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A case of human poisoning by salinomycin, an agricultural antibiotic

Phillipa Story and Alan Doube

Ionophore antibiotics are used in farming for the prevention of coccidiodomycosis in poultry and to alter gut flora in order to improve nutrient absorption in ruminants. However, this class of antibiotics affects both animal and bacterial cell physiology. Their mechanism of action at the cellular level is to selectively bind certain ions creating intra- and extracellular biochemical disturbances. The ions bound vary with different members of this class of drug, with salinomycin preferentially binding potassium. This interferes with potassium transport across mitchondrial membranes, resulting in low intracellular energy production. The Na^+/Ca^{2+} exchange mechanism may also be disrupted allowing a fatal accumulation of intracellular calcium.[1] This mechanism particularly affects skeletal muscle in all animals, and cardiac muscle in a few (eg, cattle).

In porcine studies, salinomycin has been demonstrated shortly after ingestion to have a sympathomimetic effect in animals up to three times more powerful in dose-response testing than adrenaline, with positive chronotropic, inotropic, and pressor effects.[2]

Animal poisonings with ionophore antibiotics are widely described in veterinary and related journals. There is considerable interspecies variation in morbidity and mortality that cannot simply be attributed to body mass. Horses seem to be particularly susceptible to skeletal rhabdomyolysis and early death.[1,3,6] The clinical features that are common to most species are an early period of weakness and ataxia followed by a progressive muscle weakness with hind-limb predominance. There have also been cases of cardiac muscle involvement in cattle during chronic poisoning resulting in cardiomyopathy and death from congestive cardiac failure.[4] The typical onset of rhabdomyolysis in dogs was the fifth day post-ingestion, with death, when it occurred, delayed as long as 14 days,[1] and survivors affected for up to 50 days.[5]

The clinical course of the human patient in this case fairly closely resembles that described for dogs with a progressive, bilateral, symmetrical, leg weakness ascending to the forearms and chest with absent reflexes, preserved sensation, smooth-muscle activity, and mental function. Other causes of rhabdomyolysis including trauma and infection were considered but were not present in this case.

Case report

A previously healthy, 35-year-old male was working in a factory making animal feed mixes. One of his tasks was to add salinomycin granules into a ‘worm’ screw as chicken grain feed flowed past. An accidental blowback of the salinomycin granules occurred resulting in inhalation and swallowing of a small amount despite washing out of the mouth. A few minutes later he became acutely unwell with nausea, shortness of breath, and dizziness. He arrived in the emergency department 30 minutes after exposure, where he was found to be agitated and complaining of leg

weakness, nausea, and photophobia. The patient was alert and orientated despite his emotional distress and appeared markedly pale and diaphoretic, with a bounding pulse of 110/min, blood pressure 156/76, oxygen saturation 100%, and temperature 36.2°C. Examination of the chest, abdomen and skin was unremarkable, and neurological examination revealed bilateral leg weakness and moderate photophobia. It was difficult to make a detailed neurological assessment because of the patient's agitation, but he was orientated and there were no obvious localising lesions of either the cranial nerves or limbs. On contacting the National Poisons Centre (University of Otago Medical School, P O Box 913, Dunedin, tel 0800 POISON, www.toxinz.com) for advice, we discovered that there were no human data available for poisoning with this substance. Animal data suggested that the patient might have a transient hypernatraemia and weakness. No specific antidotes were known to exist and the patient was treated supportively with oral charcoal 50 g, oxygen 10 L/min by mask, and intravenous fluids (1 L normal saline); and admitted for observation.

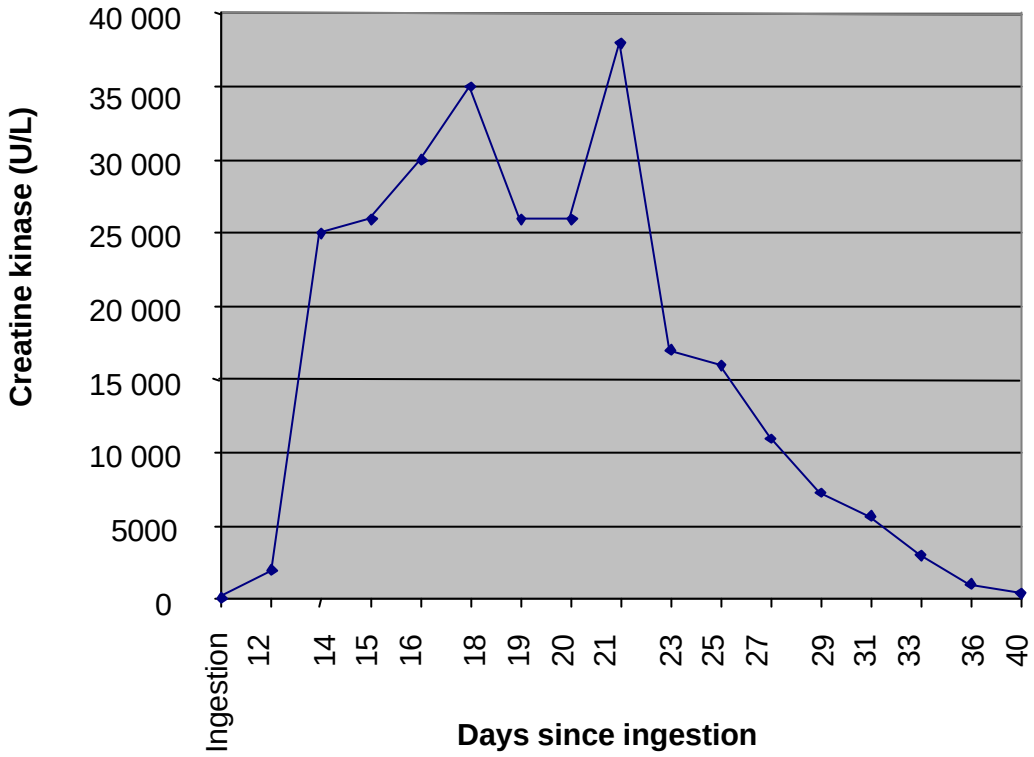
Over the next 48 hours, the patient complained of limb weakness. He was found to be areflexic with 2/5 power in his legs and 4/5 in his arms. Initial investigations showed normal electrolytes and urea, a transient hyperglycaemia of 16.6 mmol/L, and a transient leucocytosis of 16.4 x 10^9. Over the next two days, the patient made a significant recovery of muscle power, with only mild weakness detectable in the knee extensors, and all further blood tests (CBC, electrolytes, glucose) were normal. The tachycardia of 100–110/min settled over the first day with no pharmacological intervention, and he remained haemodynamically stable at all times. He received a further 2 L of intravenous fluid over the 24 hours as well as oral intake. There is no record of urine volume, but the patient was passing urine, and ward urinalysis revealed ketones only. On Day 6 post-exposure, he complained of pain in his left calf and a small, below-knee deep venous thrombosis was diagnosed on ultrasound and D-dimer assay. He was commenced on enoxaparin and warfarin and continued to show good return of muscle power with normal observations. On Day 9, the patient was discharged to his family with clinic follow up arranged. His medication on discharge consisted of warfarin and diclofenac.

