Anticonvulsants for poisoning by the organophosphorus compound soman: pharmacological mechanisms. *Neurosci Biobehav Rev*. **15**, 349–362.

Sparenborg, S., Brennecke, L.H., Jaax, N.K., Braitman, D.J. (1992) Dizocilpine (MK-801) arrests status epilepticus and prevents brain damage induced by soman. *Neuropharmacology*. **31**, 357–368.

Thomas, A., Iacono, D., Bonanni, L., D'Andreamatteo, G., Onofrj, M. (2001) Donepezil, rivastigmine, and vitamin E in Alzheimer disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months. *Clin Neuropharmacol*. **24**, 31–42.

Upshall, D.G., Gouldstone, S.J., Mazey, N., Maidment, M.P., West S.J., Yeadon, M. (1990) Conversion of a peptido-aminobenzophenone pro-drug to diazepam in vitro, enzyme isolation and characterization. *J Biopharm Sci*. **1**, 111–126.

Wade, J.V., Samson, F.E., Nelson, R.E., Pazdernik, T.L. (1987) Changes in extracellular amino acids during soman- and kainic acid-induced seizures. *J Neurochem*. **49**, 645–650.

Whelpton, R. and Hurst, P. (1985) Bioavailability of oral physostigmine. *N Engl J Med*. **313**, 1293–1294.

Wills, J.H. (1963) Pharmacological antagonists of the anticholinesterase agents. In *Cholinesterases and Anticholinesterase Agents. Handbuch der experimentellen PharmacologieErgänzungswerk XV* (G.B. Koelle, ed.). Berlin-Göttingen-Heidelberg: Springer Verlag, 883–920.