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Tetrathiomolybdate(VI) as an Antidote in Acute Intoxication by Copper(II) and Other Toxic Metal Ions

STUART H. LAURIE*

School of Chemistry, Leicester Polytechnic, P.O. Box 143, Leicester, LE1 9BH, U.K.

MARK A. BASINGER and MARK M. JONES*

Department of Chemistry and Center in Toxicology, Vanderbilt University, Nashville, Tenn. 37235, U.S.A.

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Tetrathiomolybdate(VI), MoS_4^{2-}, has been found to act as an effective antidote for acute copper(II) intoxication in mice. Both $(NH_4)_2MoS_4$ and Na_2MoS_4 were used for this purpose with approximately the same results. The sodium salt is less toxic (LD50 = 537 mg/kg, ip) than the ammonium salt (LD50 = 176mg/kg, ip). The sodium salt was found to be an effective antidote for acute intoxication for some divalent metal ions (Zn^{2+} and Ni^{2+}), but not for others (Hg^{2+}, Cd^{2+}). The sodium salt was also ineffective as an antidote in acute intoxication by arsenic(III), antimony(III) and bismuth(III), and methylmercuric chloride.

Introduction

The simple thioanions have been recognised as species capable of acting as the donor group in coordination compounds for many years [1]. There is also ample evidence [2–6] that the thiomolybdate anions are the reactive intermediates in the molybdenum-induced copper deficiency that can afflict ruminants. Many of the clinical defects observed in these ruminants can also be induced in monogastric animals by feeding them thiomolybdate salts [7]. The primary effect on copper metabolism appears to be an inhibition of copper absorption [4, 5, 8].

There has only been one report to our knowledge in which a thiomolybdate salt has been used to treat copper toxicity [9]. This can be attributed to the known toxicity of these compounds and to their lack of availability to biological investigators. The present study was undertaken to examine the potential utility of one of these species, tetrathiomolybdate(VI), as a chelate antidote for a few types of acute metal ion intoxication. For the initial studies, the ammonium salt, $(NH_4)_2MoS_4$ was used; subsequently it was realized that the corresponding sodium salt was less toxic and could be administered at a significantly higher level.

Experimental

$(NH_4)_2MoS_4$ was prepared as previously described by Mellor [10] Na_2MoS_4 was obtained from ICN pharmaceuticals Inc. Plainview, New York, and used without further purification.

The experiments were performed on male, ICR mice, weighing 32 ± 3 g (Harlan Industries, Indianapolis, IN). The animals were allowed to acclimatise for a four day period after arrival before experimental use. Food (Wayne's Lablox) and tap water were allowed *ad libitum*. For the LD50 determinations four groups of five animals each were used. For the survival ratios the animals used in each experiment are given by the denominator in the fraction given in the survival ratio column of Table II.

Solutions were prepared and administered in deionized water. Solution concentrations were prepared such that 0.1 cm^3 was administered for each 30 g body weight for all compounds except for $(NH_4)_2MoS_4$ which was prepared so that each animal received 0.2 cm^3 per 30 g body weight. Injections were given intraperitoneally (ip) with both injections being given at approximately the same site. Antidote injections were administered twenty minutes after the toxic metal dose. The animals were observed for a two week period after the injections.

*Authors to whom correspondence should be addressed.

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TABLE I. LD50 Measurements: Calculations Made Using the Method of Weil and Thompson [11].

Compound	LD50	95% Confidence Range
$(NH_4)_2MoS_4$	176 mg/kg	133–233 mg/kg
Na_2MoS_4	537 mg/kg	502–574 mg/kg

Results

The results of the LD50 determinations are shown in Table I, and those from the tests of the efficacy of the tetrathiomolybdate as an antidote for acute intoxication by various metal salts are presented in Table II.

Discussion

Although polyatomic anions have been used as chelating agents by inorganic chemists for many years, they have previously been largely ignored as potentially useful agents in the therapy of metal intoxication. The data presented in Table II show that tetrathiomolybdate, under the conditions used has an antidotal action in acute intoxication by Cu^{2+}, Ni^{2+} and Zn^{2+}. These results do not necessarily provide any information on the effect of tetrathiomolybdate on the rate of excretion of the other toxic metals examined. For the tetrathiomolybdate to act as an antidote in *acute* intoxication it must react very rapidly with the toxic metal involved. Thus this compound will not be expected to be an effective antidote in any case where its reaction to replace the ligand groups already on the toxic species is slow in comparison with the rate of action of the toxic species on sensitive biological sites.

The efficacy of the MoS_4^{2-} species in some of the cases examined here immediately suggests that related inorganic species such as WS_4^{2-}, the various thiophosphates, and some of the less toxic thio substituted 'oxyanions' might well show analogous behavior. None of the experiments reported

TABLE II. Survival Ratios for Animals Receiving Tetrathiomolybdate Twenty Minutes after the Indicated Compound. All Injections were administered Intraperitoneally Unless Otherwise Indicated.

Metal Compound	Dose Given mg/kg	LD50 of Compound Given mg/kg [Reference]	Survivals/ Total
(Antidote: Na_2MoS_4 at 100 mg/kg)			
$NaAsO_2$ (subcutaneously)	18.2	16.80(12)	0/5
$CdCl_2 \cdot 2.5H_2O$	7	7.00(13)	1/5
$CdCl_2 \cdot 2.5H_2O$	10	7.00(13)	2/5
$CuSO_4$	10	8.71(14)	6/10
CH_3HgCl	12	10.00(15)	1/5
$HgCl_2$	7	6.70(16)	0/5
$HgCl_2$	10	6.70(16)	1/5
$Ni(C_2H_3O_2)_2 \cdot 4H_2O$	62	45.70(17)	7/10
$Zn(C_2H_3O_2)_2$	50	36.10(18)	7/10
$K(SbO)C_4H_4O_6 \cdot \frac{1}{2}H_2O$	120	54.60(19)	0/5
$Bi(NO_3)_3 \cdot 5H_2O$	125	70.60(20)	1/5
(Antidote: Na_2MoS_4 at 200 mg/kg)			
$CuSO_4$	10	8.71(14)	6/10
(Antidote: $(NH_4)_2MoS_4$ at 100 mg/kg)			
$CdCl_2 \cdot 2.5H_2O$	7	7.00(13)	1/5
$CdCl_2 \cdot 2.5H_2O$	10	7.00(13)	2/5
$CuSO_4$	10	8.71(14)	5/10
$HgCl_2$	7	6.70(16)	0/5
$HgCl_2$	10	6.70(16)	1/5

here bear on the mechanism by which tetrathiomolybdate produces an increase in the survival rate. As a result, it is not possible to distinguish between the three principal possibilities: enhanced urinary excretion of the toxic metal, enhanced fecal excretion of the toxic metal or immobilization of the toxic metal as an insoluble sulfide.

The fact that the sodium salt is significantly less toxic than the ammonium salt is in accord with the known relative toxicities of these two ions and their effects on the regulation of blood levels of ammonium ion by the kidney.

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