SHORT REPORT

Toxicity of maduramicin

N Sharma, A Bhalla, S Varma, S Jain, S Singh

Emerg Med J 2005;22:880–882. doi: 10.1136/emj.2004.020883

This report documents the first presentation of seven human cases of poisoning with a compound used in poultry feed. The clinical presentation was a toxic polyneuropathy with rhabdomyolysis and acute renal failure. We describe the protracted clinical course of one of these victims along with a tabulated description of the clinical course and relevant laboratory investigations of the others.

Maduramicin is a monoglycoside polyether derived from the fungus *Actinomadura rubra*. It is classified as an ionophore and predominantly used as an anticoccidial agent, which is mixed with poultry feed in the ratio of 5 ppm.¹ There are numerous observational and experimental reports to show that this compound, if used for a long time, can be toxic to the animals fed on this mixture.^{2–6} However, toxicity data among humans inadvertently exposed to this compound has been lacking. We report seven victims with this unusual poisoning. We describe the protracted clinical course of one of these victims along with a tabulated description of the clinical course and relevant laboratory investigations of the others.

The index case was a 30 year old male poultry farm worker who was admitted to the medical emergency room of the Nehru Hospital of the Postgraduate Institute of Medical Education and Research, Chandigarh, India, after consuming a pudding of maduramicin mixed with vegetable oil, which he mistook for porridge under the influence of cannabis at a religious function. He had consumed this concoction in the company of six other friends. The approximate quantity of maduramicin ingested was 450 g in total. Within two hours, all seven victims developed vomiting and weakness of all four limbs and truncal muscles. Two victims died over the next 48 hours at the primary health centre where they were admitted and the others, including the index case, were referred to our hospital after eight days.

On arrival at our hospital, the index case complained of excessive sweating over the face and pain in the buttock area. On examination, the pulse rate was 80/minute, respiratory rate of 16/minute, blood pressure of 120/80 mmHg, and excessive sweating over the face was noted. There was no pallor, icterus, cyanosis, or dependant oedema. The examination of the lungs, heart, and the abdomen was normal but the neurological examination showed a grade IV muscle power with generalised areflexia.

Upon investigation, the following were noted: the haemoglobin was 10 mmols/L, total leucocyte counts $8.8 \times 10^9/L$, and the differential counts and peripheral blood smears were normal. The serum biochemistry was normal and the electrocardiography, chest x ray, ultrasound examination, and echocardiography were also normal. On day two of hospital admission, the pain in the buttock area and back worsened and the patient noted a darkening in the colour of the urine. Investigations revealed rhabdomyolysis (creatinine phosphokinase MM levels 17 300 U/L, serum myoglobin

present, alanine aminotransminase 1.25 $\mu\text{kat/L}$, and aspartate aminotransminase 0.60 $\mu\text{kat/L}$) following which alkalinisation of the urine was started. Over the next four days, hyperkalaemia and acute renal failure set in and he had to be taken up for haemodialysis. The arterial blood gas analysis showed mild metabolic acidosis. By day six, the muscular weakness had become worse and involved the respiratory muscles as well. Nerve conduction studies showed a polyradiculopathy. He had to undergo endotracheal intubation for mechanical ventilation for four days and later a tracheotomy for airway support. The evolution of nosocomial pneumonia by day 10 necessitated the addition of broad spectrum antibiotics that resulted in clinical resolution of pneumonia. The muscle pain subsided three weeks after admission with clinical improvement and he was discharged on day 34 after admission in a stable condition.

Data from poultry animals, particularly chickens, have shown that certain species of animal coccidiodes—that is, *Eimeria acervulina*, *E maxima*, and *E tenella*—are responsible for malnutrition. Maduramicin is used admixed with chicken feed as an anti-coccidial agent to prevent malnutrition before slaughtering for human consumption. Since the half life of this agent is 20–39 hours, its use in chicken feed is stopped five days before slaughter.¹

Maduramicin acts by affecting cation transport across the cell membrane, increasing the influx of Ca^{2+} , Na^{+} , and K^{+} in the cell wall thereby causing cell membrane disruption and cell death. As an anti-microbial agent, maduramicin has a bactericidal action on many Gram positive bacteria and coccidiosis. Maduramicin is marketed as drug coated particles with particle size of 400 μ . The LD50 is 50 g/tonne of chicken feed and it is known as the most potent and toxic of all the ionophores.¹ To the best of our knowledge, no known human toxicity has been reported.

Toxicity of maduramicin has been well documented in animals; in a herd of 277 beef breed calves, which were mistakenly given maduramicin in a total mixed ration, there was an acute toxicity with sudden death.² Another report of the gross and histopathological lesions of 20 cattle, four sheep, one steer fed ad lib, six sheep dosed with toxic poultry litter, and ten sheep fed experimental rations of maduramicin showed that the macroscopic lesions in the cattle that died were indicative of congestive heart failure.³ On gross examination, the skeletal muscle of sheep, particularly the muscles of the hindquarters, appeared pale, oedematous, and mottled, which on microscopy showed granular degeneration with foci of necrosis and regeneration. One of the sheep in the poultry litter developed signs of congestive heart failure and the hearts of the other two were dilated. On cardiac histopathology, the lesions were more pronounced in cattle and comprised of varying degrees of atrophy, hypertrophy, degeneration, necrosis of myocardial fibres, and interstitial fibrosis. In the steer fed ad lib with this material, extensive hypertrophy and atrophy of myocardial fibres were evident. Other less evident microscopic lesions were diffuse hypertrophy of myocardial nuclei in all seven cases, myocardial fibre atrophy in six, multifocal fibrosis in six, necrosis in two

