

Acute refractory hyperkalaemia and fatal cardiac arrest related to administration of liposomal amphotericin B

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ABSTRACT

A 36-year-old male with acute myeloid leukaemia was treated with liposomal amphotericin B for a breakthrough fungal infection with *Absidia corymbifera* during voriconazole and caspofungin therapy for invasive pulmonary aspergillosis.

Four episodes of hyperkalaemia developed with a highly probable relation to infusion of liposomal amphotericin B, of which the last episode was characterised by severe, refractory hyperkalaemia and fatal cardiac arrest. The available literature on severe hyperkalaemia and cardiac arrest during administration of both conventional and liposomal amphotericin B is reviewed here and revealed only four similar cases. The most likely mechanism of toxicity is the release of potassium from a variety of mammal cells including erythrocytes and endothelial cells. Whether prevention of toxicity can be established by decreasing the infusion rate is unclear but conceivable.

KEYWORDS

Cardiac arrest, fungal infection, hyperkalaemia, liposomal amphotericin B

INTRODUCTION

Although voriconazole is now standard empiric antifungal therapy for opportunistic fungal infections,¹ conventional amphotericin B deoxycholate (C-AmB) is still recommended for certain clinical conditions, for instance when (breakthrough) infections with azole-insusceptible moulds or yeasts occur or when intolerance for azoles

is present. However, an important limitation for the use of C-AmB is the appearance of hazardous side effects. In particular, administration of higher doses of C-AmB may be nephrotoxic and may lead to renal failure and severe electrolyte disturbances (hypokalaemia, hypomagnesaemia).² Aggravating infusion-related reactions have been documented as well, including fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headache and bronchospasms.² The introduction of lipid formulations of AmB (L-AmB) reduced nephrotoxicity and infusion-related side effects, which made L-AmB an attractive alternative for patients at risk for renal failure or C-AmB intolerance. However, a rare and less-documented side effect of both C-AmB and L-AmB is the potential for the development of acute severe hyperkalaemia related to its administration. Here, we describe a patient who developed a breakthrough fungal infection with *Absidia corymbifera* (a nonseptate mould related to the class of zygomycetes) during antifungal therapy with voriconazole and caspofungin for invasive pulmonary aspergillosis. Treatment with L-AmB was initiated, which ultimately resulted in a fatal cardiac arrest due to acute refractory hyperkalaemia on the 24th day of treatment with L-AmB.

CASE REPORT

A 36-year-old male was diagnosed with acute myeloid leukaemia (AML) requiring cytostatic therapy. During induction chemotherapy, the patient developed neutropenic fever caused by pneumonia of the right upper lobe and treatment with broad-spectrum antibiotics (imipenem-cilastatin) was initiated. After three days, the fever persisted

and empiric antifungal therapy with voriconazole was started. Despite this regime, his clinical condition did not improve and neutropenia persisted. Therefore, early allogenic haemopoietic stem cell transplantation was scheduled. Unfortunately, respiratory failure developed shortly after transplantation and the patient was transferred to the intensive care unit for mechanical ventilation. A bronchoscopy was performed showing white viscous plugs very suggestive of fungal infection. Bronchoalveolar lavage fluid showed a positive calcofluor together with a positive serum galactomannan antigen test, indicative for invasive pulmonary aspergillosis. Because the galactomannan antigen test showed an increased titre during voriconazole therapy, caspofungin was added. Despite this combination therapy, the patient's respiratory condition deteriorated slowly in the presence of a persistent consolidation of the upper lobe of the right lung. A lobectomy of the right upper lung was performed showing histopathological evidence of invasive fungal infection with visualisation of septate hyphae, massive inflammation and necrosis. Furthermore, a positive polymerase chain reaction for *Absidia corymbifera* was isolated from pleural effusion and liposomal amphotericin

B was initiated subsequently (5 mg/kg administered over two hours). On the 24th day of treatment with L-AmB, acute cardiac arrhythmias developed just after the L-AmB infusion was ended, resulting in ventricular fibrillation and cardiac resuscitation was started. Blood samples taken at the onset of cardiac arrest demonstrated a plasma potassium level of 9.2 mmol/l. Repetitive administration of bicarbonate and insulin/glucose did not decrease the potassium level and despite administration of calcium gluconate and multiple attempts at electric defibrillation, the cardiac arrhythmias persisted and further resuscitation was withheld. Autopsy showed no evidence of coronary artery disease or myocarditis. Massive fungal invasion was demonstrated in both lungs, thyroid gland, liver and spleen.

