Leading Article

Drug-induced rhabdomyolysis – mechanisms and management

B.D. Prendergast and C.F. George[1]

Southampton General Hospital, Tremona Road, Southampton SO9 4XY and [1]Clinical Pharmacology Group, Biomedical Sciences Building, Bassett Crescent East, Southampton SO9 3TU, UK

Since the original reports of patients with myoglobin-induced renal failure following crush injury during World War II,[1] the aetiology of acute rhabdomyolysis has diversified. The causes include polymyositis, heat stroke, prolonged convulsions, marathon running, hypokalaemia and viral illness (Epstein–Barr, influenza and coxsackie viruses). Of late, drugs, including alcohol, have assumed greater importance and in published series have been implicated in up to 81% of cases.[2] Whether all reports of drug-induced rhabdomyolysis are truly drug-related is questionable. Case reports relating to drugs taken in overdose are complicated by attendant circumstances which cause, or contribute to, acute muscle necrosis. These include seizures, hypothermia, trauma, metabolic acidosis, hypoxia and prolonged coma with immobilization, muscle compression and/or occlusion of the regional blood supply.[3] Moreover, identification of a single cause is made difficult by the consumption of drugs in combination and with alcohol; also by the contamination of ilicit substances with impurities and diluents.

Toxins themselves can have a variety of effects including vasospasm, involuntary muscle contraction, hyperthermia and interference with ATP metabolism, hypokalaemia and direct actions on the myocyte.[4] The role of alcohol is of particular importance as it accounts for at least 20% of all cases of acute rhabdomyolysis.[5] Indeed, asymptomatic rises in creatine kinase (CK) accompanied by histological evidence of myopathy have been observed in healthy volunteers consuming diets high in alcohol content.[6] In addition, subclinical and overt rhabdomyolysis are encountered frequently in alcoholics. In the absence of compression and ischaemia due to prolonged immobilization, the suggested mechanisms include inhibition of calcium metabolism by the sarcoplasmic reticulum, disruption of muscle cell membranes, inhibition of sodium–potassium ATPase and alterations in carbohydrate metabolism. Potassium, magnesium and phosphate deficiencies also appear to be relevant.[5] Finally, many of the clinical and pathological features of acute rhabdomyolysis are shared by the neuroleptic malignant syndrome and malignant hyperthermia, associated with anaesthetic agents. Diagnostic overlap, therefore, exists.

Thus, we need to distinguish between drug-induced, primary rhabdomyolysis and a secondary phenomenon whereby exposure to drugs or toxins generates circumstances which predispose to rhabdomyolysis. Table I classifies into these two categories the agents which have been linked with rhabdomyolysis. However, such distinctions are not always possible since either or both mechanisms can apply. For readers wanting more detailed discussions of the pathology involved, several review articles have been published.[4,7–9]

The spectrum of potential complications following acute rhabdomyolysis comprises hyperkalaemia, a rapidly rising serum creatinine, hyperuricaemia, hypo- and hypercalcaemia, hyperphosphataemia, disseminated intravascular coagulation (DIC), metabolic acidosis, cardiomyopathy and respiratory failure. Also the development of compression syndromes due to localized oedema in the anterior tibial, soleal, peroneal, lateral thigh, gluteal, deltoid and volar forearm compartments with consequent peripheral neuropathy.[4] Death is thought to arise from acute metabolic disturbances but the prognosis of renal, muscular and neurological dysfunction is good.[7]

The aetiology of the acute renal failure following muscle necrosis is complex and described mechanisms fall into three distinct categories:

1. Impairment of renal vascular flow due to sympathetic nervous overactivity, activation of the renin–angiotensin system, altered prostaglandin synthesis, high circulating levels of antidiuretic hormone and the deposition of microthrombi.[4,10]
2. Tubular obstruction by myoglobin casts or crystals of uric acid, with passive back diffusion of glomerular filtrate.[4,10]
3. Direct toxicity from ferrihemate, a product of the dissociation of myoglobin at pH < 5.6. In

