

Sodium dimercaptopropane sulfonate as antidote against non-metallic pesticides

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KEY WORDS sodium dimercaptopropane sulfonate; antidotes; pesticides; nereistoxin insecticides; chlordimeform; bactericide 402; tetramine; poisoning

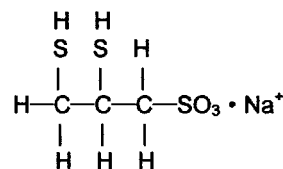
ABSTRACT

Sodium dimercaptopropane sulfonate is used in place of dimercaprol in the treatment of poisoning by heavy metals and metalloids as a well-known specific antidote. It is claimed to be less toxic. In early stage, the pharmacologists and clinical doctors in Wenzhou Medical College found this drug as antidote against non-metallic pesticides as nereistoxin insecticides, Chlordimeform, bactericide 402, and tetramine. We did a lot of animal experiments and clinical trials to confirm that this antagonist possesses a strong antidotal effect. Now it is widely used in China. Great breakthrough has been made not only in the theory but also in its practice. Furthermore, the combination use of this antidote and central anticonvulsant as diazepam indicated synergistic antidotal effect, which is probably the best utilization in the treatment of acute poisoning by tetramine.

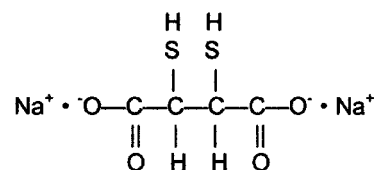
INTRODUCTION

With the advent of World War II, dimercaprol was first developed in England as an effective antidote against arsenical agents. In 1950's, scientists from the Soviet Union developed a water-soluble compound, sodium dimercaptopropane sulfonate (Na-DMPS) named as Unithiol (or Unitiol), which was able to chelate heavy metals and metalloids. Unithiol was collected in the Pharmacopeia of the Soviet Union. After a lot of efforts of scientists from several countries, this drug has been widely used in the treatment of the poisoning of heavy metals and metalloids, as a well-known specific

antidote^[1]. Considering the importance of sulfhydryl groups in human body, we first initiated the possibility



Sodium dimercaptopropane sulfonate (Na-DMPS)



Sodium dimercaptosuccinate (Na-DMS)

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Received 2003-05-27

Accepted 2003-12-29

Fig 1. Chemical structures of two well-known dithiol antidotal compounds against non-metallic pesticides.

of sulfhydryl compounds as antidotes against some non-metal toxicants. In 1970's, they screened many sulfhydryl compounds as antidotes against acute poisoning of nereistoxin insecticides (NTXI), and found that dithiol compounds were much better than monothiol compounds in the treatment for NTXI poisoning. Na-DMPS and sodium dimercapto-succinate (Na-DMS) were among the best antidotes^[2] (Fig 1). The accumulation of experimental studies and clinical trials has confirmed that they were specific effective antidotes against NTXI. In 1990's, Na-DMPS was first applied to treat the acute poisoning of chlordimeform (CDM)^[3], an organonitrogen insecticide, and bactericide 402^[4], an organosulfur pesticide, and tetramine, a rodenticide^[5]. Through thorough pharmacological and toxicological studies of these non-metallic pesticides, the application of Na-DMPS as an antidote has been widened, and the development of antidotes against pesticides has been prospected. The application of Na-DMPS as an antidote against non-metallic pesticides is a successful example, which shows important theoretical basis and practical value.

ANTIDOTES AGAINST ACUTE POISONING OF NTXI^[6,7]

Outline and present status Nereistoxin (NTX) was first isolated from a sea animal, *Lumbriconeris heteropoda* Marenz, by a Japanese scientist. He found that NTX had high insecticidal activities. Scientists from several countries synthesized a series of different NTX derivatives, some of which with closed chain by adding more sulfur atom and others with open chain. The commonly commercialized products of NTXI include Cartap (Japan), Bensultap (Japan), Nereistoxin (Japan), Evisect (Swiss), Shachongshuang (SCS, disodium of 2-di-methylamino-1,3-bisthiosulfo-propane, China), Shachongdan (SCD, monosodium of 2-dimethylamino-1,3-bisthiosulfo-propane, China), Duosaiwan (DSW, 7-*N,N*-dimethylamino-1,2,3,4,5-pentacyclooctane, China) and so on. Both *in vivo* and *in vitro* pharmacokinetic studies showed that NTXI were converted into dihydronereistoxin and further into NTX^[8,9]. Both dihydronereistoxin and NTX then are metabolized to lower toxic or nontoxic metabolites by oxidation, demethylation, and methylation. Liver microsomal enzymes are thought to be the primary metabolizing enzymes for NTX bioconversion^[10-12]. Other enzymes such as hydroxylases are also required. Non-enzymatic catalysis is also thought to be involved in the bioconversion of NTXI. Despite

