# Acta Medica Okayama

Volume 30, Issue 1

1976 February 1976 Article 5

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# Methemoglobinemia induced by chlorphenamidine\*

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### Abstract

A 76-year old farmer ingested 100 g of chlorphenamidine (Galectron), a plant acaricle, for the purpose of suicide. Gastric lavage was performed and the patient survived. Methemoglobinemia was noted after emergency treatment and was still present at 20 hours after ingestion of the compound. The patient was lethargic for at least 50 hours. Moderate neutrophilic leukocytosis and kidney injury were observed.

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Acta Med. Okayama 30, 57-60 (1976)

## METHEMOGLOBINEMIA INDUCED BY CHLOR-PHENAMIDINE

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Abstract: A 76-year old farmer ingested 100g of chlorphenamidine (Galecron®), a plant acaricide, for the purpose of suicide. Gastric lavage was performed and the patient survived. Methemoglobinemia was noted after emergency treatment and was still present at 20 hours after ingestion of the compound. The patient was lethargic for at least 50 hours. Moderate neutrophilic leukocytosis and kidney injury were observed.

Chlorphenamidine [Galecron® CIBA Agrochemical Co.; N'(4-chloro-o-tolyl)-N, N-dimethylformamidine] is a systemic acaricide with destructive capacity for many mite species (1). Its oral lethal dose is 340 mg/kg in rats and 290 mg/kg in mice (2). Toxic studies of this agent in man have not been conducted (2). Although aniline derivatives are known to produce methemo-globinemia in man (4), it is not certain whether orally administered chlophe-namidine induces methemoglobinemia in animals or man (1, 2, 3). The present paper describes a case of methemoglobinemia in man induced by oral administration of chlorphenamidine.

#### CASE REPORT

On December 19, 1971, at 10:30 p. m., a 76-year old farmer was brought to the emergency unit of the Mitoyo General Hospital. Information obtained from his family indicated that the patient took about 100 g of chlorphenamidine at 9:20 p. m. for the purpose of suicide. The family called their physician and the patient was brought to the hospital. He vomited several times in transit. Shortly after arrival, gastric lavage was performed with 3 liters of saline.

At admission, the patient was in acute distress and lethargic. The blood pressure was 100/62 mm Hg, pulse rate 84/min, respiratory rate 20/min and temperature 36.4°C. The optic fundi were normal aside from arteriolar narrowing. The neck was supple. The chest was clear to percussion and auscultation. Cardiac murmurs were absent. The liver span was normal by

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percussion. There was no peripheral edema. Cyanosis was noted on the lips, nails and skin. The peripheral pulse was moderately weak. The cranial nerves were intact. Generalized muscular weakness was present. The reflexes were symmetrical.

The initial laboratory tests included a hemoglobin level of 12.0 g/100 mland a white blood cell count of  $15,700/\text{mm}^3$  with 80% segmented neutrophils, 8% band forms and 12% lymphocytes. Serum analyses indicated: sodium, 120 meq/liter; potassium, 36 meq/liter; calcium, 4.5 meq/liter; chloride, 91 meq/liter; urea nitrogen, 15 mg/100 ml; cholesterol, 110 mg/100ml; and glucose, 110 mg/100 ml. An electrocardiogram indicated an old antero-septal infarct. On hospital day 2, the urine was dark brown and urinalysis indicated minimum microhematuria, moderate proteinuria and an absence of glucosuria.

The peripheral cyanosis observed on admisson was of unusual brownish purple color. Five hours later, the methemoglobin concentration in the blood was determined by the method of Evelyn and Malloy (5) to be 17% of total hemoglobin. The methemoglobin concentration was in the normal range in the subsequent two days (Fig. 1). Laboratory examinations performed on the



Fig. 1. Time course of methemoglobin concentration in blood.

second hospital day that were normal or negative included: total serum protein, serum bilirubin, S-GPT, alkaline phosphatase, cholinesterase, lactic dehydrogenase, amylase, fibrinogen, prothrombin time, C-reactive protein,

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anti-streptolysin-0 titer and rheumatic factor. His consciousness was completely recovered at about 50 hours after admission, but he complained of headache and blurred vision. On day 5, urinalysis became negative and he recovered to his previous behavioral state.

The presence of methemoglobinemia was confirmed by measuring the absorption curve of hemolysed blood (Fig. 2). The urine absorption curve showed an abnormal shoulder at around 450 nm (Fig. 3) compared to the normal curve.



Fig. 2. Absorption curves of hemolysed blood on the first hospital day.



Fig. 3. Absorption curves of urine collected on the second hospital day.

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#### DISCUSSION

This case may be the first report of methemoglobinemia in man induced by chlorphenamidine. In rats 72 hours after oral chlorphenamidine administration, 96% of the administered dose was accounted for in the urine and feces (1). In dogs and goats, orally administered chlorphenamidine was rapidly absorbed, metabolised and excreted (3). In the latter study, chlorphenamidine, N'-(4-chloro-o-tolyl)-N-methylformamidine, N-formyl-4-chloroo-toluidine, 5-chloroanthranilic acid and N-formyl-5-chloroanthranilic acid along with several unknown metabolites were detected in urine in both free and conjugated form (3).

A number of aromatic compounds, such as aromatic amino acids, aniline dyes, acetanilid, phenacetin, aminophenol, nitrobenzene and trinitrotoluene are capable of oxidizing hemoglobin indirectly (4). Most of these compounds do not form methemoglobin *in vitro* and are assumed to form methemoglobin as a result of conversion to some extremely active intermediate compounds (4). As described earlier the metabolites of chlorphenamidine in dogs and goats were all aniline derivatives (3). These metabolites therefore are probably capable of methemoglobinemia in man. In addition to methemoglobinemia, chlorphenamedine produced a moderate neutrophilic leukocytosis and minimum microhematuria with moderate proteinuria but did not appear to damage the liver function of this patient.

Acknowledgment: The authors wish to express their appreciation to Dr. K. Kosaka for his guidance and to Mr. T. Oukura, Mrs. T. Tsuchida and Mr. Y. Ishii for their technical assistance.

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