On Day 14, the patient re-presented to the emergency department complaining of increasingly severe pain in both legs. Examination revealed normal tone in his legs with decreased reflexes and marked tenderness of the calf muscles. Biochemistry revealed a raised creatine kinase (CK) of 25 000 U/L with mild elevations of alanine aminotransferase 294 U/L (normal 0–45U/L) and gamma-glutamyl transpeptidase 75 U/L (normal 0–60 U/L). Cardiac isomers of CK were normal, as was the echocardiogram (ECG). Haematology showed Hb144 g/L, WCC 12.6, platelets 323, and INR of 2.2, consistent with warfarin treatment.The urine was positive for myoglobin, but renal function and serum calcium remained normal. It was not clear at this stage whether the rhabdomyolysis was related to the patient's recent exposure or some other pathology.

The patient experienced ongoing muscle pain and weakness that progressed from his legs to his arm and chest over a 4-day period. He remained alert and had no cranial nerve lesions or respiratory difficulty. After initial treatment with IV normal saline and urinary alkalisation (8.4% $NaHCO_3$), the patient was managed with oral fluids and bed rest while evidence of ongoing muscle injury remained. The CK remained high (peak 38 000 U/L) for 7 days before beginning to decline, and reached almost

normal levels on Day 40 post-ingestion (435 U/L). Urine myoglobin became undetectable by Day 35 with normal renal function throughout. A muscle biopsy was not performed. Due to the description of cardiomyopathy in cattle,[4] a baseline ECG was performed which was normal. The patient suffered from several episodes of chest pain, but repeated ECGs and troponin measurements were normal. The patient made a slow and uneventful recovery and was finally discharged 40 days after the original exposure. At that time, he still had very limited exercise tolerance—eg, climbing a single flight of stairs was difficult and painful.

Figure 1. Progress of serum creatine kinase (U/L) measurements in patient over recovery period



Discussion

It is clear from this case that humans may be vulnerable to the toxic effects of ionophore antibiotics. This patient ingested an estimated 1 mg/kg of salinomycin resulting in a 6-week hospital admission with prolonged rhabdomyolysis, pain, and disability. The patient had no other discernable causes for rhabdomyolysis. It is likely that his initial presentation with diaphoresis and tachycardia is attributable to the sympathomimetic properties of salinomycin.[2] The subsequent clinical course most closely resembled that of the dog in both symptom progression and duration.[3,5] Animal research into potential antidote treatments, including administration of selenium and vitamin E have not shown any impact on toxicity,[7] and supportive measures (charcoal, oxygen, IV fluids) remain the only current treatment method.[8] It

would appear from this, and animal cases, that any patient making an initial full recovery will need to be closely followed for the advent of rhabdomyolysis, which may be delayed. From our experience, we recommend aggressive management of myoglobinuria (urinary alkalisation) and prolonged bed rest to minimise metabolic demand on ATP-depleted muscle. Although this patient did not suffer any detectable myocardial damage, it is not possible to rule this out in a future human case and an early baseline cardiac ECG is suggested.

This is the first published description of salinomycin poisoning in humans. It was clear from the patient and from product literature that the agricultural community does not widely appreciate the serious consequences that may arise from exposure to ionophore antibiotics. The authors hope that this paper will provide an important safety warning in the agricultural industry, and provide a guide for treatment and monitoring for physicians.

Author information: Phillipa A Story, Emergency Physician; Alan Doube, Consultant in General Medicine and Rheumatology, Waikato Hospital, Hamilton

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Correspondence: Dr Phillipa Story, Emergency Department, Waikato Hospital, Private Bag 3200, Hamilton. Fax: (07) 839 8772; email: kiwidoc02@hotmail.com

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