Arq Neuropsiquiatr 2001;59(3-A):596-598

FATAL RHABDOMYOLYSIS AFTER ACUTE SODIUM MONENSIN (RUMENSIN®) TOXICITY

Case report

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ABSTRACT - Myoglobinuria or rhabdomyolysis occurs when myoglobin escapes into the blood and then into the urine after acute muscle necrosis. It can be a serious medical condition leading to renal failure and death. There are many causes including exertion, crush syndromes, ischaemia, metabolic disorders, exogenous toxins and drugs, heat stroke and hereditary disorders such as malignant hyperthermia. We report the case of a 17 year-old boy who developed myoglobinuria, renal failure and death 11 days after ingesting sodium monensin, possibly with the intention of developing muscles. Sodium monensin, the active principle of Rumensin®, is a dietary additive used as a growth promoter for confined cattle. There are no previous reports of human intoxication. Accidental or experimental sodium monensin intoxication in animals produces similar findings to those seen in this case.

KEY WORDS: rhabdomyolysis, myoglobinuria, sodium monensin intoxication, muscle necrosis.

Rabdomiólise fatal aguda pós-intoxicação por monensina sódica (Rumensin®): relato de caso

RESUMO - Mioglobinúria ou rabdomiólise refere-se a necrose muscular aguda com liberação de mioglobina na circulação e na urina podendo causar, na sua forma mais grave, insuficiência renal e óbito. A etiologia é ampla, incluindo exercício intenso, síndrome do esmagamento, isquemia, toxinas exógenas, anormalidades metabólicas, medicações, altas temperaturas, além de algumas condições herdadas como hipertermia maligna. Neste relato descreve-se o caso de um paciente jovem, do sexo masculino, que desenvolveu mioglobinúria, insuficiência renal e óbito, 11 dias após ingestão de monensina sódica, princípio ativo de Rumensin®, usado como aditivo alimentar para gado confinado; a ingestão possivelmente foi feita para desenvolvimento muscular. Não há relato na literatura de intoxicação humana e o quadro clínico nos animais com intoxicação experimental ou acidental pelo Rumensin® se assemelha àquele observado no presente caso.

PALAVRAS-CHAVE: rabdomiólise, mioglobinúria, intoxicação por monensina sódica, necrose muscular.

Myoglobinuria or its official term on *Index Medicus*, rhabdomyolysis, occurs when myoglobin escapes into the blood and then into the urine after acute muscle necrosis[1]. There is a whole list of causes, including hereditary syndromes such as malignant hyperthimia, exertion, crush syndromes, ischaemia, metabolic disorders, exogenous toxins and drugs, heat stroke and undefined[1]. It seems that at the cellular level, an essential role is played by an excessively high intracytoplasmatic calcium level, which affects metabolic processes. The main symptoms are muscular weakness, myalgia, malaise and fever. Laboratory tests reveal high level of serum enzymes CK, GOT, GPT, aldolase and LDH. The urine is dark brown. Demonstration of high serum myoglobin level or its presence in urine confirms development of rhabdomyolysis. In unfavorable conditions, rhabdomyolysis may result in acute renal failure, the main hazard of the syndrome[1,2].

Sodium monensin, the active principle of Rumensin® (trademark for Elanco's brand), is a dietary additive used as a growth promoter for confined cattle. This product revolutionized the production of beef cattle after it was introduced in 1975. It is the most widely used product of its type in cattle fed in the United States. When mixed into the feed of beef and dairy cattle, it greatly improves the ability of the animals to utilize the nutrition. The animals grow faster

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Received 30 January 2001, received in final form 24 March 2001. Accepted 28 March 2001.

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on less feed, resulting in lower-cost beef. At the same time, Rumensin® also prevents and controls a serious disease of cattle, coccidiosis.

One of the most striking findings on experimental or acidental sodium monensin intoxication in animals[3-9] is muscle necrosis. There are no reports of human intoxication (Medline till 2000) and, to our knowledge, this is the first report in the literature of fatal rhabdomyolysis after Rumensin® ingestion.

CASE

A 17-year-old Caucasian boy, a cattle breeding worker, was admitted to the neurological ward of the Medical School Hospital (Hospital de Base, registration number 1104433) on August 22, 2000, with a history of ingestion of an undetermined amount of Rumensin® (sodium monensin). The reason for ingestion is uncertain but he may have hoped to develop muscles. He only admitted to the ingestion 6-7 days after admission. On August 17, 2000, he presented to the emergency room at the local small hospital near the farm with sickness, nausea and abdominal pain that were treated symptomatically with dipyrone, metoclopramide hydrochloride and furosemide. Two days later there were weakness and severe muscular pain mainly in the lower limbs and a dark brown colored urine was observed, followed by tachycardia, sudoresis and drowsiness. On the fifth day (August 22, 2000), he was removed to the Medical School Hospital, Neurology Department, Neuromuscular Division. On admission blood pressure was normal, he was febrile (38°C), had mild edema of the lower limbs and pain on muscular palpation. There were no focal signs on neurological examination, the reflexes were diffusely absent, he was fully conscious and orientated and cranial nerves were normal. Severe muscular pain restricted normal lower limb movements.

