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The Dynamic of Methemoglobinemia Induced by Sodium Nitrite and its Reduction after Methylene Blue Administration in Sheep

KEYWORDS: methemoglobinemia, sodium nitrite, methylene blue, poisoning, sheep

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ABSTRACT *The aim of the study was to determinate the speed of methemoglobin formation after administering of sodium nitrite in sheep, on intervals starting with the moment prior the administration, and 15, 30, 45, 60, 75, 90, 105 and 120 minutes after ingesting the toxic substance. Also, the speed of methemoglobin reduction was studied, after intravenous injection of methylene blue - as an antidote. In the first 60 minutes after ingestion of the toxic substance was registered a significantly increasing of speed Met-Hb formation (when the average of the methemoglobin levels reach a peak of 21.95 mg/kg), followed by a decreasing (also significant) of the average value of 6.62 mg/kg, after 120 minutes. After methylene blue administration, as antidote (8-9 mg/kg, repeated at every 6-8 hours), in sodium nitrate poisoning in sheep, we have observed an obvious decreasing of the methemoglobin values even after 5 minutes.*

INTRODUCTION

A high priority in the veterinary medicine pathology are the toxic-metabolic involvement of the fertilizers, in inducing clinical and subclinical methemoglobinemia in animals, beside the identification of the nitrates residues in vegetables products and derivate, correlated with the clinical poisoning or/and the toxic effects on long terms, in human and animals (3,6).

The development, the diversification and the intensification of the agriculture in all their fields of activity induce new veterinary directions in the animal husbandry and also become compulsory the intimate knowing of the toxic mechanisms of different substances (fertilizers, pesticides) and drugs, including the advantages and the disadvantages of using them. Many chemical compounds are able to convert the normal hemoglobin into methemoglobin (Met-Hb). Most of the toxic met-hemoglobin inducing agents are included in the list of the substances used in agriculture or in different technological processes (2, 4). The toxic compounds which are well-known as methemoglobin inducing agents (after bivalent iron oxidization of the hemoglobin), are reducing the functional content of hemoglobin from the blood. So, the methemoglobin, as a product of hemoglobin oxidation, loses the capacity of coupling and transporting the oxygen to the tissues level (7, 12). When a small amount/percent of hemoglobin (0,5-2%) is converted in methemoglobin (as a pathological hemoglobin), by the presence of different endo/exotoxic methemoglobin inducing agents, is reconverted back to hemoglobin inside of the red blood cells (through the action of the compensatory reducing systems from the body).

MATERIALS AND METHODS

To study the rate of methemoglobin inducing and its speed of reduction, after intravenous injection of methyl blue - as an antidote (1, 5, 14), were performed an experimental intoxication with sodium nitrite in sheep, The speed of methemoglobin formation in intoxicated animals, was determined on intervals starting with the moment prior the administration and 15, 30, 45, 60, 75, 90, 105 and 120 minutes after ingesting the toxic susbstance (in dose of 25 mg/kg).

It is estimated that the lethal doses for sodium nitrite (Natrii nitris) are 0, 1-0, 5 g/kg in sheep (5).

For evaluation of the rate (the speed) of methaemoglobinaemia reducing, we have given to several individuals in each experimental batch, methylene blue - as an antidote - followed by determining the Met-Hb values after 5, 10, 15, 20 and 25 minutes after antidote administration.

The antidote, methylene blue, is recommended at a dose of 8-9 mg/kg, administered intravenously, every 6-8 hours (10).

The poisoning evolution was followed by clinical examination, laboratory investigations (hemoglobin and methemoglobin) were performed on collected blood samples (8, 11, 13).

The results were statistically processed, obtaining the average and the standard error of the average (X±Sx). For statistical signification assignment, the differences between groups were compared through Student Test.

RESULTS

The poisoning evolution was followed by clinical examination of animals and laboratory determinations performed on collected blood samples (hemoglobin determination and Met-Hb).

Following experimental intoxication with sodium nitrite in sheep, was registered a distinct increasing of the methemoglobine average, in correlation with an obvious worsening of the clinical signs, correlated with the administration of sodium nitrite.

In the first 60 minutes after ingestion of the toxic substance (when the average of the methemoglobine levels reach a peak of 21.95 mg/kg) was registered a highly significant ($p<0,01$) increasing of speed Met-Hb formation, followed by a decreasing (also statistically significant) of the average value of 6.62 mg/kg, after 120 minutes (Table 1, Chart 1).