Table I   Therapeutic agents causing primary and secondary rhabdomyolysis

Category	Drug(s)	Primary	Secondary
Ulcer healing			
1.3.1	Cimetidine	+	
1.3.6	Carbenoxolone	+	
Laxatives			
1.6	Any causing hypokalaemia	+	
Diuretics			
2.2	Any causing hypokalaemia	+	
Fibrinolytic drugs			
2.10	Streptokinase		+
	Alteplase		+
Antifibrinolytic drugs			
2.11	E-Aminocaproic acid	+	
Lipid lowering drugs			
2.12	Fibrates	+	
	HMG-CoA reductase inhibitors	+	
Bronchodilators			
3.1.1	Terbutaline		+
3.1.3	Theophylline	+	+
Antihistamines			
3.4		+	+
Hypnotics/anxiolytics			
4.1	Benzodiazepines	+	+
	Barbiturates	+	+
Drugs used in psychiatry			
4.2.1	Phenothiazines and butyrophenones	+	+
4.2.3	Lithium	+	+
Antidepressants			
4.3.1	Tricyclic and related antidepressants		+
4.3.2	Monoamine oxidase inhibitors	+	
4.3.4	5HT uptake inhibitors		+
Analgesics			
4.7.2	Opioids	+	+
Antiepileptics			
4.8.1	Sodium valproate		+
Antibacterial drugs			
5.1.8	Cotrimoxazole	+	
5.1.9	Isoniazid		+
Antifungal drugs			
5.2	Amphotericin B	+	
Antiprotozoal drugs			
5.4.8	Pentamidine	+	
Hypothalamic and pituitary hormones			
6.5.2	Vasopressin	+	
Cytotoxic drugs			
8.1		+	
Intravenous nutrition			
9.3		+	
Vitamins			
9.6	Retinoids	+	
Drugs used in gout			
10.1.4	Colchicine	+	
Anaesthetic agents			
15		+	
Emetics	Any causing hypokalaemia	+	
Other substances causing rhabdomyolysis			
Drugs of abuse	Alcohol	+	+
	Amphetamines		+
	Caffeine		+
	Cocaine	+	+
	Ecstasy		+
	LSD		+
	Toluene	+	
'Industrial substances'	Dyes	+	
	Herbicides	+	
	Solvents	+	
	Toxic metals/gases	+	

animals ferrihemate infusion produces a dose-dependent deterioration in renal function with depression of renal tubular transport mechanisms,[4,11] cell swelling and death.[12]

Successful management depends upon early diagnosis and, therefore, a low threshold of clinical suspicion (even in the absence of overt muscle pathology). Indeed, many authors advocate routine estimation of serum CK and urinary myoglobin in all instances where rhabdomyolysis is possible. Several procedures have been proposed to localize areas of muscle necrosis including ultrasound scanning, computerized tomography[13] and radioisotopic techniques[14] but these are neither universally applicable nor necessary.

The initial treatment is aimed at correcting acute metabolic disturbances, particularly hyperkalaemia, hyperthermia and hypovolaemia. Further muscle necrosis can be prevented by controlling seizures, restlessness and muscle contractions. Oral absorption of the causative agent can be reduced by gastric lavage and activated charcoal and, for some substances, elimination encouraged by diuresis, haemofiltration or haemodialysis. In cases of the neuroleptic malignant syndrome or malignant hyperthermia, the prompt infusion of 1 mg/kg dantrolene sodium is recommended which can be repeated, if necessary, to a total of 10 mg/kg. Bromocriptine is an alternative treatment for the neuroleptic malignant syndrome.

The mainstay for prevention and treatment of myoglobinuric acute renal failure is sodium bicarbonate. The object is to maintain an alkaline urine and prevent dissociation of myoglobin to its nephrotoxic metabolite, ferrihemate. Diuretics, notably mannitol, also have a role by promoting a diuresis, thereby diluting nephrotoxic substances, and 'flushing through' blocked renal tubules.[4,12] Several protocols have been reported: Eneas et al.[15] treated 20 oliguric patients with myoglobinuria. Seventeen received 25 g mannitol and 100 mmol sodium bicarbonate in 1 litre 5% w/v dextrose administered intravenously over 4 hours and two were given intermittent intravenous mannitol and sodium bicarbonate. The last patient received only intravenous mannitol. Of the 20, nine developed a diuresis with resolution of their renal failure: the other 11 failed to respond and required dialysis. Later, Ron et al.[16] described seven crush victims who were at high risk of severe rhabdomyolysis.

Each received immediate parenteral crystalloid solutions containing sodium bicarbonate (44 mmol) in alternating 500 ml infusions. If the urine output fell to below 300 ml/h, mannitol (1 g/kg) was administered in a 20% solution. Further sodium bicarbonate was infused if the urinary pH fell below 6.5 and acetazolamide given if plasma pH approached 7.45. None of the patients developed acute renal failure.