different results and conclusions about bioconversion of NTXI, the enzymatic catalysis is believed to be the primary pathway. NTXI belongs to a new generation of bionic pesticides, not only being a replacement of organic nitrogenous and chlorinated insecticides but also one of compensation for organophosphorus insecticides. SCS is widely used in China. SCD is monosodium salt of SCS. Pharmacologist and toxicologists use SCD in laboratory researches owing to its ease for crystallization and purification. Both insecticides possess are similar in pharmacological and toxicological effects.

Pharmacologic and toxicologic studies NTXI are neural toxins. They exert their actions on central nervous system (CNS) and peripheral nervous system by activating M-cholinergic receptors and blocking N-cholinergic receptors. The cause of death is primarily the respiratory failure due to respiratory muscle paralysis^[13-16]. When exposed to NTXI, peripheral inhibition of breath is the primary cause of death. When NTXI are ingested to animals and human bodies, these compounds are biologically metabolized to toxically active NTX or dihydronereistoxin. NTX competitively blocks N₂-cholinergic receptor of neuromuscular junction and therefore paralyzes the respiratory muscles. It is believed that NTX is converted to dihydronereistoxin in the target cells and two sulfhydryl groups of dihydronereistoxin can block N₂-cholinergic receptors. The blocking action belongs to *d*-tubocurarine type. NTXI cause stimulating effect on CNS. Animals exposed to NTXI usually have increased activity, convulsion, and entasia. In clinics, patients with the acute poisoning of NTXI have symptoms of dysphoria and convulsion. Higher doses of NTXI may inhibit the activity of cholinesterase (ChE)^[17]. However, as compared with the experiment in organophosphorus pesticide, pralidoxime methylchloride could only partly recover the activity of ChE inhibited by SCS in rats^[18].

Curing protocols for the acute poisoning of NTXI

Extermination and heteropathy of NTXI When exposed to NTXI via oral ingestion, the stomach must be washed thoroughly by 2 % sodium bicarbonate solution; 25-50 mL 1 % copper sulphate can also be used to induce vomiting. Copper sulphate can inhibit the conversion of NTXI (biologically inactive) into NTX and dihydronereistoxin (biologically active) in human gastroenteric tracts thus reducing the toxicity of these insecticides^[19]. The treatment such as supplement of liquid and use of diuretics is also applicable. Atropine

can antagonize the stimulation of M-cholinergic receptor by NTX. Experiments of use of belladonna alkaloids have also been done in the treatment of the acute poisoning of NTXI. SCD showed that scopolamine and atropine alleviated toxic symptoms, delayed the death and reduced mortality^[20,21], with the scopolamine better than atropine^[20,21]. In clinics, the dosage of atropine should be carefully monitored to avoid overdosage when it is used for the treatment of the acute poisoning of NTXI^[22]. The reference dosage is 1-3 mg for minor poisoning, 4-8 mg for medium one, and moderately increased dose for severe one. However, atropinization should be avoided. Acetylcholinesterase carbamate inhibitor neostigmine, acetylcholine releaser Ca^{2+} and 4-aminopyridine are also used to antagonize the blocking of neuromuscular transmission by NTX via directly or indirectly stimulating N_2 -cholinergic receptor, with 4-aminopyridine better^[23].