Examining this case carefully after this unexpected death, we found three previous episodes of sudden hyperkalaemia: on day 9, 10 and 11 of L-AmB therapy, plasma potassium levels were also increased at the end of L-AmB infusion (table 1). On two of these episodes short-term sinus bradycardia (40 beats/min) occurred which resolved after correction of the plasma potassium level with glucose/

Table 1. Laboratory results prior, during and after L-AmB infusion (5 mg/kg)

pH	Day 9	Day 10	Day 11	Day 24*	Units	Reference
18.00	7.40	7.42	7.32	7.40		7.35-7.45
22.00	7.40	7.24	7.30	7.17		
23.00	NA	7.31	7.18	7.30		
Bicarbonate						
18.00	23.2	24.7	23.3	32.5	mmol/l	22-28
22.00	23.7	21.1	21.4	27.0		
23.00	NA	22.6	20.9	34.5		
Sodium						
18.00	131	131	126	135	mmol/l	136-145
Potassium						
18.00	3.4	4.7	4.9	4.2	mmol/l	3.5-4.9
22.00	4.7	6.1	6.9	8.9		
23.00	NA	4.6	7.0	9.2		
Creatinine						
18.00	80	93	115	83	µmol/l	60-110
23.00	NA	111	NA	NA		
Creatine kinase						
18.00	NA	NA	31	8	U/l	<170
23.00	NA	39	NA	NA		
Glucose						
18.00	6.6	7.2	6.4	7.1	mmo/l	3.8-8.0
23.00	5.4	14.4	17.8	12.1		
Calcium ionised						
18.00	1.10	1.07	1.08	1.06	mmol/l	1.10-1.30
23.00	1.10	1.00	1.21	1.74		
Event	None	Sinus bradycardia	Sinus bradycardia	Ventricular fibrillation		
Intervention	None	Glucose/insulin	Glucose/insulin	Sodium bicarbonate Calcium gluconate		

Infusion was started at 20.00 hrs and completed at 22.00 hrs. *Glucose/insulin was also given. NA = not available.

insulin. Renal function deteriorated during this period, demonstrated by an increase in serum creatinine, but recovered within a few days while L-AmB was continued. Why the patient developed refractory hyperkalaemia on the 24th day of treatment remains unclear; renal function had recovered to within normal limits, and there were no signs of rhabdomyolysis, haemolysis or severe acidosis. Also no medication errors could be identified and the infusion rate of L-AmB was unchanged (375 mg, dissolved in 200 ml dextrose 5% administered in two hours). On the other hand, our patient was being treated with many drugs that may induce hyperkalaemia, including ciclosporin, mycophenolate mophetil, propofol, nadroparin and cotrimoxazole; however, there seemed to be a highly probable time-relationship between the administration time of L-AmB and the occurrence of hyperkalaemia.

DISCUSSION

Reviewing the literature, we identified four previous well-documented cases of acute, severe hyperkalaemia and cardiac arrest in relation to administration of either C-AmB or L-AmB (table 2). Craven described a case of repeated acute hyperkalaemia and ventricular fibrillation after a single dose of 1.4 mg/kg C-AmB administered in 45 minutes in an anuric patient a few hours prior to haemodialysis.³ Laboratory results revealed no evidence of progressive haemolysis or rhabdomyolysis. This author noted that in two other patients, prolonged infusion (four hours) during haemodialysis demonstrated lower peak concentrations of C-AmB without development of