Table 1 Comparison of clinical/pathological features of maduramicin toxicity in different species.²⁻⁶

Animal species	Clinical/pathological features
Calves	Sudden cardiac death
Sheep	Leg muscle weakness, myonecrosis, cardiomyopathy, arrhythmias
Cattle, steer	Cardiac arrhythmias, heart failure, cardiomyopathy
Chicken	Watery diarrhoea, macrocytic anaemia, leucopenia, lymphopenia
Humans	Muscle weakness, myonecrosis, acute renal failure, polyneuropathy

cases, and focal endocardial thickening in two. This suggests that this form of maduramicin based poultry litter intoxication is chronic, the pathology of which is characterised by dilated cardiomyopathy with congestive heart failure and mild (cattle) to severe (sheep) skeletal muscle lesions.³

An experimental feeding trial was conducted in order to substantiate a hypothesis on the aetiology of cardiomyopathy in beef cattle in Israel. It was postulated that residues of the maduramicin in poultry litter fed to cattle were the cause of cardiomyopathy. The clinical, biochemical, necropsy, and histopathological findings showed that maduramicin is cardiotoxic to poultry litter.⁴ This finding has also been well documented in another experimental feeding trial from South Africa.⁵

Another study in chicken fed with maduramicin medicated feed at 5 and 10 ppm for 21 days showed that it caused growth retardation.⁶ Clinical signs seen were watery diarrhoea, depression, dullness, and ruffled feathers in chickens from second week of the medication at 10 ppm, but these features were seen from the third week in the birds given maduramicin at 5 ppm. A macrocytic anaemia was evident in both the medicated groups. Leucopenia because of lymphopenia was observed in the 10 ppm group on day 21. A comparison of the clinical features of toxicity in different species is given in table 1. It is evident that the clinical toxicity of maduramicin in humans is very similar to that in sheep. Cardiotoxicity was not seen in any of our patients.

In our patients (table 2), maduramicin consumption caused very early manifestations of quadripareisis and death in two cases. In the index case, admitted at our hospital, the onset of polyradiculopathy and rhabdomyolysis with acute renal failure 8–10 days after the consumption were like those of a toxic neuromyopathic effect seen in animals, particularly sheep. All victims experienced a peculiar sweating over the facial region that could be attributed to an associated autonomic neuropathy caused by this agent as an accompaniment of toxic polyradiculopathy. Cardiomyopathy was not seen in any of the five victims admitted at our hospital. The variable clinical course of all subjects—with patients 1 and 2 succumbing to rhabdomyolysis and polyneuropathy, the index case having polyneuropathy with severe rhabdomyolysis and acute renal failure, and patients 3 and 4 having mild rhabdomyolysis—alone could be related to an inter-individual differential sensitivity to the toxic effects or to an inequitable distribution of maduramicin in the pudding that was prepared. The fatal clinical course that occurred in victims 1 and 2 was in all probability related to the degree of rhabdomyolysis with hyperkalaemia, metabolic acidosis, and hypocalcaemia that set in very early after admission. The cause of death in victim 1 was attributed to hyperkalaemia and that of victim 2 to an acute onset of respiratory failure. In both the diseased victims the values of creatinine phosphokinase MM isoenzyme were markedly elevated when compared with the surviving victims.

In conclusion, of seven patients presenting with maduramicin toxicity, death occurred in four cases, a toxic polyneuropathy in four, a varying degree of rhabdomyolysis in five, and pigment induced acute renal failure in four of our patients.

Authors' affiliations

N Sharma, A Bhalla, S Varma, S Jain, S Singh, Department of Internal Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh - 160012, India

Competing interests: none declared

Correspondence to: Dr Navneet Sharma, Assistant Professor of Internal Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh - 160012, India; navneet_433@sify.com

Accepted for publication 5 January 2005

Table 2 Clinical features, laboratory findings and outcomes of four patients of maduramicin poisoning

Victim	Facial sweating, muscle pains, and areflexia	Serum K/Ca mmols/L	CPK-MM isoenzyme U/L (normal = 24–170 U/L)	Renal function tests Ur/Cr	Serum AST/ALT μ kat/L	NCV and EMG	Blood pH/HCO ₃	Outcome
1	++	6.2/2.0	92200	24.9/150	1.28/1.57	PN	7.25/16	Died 24 hours after admission
2	++	6.2/1.8	163250	12.5/100	1.80/1.48	PN	7.24/20	Died 48 hours after admission of respiratory failure
3	+	4.2/2.55	230	10.7/133	0.17/0.17	PN	7.36/22	Survived
4	+	3.6/2.20	769	Normal	0.70/0.28	Normal	7.42/24	Survived

+, mild symptoms; ++, severe symptoms; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CPK-MM, creatinine phosphokinase MM isoenzyme; EMG, electromyography; HCO₃, serum bicarbonate in mmols/L; NCV, nerve conduction velocity; PN, polyneuropathy; Ser K/Ca, serum potassium/serum calcium; Ur/Cr, blood urea in mmols/L/serum creatinine in μ mol/L.

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