Specific antidotes Chen *et al* first used Na-DMS as an antidote against the acute poisoning of SCD to mice, and found that it was effective^[24-26]. The antidotal effect of DMS was both prophylactic and therapeutic in SCD-poisoned rabbits, as DMS decreased the mortality and prolonged the survival time^[26]. Na-DMPS and Na-DMS were compared for their effects on LD_{50} of SCD in mice. Na-DMPS (250 mg/kg) or Na-DMS (1000 mg/kg) ip 20 min before SCD increased LD_{50} of ig SCD from 97 to 374 or 251 mg/kg, respectively. The prophylactic effect of Na-DMPS was better than that of Na-DMS ($P < 0.01$). The therapeutic effect of Na-DMPS was also demonstrated in SCD-poisoned conscious rabbits^[27]. The pharmacodynamic studies of Na-DMPS against the acute poisoning of SCD showed that Na-DMPS completely antagonized the blocking of neuromuscular transmission in anesthetized rabbits and respiratory inhibition by SCD^[27,28]. They also studied dose-effect relationship of Na-DMPS on acute poisoning of SCD^[29]. Lu *et al* tested the combination of Na-DMPS with a central sedative hypnotic diazepam in the treatment of the acute poisoning of SCD. The combination reduced animal's mortality, antagonized convulsion, and completely abolished abnormal electronic surge in EEG^[30,31]. Twenty minutes before exposure to SCD, Na-DMPS showed very good protection. Small amount of Na-DMPS (icv or ip) increased LD_{50} of SCD in mice ($P < 0.01$), and reduced the mortality of rats, and completely inhibited their convulsion^[32]. Experiments using Na-DMPS against the acute poisoning of NTXI showed that it had effective treatment of the

acute poisoning of Evisect^[2], Cartap^[27], Bensultap^[33], NTX^[27] and DSW^[33]. In clinic trials, Die *et al* first reported the treatment for the acute poisoning of SCS in 5 humans by using Na-DMPS alone or in combination with Na-DMS^[34]. All five patients were saved, with three persons being treated with Na-DMPS, one with Na-DMS and one with Na-DMPS in combination with Na-DMS. Chen *et al* reported that 23 patients in Zhejiang and Hubei provinces with the acute poisoning of SCS were cured by Na-DMPS or Na-DMS^[35]. Four patients with severe poisoning were treated with initial dose of 0.25 g Na-DMPS (iv), and then with repeated doses of 0.25 g (im) at intervals of 6 h; two patients with mild poisoning were treated with initial dose for 2 to 3 times at intervals of 6 h; and twelve patients with minor poisoning were treated with initial dose of 0.25 g (im), and then with repeated doses for 1 to 3 times at intervals of 6 h. Other four patients with severe acute poisoning of SCS were treated with Na-DMS: three were treated with initial dose of 1.0-2.0 g Na-DMS (iv), and then repeated doses (im) for 2 to 4 times at interval of 2 to 4 h; one was treated with initial dose of 0.5 g (im) Na-DMS, and then repeated doses for 3 times at interval of 6 h. All toxic symptoms of SCS were relieved and patients were cured^[35]. Other clinical treatments with Na-DMPS also showed that this drug was very effective^[36-39]. He RH *et al* studied the therapeutic value of severe SCS poisoning patients with the traditional comprehensive therapy using scopolamine (170 cases) and with above therapy in addition of Na-DMPS (180 cases). The healing rate of the later group was 96.67% and much higher than that of the former group (89.41%) ($P < 0.01$). The average mending time (7.41 ± 1.55) h was obviously shorter than that in the former group (9.69 ± 1.76) h ($P < 0.01$). Na-DMPS significantly reduce the mortality of acute SCS poisoning (personal communication). Li and Zhou reported the treatment of Na-DMPS and/or Na-DMS for the acute SCS poisoning in 39 patients with emphasis on rapid extermination of toxins, administration of enough amounts of antidotes, monitoring respiratory function and other nursed patients back to health^[40]. Another report also showed the nursing experience dealing with the acute poisoning of SCS^[41]. Na-DMPS and Na-DMS are effective to antagonize the blocking of neuromuscular transmission and peripheral inhibition of NTX and recover automatic respiration. SCS may cause death due to CNS convulsion. The CNS muscular relaxants like diazepam, methocarbamol and mephenesin are antidotal. They raise 3-4 times LD_{50}

in mice by SCD, ($P < 0.001$)^[42]. Na-DMPS has no antidotal effects on severe atropine poisoning in acute poisoning by SCS^[43]. The combination of Na-DMPS with CNS muscular relaxant is more effective than Na-DMPS alone. In conclusion, Na-DMPS is a specific antidote against the acute poisoning of NTXI with rapid effect and low side actions. SCD inhibits the activities of succinic acid dehydrogenase (AD) of mitochondrion and consequently suppresses cell respiration in mice. Na-DMPS can antagonize the inhibiting effects of SCD on the activities of AD. The antagonistic actions play an important role in preventing and curing SCD poisoning^[44].