Despite a lack of matched controls, this evidence convinced others (Curry et al.[4]) to recommend a similar protocol which incorporated acetazolamide 250 mg intravenously if the arterial pH exceeded 7.45 or aciduria persisted despite alkalaemia. However, the carbonic anhydrase inhibitor is needed rarely and is contraindicated in salicylate poisoning because of the potential for trapping salicylate in the central nervous system. Failure of any of these regimes to achieve a diuresis indicates the need for dialysis.

Knochel[17] has expressed concern that the use of large quantities of sodium bicarbonate can exaggerate a tendency to hypocalcaemia and has advocated a simpler regime comprising a single dose of mannitol as 100 ml 25% solution over 15 min, together with frusemide 40–120 mg intravenously and a further dose of frusemide of 200 mg over 2 h if there is no initial response. However, proponents of bicarbonate therapy have found that complications are rare in practice if metabolic alkalosis is avoided.

Further sequelae of rhabdomyolysis require only supportive therapy. Thus, DIC should be treated with clotting factors only if there is bleeding and heparin is of no benefit. Epsilon-aminocaproic acid, a fibrinolytic inhibitor, can itself cause rhabdomyolysis and should be avoided. Hypocalcaemia will usually correct itself spontaneously and any attempt at its treatment can be complicated by rebound hypercalcaemia. The late development of compartment syndromes can be prevented by careful clinical and/or intracompartmental pressure monitoring with decompressive fasciotomy when necessary.

We conclude that drug-induced rhabdomyolysis is a frequent and often unrecognized problem which occurs most commonly in drug overdosage. It should be looked for in severely poisoned patients and treated aggressively if complications are to be avoided.

References

1. Bywaters, E.G.L. & Beall, D. Crush injuries with impairment of renal function. *Br Med J* 1941, **1**: 427–432.
2. Gabow, P.A., Kaehny, W.D. & Kelleher, S.P. The spectrum of rhabdomyolysis. *Medicine* 1982, **61**: 141–152.
3. Penn, A.S., Rowland, L.P. & Fraser, D.W. Drugs, coma and myoglobinuria. *Arch Neurol* 1972, **26**: 336–343.
4. Curry, S.C., Chang, D. & Connor, D. Drug and toxin induced rhabdomyolysis. *Ann Emerg Med* 1989, **18**: 1068–1084.
5. Haller, R.G. & Knochel, J.P. Skeletal muscle disease in alcoholism. *Med Clin North Am* 1984, **68**: 91–103.
6. Song, S.K. & Rubin, E. Ethanol produces muscle damage in human volunteers. *Science* 1972, **175**: 327–328.
7. Koppel, C. Clinical features, pathogenesis and management of drug induced rhabdomyolysis. *Med Toxicol Adverse Drug Exp* 1989, **4**: 108–126.

8. Lane, R.J.M. & Mastaglia, F.L. Drug induced myopathies in man. *Lancet* 1978, **2:** 562–566.

9. Cassidy, M.J.D. & Kerr, D.N.S. Renal disorders. In: Davies, D.M. (ed.) *Textbook of Adverse Drug Reactions*, 4th ed. Oxford University Press, Oxford, 1991, pp. 317–318.

10. Better, O.S. & Stein, J.H. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 1990, **322:** 825–829.

11. Braun, S.R., Weiss, F.R., Keller, A.L. *et al.* Evaluation of the renal toxicity of heme pigments and their derivatives: a role in genesis of acute tubular necrosis. *J Exp Med* 1970, **131:** 443–460.

12. Knochel, J.P. Rhabdomyolysis and myoglobinuria. *Semin Nephrol* 1981, **1:** 75–86.

13. Vukanovic, S., Hauser, H. & Curati, W.L. Myonecrosis induced by drug overdose: pathogenesis, clinical aspects and radiological manifestations. *Eur J Radiol* 1983, **3:** 314–318.

14. Cornelius, E.A. Nuclear medicine imaging in rhabdomyolysis. *Clin Nucl Med* 1982, **7:** 462–464.

15. Eneas, J.F., Schoenfield, P.Y. & Humphreys, M.H. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. *Arch Intern Med* 1979, **139:** 801–805.

16. Ron, D., Taitelman, U., Michaelson, M. *et al.* Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984, **144:** 277–280.

17. Knochel, J.P. Rhabdomyolysis and myoglobinuria. In: Suki, W.N. & Eknoyan, G. (eds). *The Kidney in Systemic Disease*, 2nd ed. John Wiley & Sons Inc., New York, 1981, pp. 263–284.