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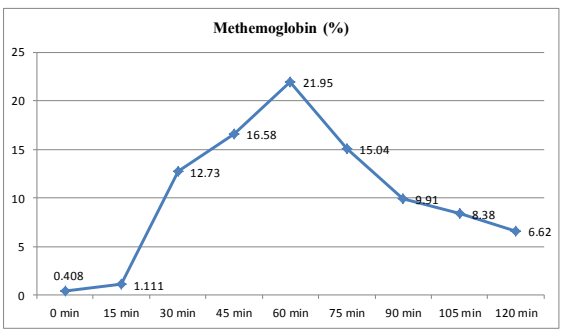
Table 1. The values of the blood methemoglobin after the administration of sodium nitrite

Specification	N1	N2	N3	N4	N5	N6	N7	N8	N9
Minutes after administration of sodium nitrite	0	15	30	45	60	75	90	105	120
MetHb (%)	0.408	1.111	12.73	16.58	21.95	15.04	9.91	8.38	6.62
P (difference signification)		P<0.05	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01

P<0.05 - significant differences, P<0.01- highly significant differences

Chart 1. The dynamic (speed) of the blood methemoglobin induction after administration of sodium nitrite



Methylene blue is considered the antidote of election in case of poisoning with methemoglobin inducing substances (2, 14). This substance is incompatible with oxidizing and reducing compounds. In the body has a high reactivity towards both reducing and oxidizing substances, which affects the oxidation-reducing processes in tissues. If the cellular respiration stops, this can replace the function of the respiratory enzyme.

Through his specific action (converting the methemoglobin in hemoglobin), the methylene blue is the substance most commonly used by practitioners in different states of methemoglobinemia.

Methemoglobin reduction under the action of methylene blue is potentiated by the presence and action of Met-Hb-reductase II (12).

The recommended dose of methylene blue is 8-9 mg/kg, by intravenous administration, repeated at every 6-8 hours. Was administered the recommended dose and concentration (1%), in normal saline solution (0,9%).

The reducing action of methylene blue is very fast, which is why it is recommended by specialists in severe and medium methemoglobinemia (10, 14).

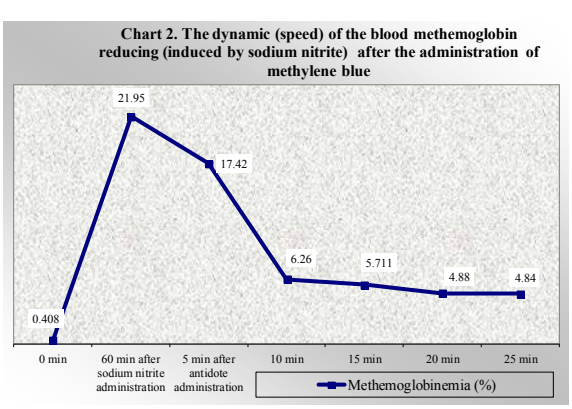
Table 2. The average values of the blood methemoglobin (induced by sodium nitrite) after methylene blue administration

Specification	N1	N2		N3	N4	N5	N6	N7
Minutes after administration of sodium nitrite	0	60	Minutes after administration of methylene blue	5	10	15	20	25
MetHb (%)	0.408	21.95		17.42	6.26	5.71	4.88	4.84
P (difference signification)		P<0.01		P<0.05	P<0.01	P<0.01	P<0.01	P<0.01

P<0.05 - significant differences, P<0.01- highly significant differences

Thus, following the administration of methylene blue as an antidote, in sodium nitrite poisoning in sheep we have observed an obvious decreasing of the methemoglobin values, even after 5 minutes as a result of the antidote administration (Table 2, Chart 2).

Was registered a decreasing of the methemoglobinemia average from 21.95 mg/kg to 4.84 mg/kg, after 25 minutes after administration of methylene blue.



On this idea it is important to notice the restrained information in this area of interest, especial for the farmers, and the luck of a national specialized system of information concerning the eco-toxicological impact of the methemoglobin inducing pollutant substances to the human and animal health, correlated with the luck of possibilities of rapid way of acting in such cases of toxicological injuries, require an imperative solution for reducing the pollution degree of vegetables and drinking water and also for synthesizing and ruling out a national system of information about methemoglobinemia and methemoglobin inducing compounds, integrated subsequently in European centralized specialty information systems.

CONCLUSIONS

Our studies were based on experimental inducing of some methemoglobin inducing substances (poisons) in livestock (sheep). In these animals, poisoning with such substances may result very often from improper dosage of substances used as fertilizers in agriculture (sodium nitrite) or as incidental oral poisoning.

Was performed an experimental poisoning with sodium nitrite in sheep, after sodium nitrite administration and was determinate the speed of methemoglobinemia formation and reduction, after intravenous injection of an antidote (methylene blue) administration.

Following experimental intoxication with sodium nitrite,

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was registered increased levels of methemoglobinemia, 21, 95%, after 60 minutes (statistically significant).

Following administration of methylene blue as antidote in sodium nitrate poisoning in sheep, it was observed a highly significant decrease of methemoglobinemia values, even after 5 minutes of antidote administration. After 25 minutes from the methyl blue administration, is observed a decrease of methemoglobinemia average, to 4.84 mg/kg.

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