ANTIDOTES AGAINST ACUTE POISONING OF ORGANONITROGEN INSECTICIDE CDM

Outline CDM is a pesticide developed by Ciba-Geigy Corp in Swiss in 1962. Since 1968, the pesticide has been widely used all over the world including China^[45]. It has medium toxicity. Because it is harmful to humans, the Chinese government issued a general order to prohibit its production and application in 1989. However, the incidence of acute poisoning of CDM occurred one after another in 1990's and 2001^[46-53]. There is no specific antidotes against CDM. In clinic, besides the extermination of toxicant source, methyl-thioninium chloride has been used as a heteropathy, which is effective for minor poisoning but not satisfying for medium and severe poisoning.

Exposure to CDM and its toxic symptoms After mice, rats, rabbits, and pigeons were exposed to CDM, the following toxic symptoms usually occurred: coma, suppression of respiration, severe reduction of blood pressure, bradycardia, and cyanopathy. Cardiac damage and respiratory failure are common causes of death. When measured by Evelyn-Malloy method, the level of methemoglobin in CDM-exposed animals is in normal range^[54]. However, sodium nitrite can induce elevation of methemoglobin level in CDM-exposed mice^[55]. After exposed to CDM via gastroenteric tract, respiratory tract and skins, the intoxicated patients have three major symptoms: sleepiness, cyanopathy, and hemorrhagic cystitis. In many Chinese literatures, the toxic symptoms of CDM or its metabolites are mistakenly described to be similar to pharmacological and toxicological effects of lidocaine in severe poisoning. They considered that the cyanopathy was possibly secondary to methemoglobinemia caused by the metabolites of CDM. After several experiments, Zhu *et al* provided

new explanation of the poisoning mechanism of CDM^[56].

Curing protocols for the acute poisoning of CDM

Exterminating toxicant and treatment by oxidoreductive agents When exposed by oral ingestion of CDM, the patients should be performed a complete stomach washing and simultaneous catharsis and then administration of common antidote with equal parts of active carbon, magnesia and tannin. For patients with severe cyanopathy in the acute poisoning of CDM, methylthioninium chloride can be used usually, with initially a small amount and slow intravenous injection. A large amount of methylthioninium chloride is more harmful than beneficial, because it has the hemoglobin oxidized to methemoglobin thus worsening cyanopathy.

Specific antidotes The experiment with Na-DMPS or methylthioninium chloride in the protection of rats and mice exposed to CDM showed that both Na-DMPS and methylthioninium chloride had significant protective effects on the lethal action of CDM with the former better than the latter ($P < 0.05$)^[55]. In mice the lethal dose of ig CDM was 258.9 mg/kg, and after Na-DMPS and methylthioninium chloride were given 10 min before CDM it was 518.2 and 330.0 mg/kg, respectively. In rats the lethal dose by constantly iv CDM was 103.9 mg/kg, and after Na-DMPS and methyl-thioninium chloride was given 5 min before receiving CDM it was 138.1 and 122.4 mg/kg, respectively^[55]. Na-DMPS and methylthioninium chloride had been administered before mice and rats were exposed to CDM, the combination of Na-DMPS and methylthioninium chloride was more effective in the protection than the single use of Na-DMPS ($P < 0.01$). In the pigeons exposed to CDM, Na-DMPS and methylthioninium chloride delayed their death with the former more effective than the latter. Therefore, Na-DMPS is possibly a more effective antidote against CDM^[56]. However, both drugs, when given by mixing them together or in the same administration route, the efficacy was reduced, suggesting that there is a chemical reaction between these two antidotes^[57]. In the treatment of the acute poisoning of CDM, Shen HZ first reported Na-DMPS successfully cured a severe poisoning of CDM boy^[58]. Lu *et al* reported that they initially treated a patient with acute poisoning of CDM with methylthioninium chloride and got unsatisfactory effects, then they treated the patient with Na-DMPS and achieved very good result^[38].

