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Comparative assessment of the effects of salinomycin and monensin on the biodistribution of lead and some essential metal ions in mice, subjected to subacute lead intoxication

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ABSTRACT

In this study, we present a comparative assessment of the effects of two polyether ionophorous antibiotics (monensin and salinomycin) on the concentrations of lead (Pb), cooper (Cu), zinc (Zn) and iron (Fe) in the kidneys, spleen, liver and brain of Pb-intoxicated animals. Our data demonstrated that the intoxication of ICR male mice with Pb salt resulted in a significant accumulation of Pb in all studied organs of the mice compared to the untreated control animals. The biodistribution of the toxic metal was in the order kidneys > spleen > liver > brain. The treatment of the Pb-intoxicated animals with tetraethylammonium salts of monensic and salinomycinic acids significantly decreased the concentration of the toxic metal ion compared to the toxic control. The effect varied in the interval 38% (for kidneys) to 52% (for brain) compared to the toxic control group (Pb). The tetraethylammonium salt of salinomycinic acid was more effective in reducing the Pb concentration in the brain of the Pb-treated mice compared to monensin. Pb-intoxication did not affect significantly the Zn endogenous concentration compared to the normal values. The treatment of ICR male mice with Pb-salt decreased the Cu concentration in the spleen and increased the Cu concentration in the liver compared to the untreated control animals. The detoxification of the Pb-intoxicated mice with tetraethylammonium salts of salinomycinic and monensic acids restored the Cu concentration in the spleen, but did not affect the Cu levels in the liver. The Pb-intoxication of the ICR mice resulted in a significant decrease of the Fe-concentration in the spleen and liver compared to the untreated control animals. The administration of the tetraethylammonium salts of salinomycinic and monensic acids to the Pb-treated animals restored the levels of Fe in both organs.

1. Introduction

Lead (Pb) exposure is a major health problem in both developed and developing countries [1–4]. Pb affects the function of many organs in particular spleen, liver, kidneys and brain [3]. The nervous system is most sensitive for Pb-induced toxicity [5–8]. Pb disturbs also the function of hematopoetic system [9]. This toxic metal mimics the biochemistry of calcium and other divalent biometal ions, which has been considered as primary mechanism for Pb-induced toxicity [10]. It has been established that there is no safe level of exposure to Pb. Chronic toxicity occurs at blood levels of 40–60 μg/dL and if not treated in time results in persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma [11].

DMSA (2,3-dimercaptosuccinic acid) is a chelating agent approved by FDA for the treatment of Pb intoxications. Studies on animals and humans, however, demonstrate that DMSA preferentially mobilizes soft tissue Pb whereas bone lead deposit appears unaffected [12]. Furthermore, higher losses of copper in humans are observed when this chelating agent is administered for the treatment of Pb toxicity [13]. Recently, it has been found that monensin is much more effective than the traditional chelating agent DMSA and its analogues in reducing Pb concentration in rats, subjected to Pb intoxication [4,14]. Among the polyether ionopohorous antibi-

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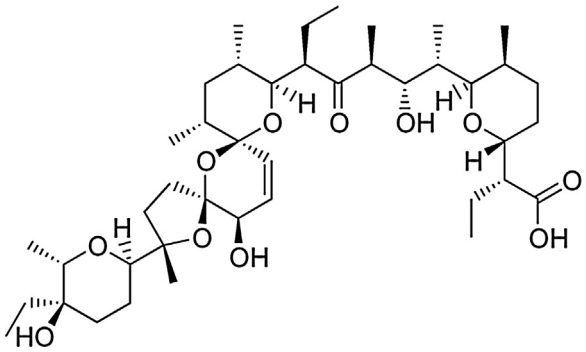
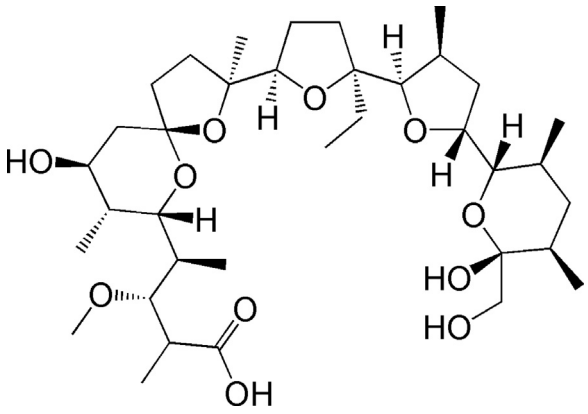


Scheme 1. Structure of Salinomycinic acid (SalH).