On laboratory testing at admission, serum creatine kinase (CK) was 233,200 U/L (normal < 80 U/L); lactate dehydrogenase was 13,100 U/L (normal 240 - 480 U/L); glutamic oxalacetic transaminase was 8,970 U/L (normal 10 - 50 U/L); glutamic pyruvic transaminase was 2,166 U/L (normal 10 - 50 U/L); creatinine was 2.0 mg/dL (normal 0.2 – 1.4 mg/dL); potassium was 5.2 mEq/L (normal 3.5 - 4.5 mEq/L); sodium was 133 mEq/L (normal 135 - 145 mEq/L); haemogram revealed leukocytosis (17,800) and erythrocyte sedimentation rate was 50 mm (normal 3 - 7 mm, first hour). Serum calcium, glycemia, coagulation tests (platelets, prothrombin and thromboplastin time), amylase, bilirubin, serum albumin and globulin proteins, alkaline phosphatase and magnesium were normal; chest X-ray was normal; serum was negative for brucellosis, hepatitis A/B/C and HIV.

Over the next few days he developed acute renal failure and was hemodialysed but suffered pulmonary congestion and died on August 28, 2000. The CK levels decreased from 233,200 U/L on August 22, to 56,650 U/L on August 28.

The histochemistry staining of the *Deltoideus,* using H&E, Gomori, PAS, NADH, SDH, ATP-ase (pH 9.4, 4.63 and 4.35) showed a preserved mosaic pattern, necrosis with macrophage invasion and intrassarcoplasmic lipid deposits, suggestive of rhabdomyolysis.

Postmortem examination of cerebellum and kidney at the Birmingham University Hospital, England, was reported as follows: "The cerebellum has no detectable abnormality. The kidney shows extensive deposition of casts particularly in the medulla. These are orange/brown. There are several calcified tubules in the cortex, with iron. Otherwise the kidney appears close to normal. Immunoperoxidase study shows deposition of myoglobin in casts. Features are those myoglobinuria. Diagnosis: myoglobinuria".

DISCUSSION

To our knowledge, this is the first report of sodium monensin intoxication in humans, leading to death after acute rhabdomyolysis with renal failure. Myogloblinuria is one of the most striking findings in animals after experimental exposure or accidental intoxication and should be considered in a differential diagnosis of toxic rhabdomyolysis in persons dealing with Rumensin®.

Monensin, a polyether antibiotic, was discovered in 1967 as a metabolic product of *Streptomyces cinnamonensis*[10]. The compound has been characterized as a Na^+-selective carboxylic ionophore. Ionophores are compounds that form lipid-soluble cation complexes that can traverse cell membranes rapidly. When initially isolated, monensin was considered a coccidiostatic drug but later, it was determined that monensin was effective in cattle as a growth-promoting agent via its action on rumenal flora to increase the production of propionic acid. Improved feed efficiency occurred with continuous administration of low doses of monensin. The compound is currently used in beef cattle rations[10]. Monensin toxicity has been documented in a number of species, with horses showing the greatest sensitivity.[10, 11] The LD_{50} - the amount of a toxic agent that is sufficient to kill 50% of a population of animal usually within a certain time (also called lethal dose) - estimates for monensin in farm animals are 2 to 3 mg/kg body weight for the horse, 16.8 mg/kg body weight for swine, 11.9 mg/kg body weight for sheep and 26.4 mg/kg body weight for goats.[12] In an experimental acute toxicosis in cattle Van Vleet et al[10] found that after monensin treatment (40 mg/kg in a single dose), calves developed anorexia and diarrhea followed by a marked increase in serum CK from days 2 to 4 and often myoglobinuria from days 4 to 9.

Microscopic alterations in skeletal muscle included sarcoplasmic vacuolation and necrosis of muscle fibers, similar to that present in myocardium. Geor and Robinson[13] found loss of appetite, respiratory distress and sudden death after sodium monensin toxicosis in cattle; sodium monensin was included in the feed at 13 times the recommended level; skeletal muscle necrosis was found on post-mortem examination. The LD_{50} of sodium monensin for cattle is not firmly established[10] and death occurred in five of 10 cattle given 22.4 and 39.8 mg/kg of body weight after 6 to 12 days' exposure.[12] Baird et al[3] found similar features of sodium monensin toxicity in ostriches including lethargy, ataxia, dyspnoea, recumbency and death; a marked increase in the CK serum activity indicated an acute myopathy.

In humans we found a report in a non-scientific magazine describing sodium monensin toxicity in 2 persons leading to death 6 to 7 days after exposition[14]. In this report a homemade cake was prepared using yellow flour (Rumensin®) that was kept in a jar outside the original bag and was used as ordinary Brazilian flour. It was supposed that the 6 subjects exposed consumed at least 10 times the recommended doses for cattle.[14] In the present case the clinical picture was quite similar to experimental sodium monensin toxicity in cattle. Muscular pain, myoglobinuria, renal failure and death followed initial gastrointestinal complaints 11 days after sodium monensin exposure. The pathological findings confirmed the clinical and laboratory myoglobinuria showing a preserved mosaic pattern of fiber types, necrosis with macrophage invasion and intrassarcoplasmic lipid deposits on skeletal muscle biopsy. Post-mortem renal histopathology showed casts of myoglobin (myoglobinuria) in the medulla; there was no abnormality in the cerebellum. Probably the gait disturbance described in animals as "incoordenation"[3,5] is due to the rhabdomyolysis rather than cerebellar ataxia.

Acknowledgment – The authors thank Dr. J. D. P. Bland FRCP, Kings College Hospital, UK, for helpful suggestion in manuscript preparation.

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