STUDIES ON ANTIDOTES AGAINST THE ACUTE POISONING OF THE ORGANOSULFUR PESTICIDE BACTERICIDE 402

Outline and present status In 1958, the Institute of Organic Chemistry, Chinese Academy of Sciences, studied the plant bactericide allicin and found that ethyl allicin was a very potent bactericide. After semi-synthesis from ethyl allicin, bactericide 401 was made. The oxidation of bactericide 401 leads to the synthesis of bactericide 402 with chemical name of ethylthioethylsulfonate. Bactericide 402 is widely used in countryside for prevention of diseases in plant seedlings, which has advantages of promoting seedlings to sprout, and disinfecting silkworm tools. Bactericide 402 is a yellowish transparent liquid and is volatile with strong garlic smell. It is stable in acidic solution, while it easily decomposes into an inactive compound in a basic solution. It is a broad-spectrum bactericide with mild toxicity. Its metabolites can react with the sulfhydryl and amino groups of proteins thus interfering with the function of a lot of enzymes. It can also chelate with zinc and copper ions thus inactivates a lot of metallic proteins and enzymes and blocking the normal functions of a cell. Therefore, it can damage nerve system, liver and kidney functions. It also erodes the skin and mucous membrane thus burning gastroenteric tract and causing acute pain when ingested orally. It stimulates the nerve systems with symptoms of excitation, headache, dizziness, fatigue or epilepsy-like surge. When contacted with skin, it causes skin putrescence. Severe acute poisoning of bactericide 402 will lead to respiratory failure, disturbance of consciousness and shock. Bactericide 402 in emulsified oil is stored in ampule for usage. Incidence of the acute poisoning of bactericide 402 was reported one after another, especially due to mistaken ingestion by children. The cure of bactericide 402 is conducted by a heteropathy. There is no special antidote for the acute poisoning of bactericide 402. Chen *et al* discovered that Na-DMPS had effective antagonism against the acute poisoning of bactericide 402 in animals^[4]. Furthermore, its efficacy as an antidote was confirmed in clinics.

Treatment protocols

Exterminate sources and heteropathy During the early stage after oral ingestion of bactericide 402, stomach washing can not be performed. Because bactericide 402 is a strong acid, patients are suggested to drink 100 mL water or drink milk, soybean milk, or

chick albumin to neutralize or dilute the toxicant. Sodium bicarbonate is also not allowed, since it can produce carbon dioxide and lead to heavy bleeding in stomach and even gastric perforation. Emetics should be prohibited since vomiting can worsen the stomach hemorrhage. During the early stage, cimetidine and aluminium hydroxide can be prescribed to protect the mucous membrane of stomach and may effectively stop stomach hemorrhage. Supplement of liquid or blood transfusion for severe patients can be used to maintain the blood volume and the balance of electrolytes.

Specific antidotes Willis reported that cysteine and glutathione effectively antagonized the suppression of sulfhydryl enzymes of allicin, the primary component from garlic^[59]. Chen *et al* compared the antidotal effects of dithiol compounds Na-DMPS, Na-DMS with BAL on the acute poisoning of bactericide 402 in mice. The LD₅₀ and LD₉₉ of bactericide 402 were found to be 118 and 198 mg/kg, Ig, respectively. Both Na-DMPS and Na-DMS had significant effects of ED₅₀ 214 and 212 mg/kg, respectively, while dimercaptol was less effective although it could delay the death of mice^[4]. When studying the different administration time and route, they discovered that, when Na-DMPS was mixed with bactericide 402, it had no more potent antidotal effect ($P < 0.01$)^[60]. This result suggests that Na-DMPS has chemical reactions with bactericide 402 and eliminates toxicity of the latter including alleviating the stimulation of bactericide 402 on stomach mucosa^[4]. An experiment with swelling on mouse ear showed that Na-DMPS had no antagonism against inflammation induced by xylene, but reduced the bactericide 402-induced inflammation, when used topically or intraperitoneally ($P < 0.01$). When Na-DMPS was mixed with bactericide 402, it also reduced the antibiotic effects of the latter on *Escherichia coli* and *Staphylococcus aureus*^[60]. When Na-DMPS was mixed with bactericide 402, chemical detection showed that the sulfhydryl groups disappeared, and the thin layer chromatography showed that a new spot formed, suggesting that Na-DMPS reacted with bactericide 402 to form a new chemical compound. The mechanism of Na-DMPS as an antidote against bactericide 402 is possibly contributed by its reaction with the latter thus protecting the sulfhydryl enzymes in normal cells^[60]. In the clinical treatment of the acute poisoning of bactericide 402, when Na-DMPS was used, the toxic symptoms disappeared quickly and the hospitalization duration was shortened^[61,62]. Yu *et al* reported a protocol with Na-DMPS in the treatment of