Scheme 2. Structure of Monensic acid (MonH).

otic salinomycin is the least toxic representative [15]. Furthermore, this antibiotic is a promising novel anticancer agent as summarized in [16]. To the best of our knowledge there is still no information regarding the potential application of salinomycin as a chelating agent for the treatment of toxic metal intoxication.

Herein, we compare for the first time the effects of tetraethylammonium salts of monensic and salinomycinic acids on Pb content and the endogenous levels of copper, zinc and iron in tissues of mice, subjected to subacute Pb intoxication.

2. Materials and methods

2.1. Chemicals

The sodium salts of monensin and salinomycin were obtained from Biovet Ltd. (Peshtera, Bulgaria). Tetraethylammonium hydroxide (Et_4NOH), nitric acid (HNO_3), lead nitrate ($Pb(NO_3)_2$) and diethyl ether (Et_2O) were purchased from Merck (Darmstadt, Germany).

2.2. Preparation of monensic and salinomycinic acids

Monensic acid A monohydrate (Scheme 1) and Salinomycinic acid (Scheme 2) were prepared from sodium monensin and sodium salinomycin as reported previously [17–19]. Details of the purity and spectral characteristics of both compounds are presented in [18,19].

2.3. Experimental design

Sixty-day-old adult male imprinting control region (ICR) mice, weighting 25–30 g were obtained from the animal care unit, Slivnica, Bulgaria. The animals were housed at the Institute of Experimental Morphology, Pathology and Anthropology, Bulgarian Academy of Sciences (BAS) and were maintained at 23 °C under controlled light/dark cycle (12:12 h) in individual, standard hard-bottomed polypropylene cages. The animals were allowed to acclimate for one week prior to dosing. Twenty mice were randomized into four groups of five mice each as follows.

The first group served as untreated control group. The animals from this group were maintained on *ad libitum* standard pellet diet and water (distilled) during the experimental protocol.

The second group animals (toxic control) was exposed to $Pb(NO_3)_2$ (80 mg/kg body weight) through drinking (distilled) water once daily for two weeks. During the next 14 days of the experiment, the animals from this group were allowed to drink distilled water and food *ad libitum*.

The third group (monensin-treated mice) was subjected to intoxication with $Pb(NO_3)_2$. The compound was obtained in distilled water once daily for two weeks in a dose of 80 mg/kg body weight. The animals from this group were treated with tetraethylammonium salt of monensic acid (20 mg/kg body weight in distilled water) from the 15th to the 28th days of the experimental protocol.

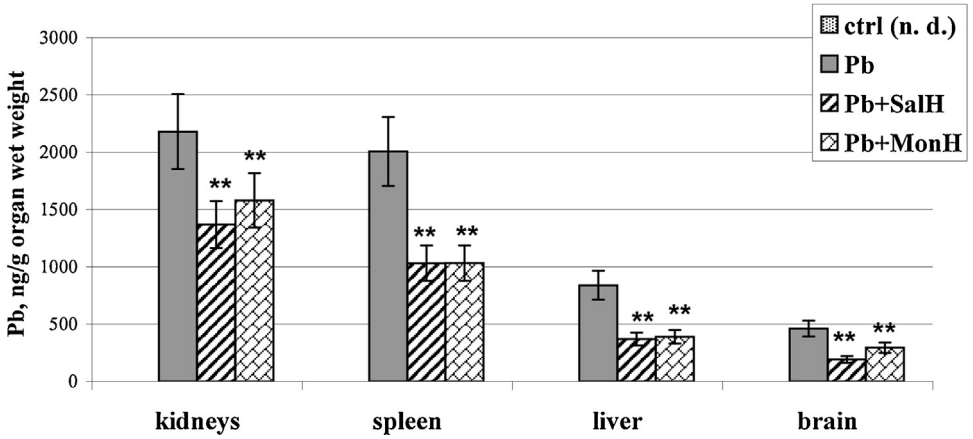


Fig. 1. Effects of tetaethylammonium salts of monensic and salinomycinic acids on the concentration of Pb in kidneys, spleen, liver, and brain of experimental mice subjected to subacute Pb intoxication. Legend – ctrl (n.d.): no detectable Pb concentration in the organs of untreated control mice. Pb: Pb concentration in organs of Pb-treated mice. Pb + Mon: Pb concentration in organs of Pb-intoxicated mice, subjected to treatment with tetraethylammonium salt of monensic acid. Pb + Sal: Pb concentration in organs of Pb-intoxicated mice, subjected to treatment with tetraethylammonium salt of salinomycinic acid. Each column represents mean ± SD, $n = 5$; double asterisk (**) indicates the significant difference between the monensin-treated group or salinomycin-treated group and Pb-treated controls ($p < 0.05$).