the acute poisoning of bactericide 402 in 8 children, with an emphasis on the importance in nursing^[63]. From the experiments on animals and clinical trials, the best protocol to cure the acute poisoning of bactericide 402 is parenteral or topical administration of 6.25 % Na-DMPS^[60].

ANTIDOTES AGAINST ACUTE POISONING OF TETRAMINE^[64,65]

History and present status The chemical name of tetramine is tetramethylenedisulphotetramine. In 1933, it was first synthesized by sulfamide and formaldehyde, and it is a potent rodenticide with neural toxicity. Its chemical component is stable. Tetramine is severely toxic and non-selective. In early 1990's, the Chinese government prohibited its production, sale and use. There are incidences of acute poisoning of tetramine one after another. Besides spotted incidences of acute poisoning due to suicide or mistaken ingestion, mass poisoning such as criminal sabotage sometimes also happened, with poisoned persons over one hundred^[66]. The causes of large-scale tetramine poisoning usually are sabotage and environment pollution. The tetramine poisoning causes the problem of public security. Previously, there is no specific antidote against the acute poisoning of tetramine, and the treatment usually is performed by heteropathy. The acute poisoning of tetramine has the following characteristics: rapid incidence, severe state of convulsion, speedy lethality, and high mortality. The poisoning attack often happens 0.5 to 2 h after ingestion. The respiratory failure is the primary cause of death of tetramine. The EEG change has some relationship with toxicity. The dynamic monitoring of EEG is an important indicator for judgment and instruction of treatment^[66]. The serologic examinations for liver functions and myocardial enzymes also reflect the toxic severity and damaging degrees of liver and heart, and are used to predict the prognosis^[67].

Pharmacologic and toxicologic studies Tetramine barely dissolves in water, slightly in acetone, and not in ethanol. It is stable in acidic and basic solutions. The saturated tetramine still keeps stable biological activity after five months of storage. It is absorbed through gastroenteric tract and respiratory tract. Tetramine stores in human body in its original form. No biological transformation of tetramine has been reported. Tetramine eliminates from urine via renal filtration. There

was a report that serum tetramine was still detectable 10 d after ingestion. LD₅₀ for the oral administration was 0.1–0.3 mg/kg in rats, and 0.1 mg/kg for men. The lethal dose for human is about 12 mg/kg. Due to the stability and severe toxicity, it easily leads to the second poisoning. The observation in animal experiments and human clinics shows that tetramine has severe neurotoxicity. But it is a stimulator of CNS, leading to convulsion and entasia. It has no effect on peripheral nervous system, skeletal muscle, and neuromuscular junction. Tetramine does not affect the parasympathetic systems in spleen, kidney, intestine, and bladder. Experiments on frog brain by damaging different brain region showed that the primary action site of tetramine was in brain stem. Removing cortex did not stop frog convulsion, while removing the region below medulla completely stopped its convulsive epilepsy^[68]. γ -Amino-butyric acid (GABA) is an inhibitory neurotransmitter in vertebrate and invertebrate animals. The convulsion caused by tetramine is related to its antagonism to GABA action^[69]. Roberts *et al* used ventral ganglions in isolated arthropod horseshoe crab to test seven convulsive agents against GABA's inhibition and found that the potency of tetramine was 2705 times weaker than that of picrotoxinin^[70]. Tetramine antagonized the depolarizing action of GABA to isolated rat jugular sympathetic ganglion, but it did not antagonize the action of carbachol. The action of tetramine against GABA is non-competitive and reversible but is not similar to the action of bicucullin^[71]. Tetramine dose-dependently antagonized the inhibition of GABA on crab neuromuscular transmission^[72]. Therefore, tetramine possibly also blocks GABA receptor or affects the receptor function by blocking amino acid channels^[73]. When concentrations of amino acids in the brain of the mouse that exposed to tetramine were measured, the concentration of GABA increased while that of glutamic acid decreased, suggesting that the levels of these amino acids are related to the convulsion caused by tetramine^[74]. Experiments with autoradiography showed that tetramine reduced the affinity of [³H]GABA with its receptors in rat brain sections of different regions, indicating that tetramine is the blocker of GABA receptor^[74].

Treatment protocols

Exterminate sources and heteropathy When exposed to tetramine by oral ingestion, stomach washing, diuretics, enemas, and catharsis should be used as soon as possible. Anticonvulsive agents can be used for heteropathy of the acute poisoning of tetramine.

Diazepam and sodium phenobarbital are the first choice as the anticonvulsive agents. For severe patients, both diazepam and sodium phenobarbital cannot control the convulsion. A combination of diazepam, sodium phenobarbital and sedatives can be used. For patients with convulsion and abnormal surge in EEG, sodium valerate is also suggested to take^[65].

Specific antidotes Experiments with six sulfhydryl agents as antidotes to treat the acute poisoning of tetramine were tested in tetramine-exposed mice^[75]. Na-DMPS and Na-DMS were that significantly decreased the number of convulsive animals, delayed the surge of convulsion, and reduced mortality ($P < 0.01$), and Na-DMPS was more desirable. The excitation of CNS by the toxicant was also reduced ($P < 0.01$). Na-DMPS showed excellent inhibition of tetanic convulsion on acute poisoning with tetramine in animals. In mice the LD₅₀ of ig tetramine was 0.262 mg/kg and LD₅₀ of ip Na-DMPS as antidote was 0.502 mg/kg ($P < 0.01$). Rats after using ip Na-DMPS 0.8 mg/kg showed the elongation of latent period of convulsion ($P < 0.01$) and lethal time ($P < 0.01$), reduce of convulsive time ($P < 0.01$) and decrease of mortality ($P < 0.05$). In Na-DMPS treated rabbits, latent period and lethal time were elongated. Icv administration of trace of Na-DMPS also reduced the mortality and the incidence of convulsion of acute poisoning in mice and the emergence of tetanic convulsion wave in rats^[76]. Satisfactory protective effect was found when Na-DMPS was given 20 min before poisoning ($P < 0.01$). Na-DMPS had no antidotal effect on tetramine-exposed mice when in mixture. Either Na-DMPS or diazepam could rise LD₅₀ of tetramine in mice and could reduce the convulsion and death rate of rats with acute tetramine poisoning. The combined administration of Na-DMPS and diazepam showed a better effect on antagonizing tetramine ($P < 0.01$). Electroencephalogram showed that Na-DMPS given ip 30 min before poisoning could inhibit the occurrence of tetanic convulsion wave, which could be dispelled by iv diazepam^[77]. Another combined therapy was studied about the antidotal effects of vitamin B₆ combined with Na-DMPS which turned out to be an excellent way for acute tetramine poisoning. They suggested that this may be used to clinical work to rescue patients poisoned by tetramine^[78]. A clinical trial compared Na-DMPS as an antidote in 11 patients with the acute poisoning of tetramine with regular heteropathy in 5 patients. It was found that Na-DMPS possessed unexpected effects and cured all 11 patients while 4 of 5

patients in heteropathy group died and the survivor suffered from memory damage^[5]. Another clinical trial observed Na-DMPS as antidote to treat 39 patients with the acute poisoning of tetramine (20 severe poisoned and 19 medium poisoned)^[79]. Initially, 0.125-0.25 g Na-DMPS was administrated intramuscularly. Based on the convulsion situation, 0.125 to 0.25 g Na-DMPS was repeated every 0.5 to 1 h until the convulsion was completely controlled^[79]. After the new discovery of Na-DMPS as an antidote used for acute poisoning by tetramine, a lot of physicians adopted Na-DMPS and mostly considered this antidote to be specific^[5,79,80], excellent, or more effective^[81-91]. But its precise effects still lack general recognition, even denied antidotal effects^[92,93]. It is necessary to do a large scale of clinical verification^[91]. Fu and Wei *et al* reported Na-DMPS with vitamin B₆ rescued patients poisoned by tetramine and were all alive^[94,95]. Zhang *et al* studied Na-DMPS on the antagonism of tetramine to GABA receptor on mice, used automatic analyzer to determine the contents of free GABA and glutamic acid in brain and used autoradiography to observe the [³H]GABA bindings in the rat brain slices. In conclusion, the inhibitory effects of Na-DMPS on the antagonism of tetramine to GABA receptor are due to the increase in the GABA binding to its receptor in brain^[74].

HOPE AND PROSPECTS

In animals, there are many SH-group compounds, such as the minor, SH amino acids and SH-peptides, and the major, SH-enzymes and SH-proteins, which form the rich SH-group pools related to the biological life. The chemical structure is the foundation of the substance. Its special physico-chemical properties enable the SH-groups to regulate the cellular function, and to transfer the cellular signals^[96]. In addition, it decreases the toxicants in body through special redox reactions. Because the SH-groups and ions of heavy metal or metalloid can form the more stable chelating complex compounds. The SH group compound has been used as the antidote for some metallurgical and chemical industrial toxicants. Since the early war times, it has become the clinical therapy in the toxic war gas. With the development of pharmacology, toxicology, and other related sciences, such as biochemistry and biophysics, *etc*, endogenic and exogenic SH compounds have been used as the specific antidotes, especially the Na-DMPS. Na-DMPS is an effective antidote against

NTXI, CDM, bactericide 402, and tetramine. Due to lack of specific antidotes for a lot of pesticides especially, of non-metallic pesticides, it is urgent for pharmacologists and toxicologists to develop and solidify their researches on the antidotes against these pesticides. In addition to its effectiveness in the detoxication of heavy metals and metalloids by chelating action, Na-DMPS is also a specific antidote for several non-metallic pesticides. With the recent advance of scientific knowledge about the mechanisms of action of Na-DMPS about antidotal effects against pesticides other than chelating action, they shall widen its application in other pesticides, either low or high molecular weight, either inorganic or organic compounds and either great use for insecticides or raticides. China is a large agricultural nation, and many cases of poisoning by pesticides have taken place, especially in village. In recent years, it spreads to cities and affect social stability severely. For example there were more than 300 people poisoned and 42 died during the tetramine criminality in Nanjing city on 2002 Sep 14. Chinese researchers carried out the study on Na-DMPS for intoxication of pesticides and have found it has specific antidotal effect on many kinds of non-metallic pesticides. Great break through has been made not only in theory but also in practice and the research reaches international advanced level. These findings have been collected in the "Practic Internal Medicine", 11th ed^[97]. The developing which has been talked in the preface can meet the requirements of different clinical doctors. Chinese's finding that Na-DMPS can be used as specific antidote against tetramine and NTXI, has been edited by Ding Quan-Fu in "Pharmacology" 4th ed, normal textbook in the technical college of medical university^[98]. More than 10 years ago Na-DMPS was adopted as antidote of SCS in the experimental textbook in Wenzhou Medical College and got very satisfactory results, which provided new antidotal knowledge and development for the doctors and medical students (personal communication). On the other hand, Na-DMPS can strengthen its antidotal effect against acute tetramine poisoning when combined with diazepam or vitamin B₆, through the experimental researching and clinical observation. For example, atropine sulfate combined with pralidoxime chloride is the routine best choice, which is a combination of symptomatic therapy and causative therapy when treating the acute poisoning by organophosphorus insecticides. In poisoning by toxicants, the combined therapy is often used and has both theoretical and practical

significances. Chen XY *et al* has recently reported Na-DMPS has protective effect against neuronal damage following ischemia and reperfusion in the rat brain^[99]. Na-DMPS, as an exogenous dithiol compound icv significantly increased the latencies and decreased the number of errors in cerebral ischemia reperfused mice. Meanwhile, Na-DMPS icv was found to be able to prevent the rise of malondialdehyde level induced by this experiment^[100]. Sulfhydryl group compounds also have regulating actions to neuronal transmitters^[101]. To explore the relationship between Na-DMPS and neurotransmitters or receptors will get brilliant achievement in neuropharmacology and neurotoxicology as against convulsion induced by tetramine and other central convulsants^[73,74,102].

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