hyperkalaemia. Burke *et al.* described a case in which L-AmB (5 mg/kg) was prescribed for cryptococcal meningitis.⁴ However, C-AmB in the same dosage was administered mistakenly on two consecutive days. This overdose resulted in cardiac arrhythmias, severe hyperkalaemia, haemolysis and acute renal failure. A similar medication error with an overdose of C-AmB resulting in severe hyperkalaemia, cardiac arrest and death has been described previously.⁵ Barcia described a child with a disseminated candida infection who developed acute hyperkalaemia during infusion of L-AmB (5.0 mg/kg over one hour) accompanied with cardiac arrhythmias.⁶ During resuscitation laboratory results demonstrated a potassium level of 16.0 mmol/l without signs of haemolysis or rhabdomyolysis.

Pathogenesis

Conventional amphotericin B deoxycholate (C-AmB) is a natural product of *Streptomyces nodosus* and works by selective binding with ergosterols of the fungal membrane thereby forming channels into the cell membrane. Formation of these channels will increase cell permeability and may lead to efflux of cellular potassium and other intracellular components, resulting in metabolic disruption, osmotic imbalance and cell death. The selectivity of C-AmB action is due to its 8.5-fold higher affinity for the ergosterol component of fungal cell membranes than for cholesterol, which is the predominant sterol found in mammalian membranes. However, C-AmB may also interact with cholesterol-containing human cell membranes, which in turn may result in cellular injury and end-organ dysfunction. This cellular injury has been illustrated

Table 2. Case reports of severe hyperkalaemia and cardiac arrhythmias related to administration of liposomal amphotericin B (L-AmB) or conventional amphotericin B (C-AmB)

Author, year	Diagnosis	Sex	Age	Therapy	Dose mg/kg	Infusion time	Day of therapy	Potassium (mmol/l)	Cardiac event	Outcome
Groot, 2008	Acute myeloid leukaemia Invasive pulmonary aspergillosis + zygomycosis	M	36	L-AmB	5.0	2 hours	24	9.2	Cardiac arrest	Death
Burke, 2006	SLE nephritis Cryptococcal meningitis	F	41	C-AmB	5.0 AOD	2 hours	3 4	9.5 9.1	VT VT	Death on day 6 from MOF
Barcia, 1998	Acute lymphoblastic leukaemia Disseminated candida infection	M	4	L-AmB	5.0	1 hour	3	16.0	Cardiac arrest	Death
Cleary, 1993	Histiocytosis + severe organ involvement + unconfirmed Candida fungaemia	F	7	C-AmB	5.0 AOD	2 hours	3	12.2	Cardiac arrest	Death
Craven, 1985	SLE nephritis Cryptococcal endophthalmitis	F	19	C-AmB	1.4	45 minutes	15 16	8.4 9.1	VF VF	Death day 53 from progressive disease

SLE = systemic lupus erythematosus; M = male; F = female; AOD = accidental overdose; VT = ventricular tachycardia; VF = ventricular fibrillation; ECG = electrocardiogram.

in animal studies, and demonstrated that high plasma concentrations and rapid infusions of C-AmB resulted in acute hyperkalaemia and haemolysis.^{7,8} Doses between 5 and 15 mg/kg of C-AmB over 15 seconds to 5 minutes caused severe hyperkalaemia and consequently ventricular arrhythmias which were lethal within 15 minutes.⁸ The authors found little evidence of haemolysis and suggested potassium efflux from other cells than red blood cells. This was confirmed by others who demonstrated an increased permeability of endothelial cells after C-AmB administration resulting in massive cellular potassium efflux.⁹

These findings do raise the question what the infusion rate of AmB should be. Clinical studies regarding the relationship between the infusion rate of C-AmB and toxic effects show varying results. Ellis *et al.* compared an infusion rate of 45 minutes *vs* four hours in a large cohort and found higher toxicity in the rapid infusion group.¹⁰ Increased toxicity consisted of chills, tachycardia, nausea and vomiting. They did not report any cases of elevated potassium concentrations or cardiac arrhythmias in any of the treatment groups. On the other hand, other investigators concluded that rapid infusion of C-AmB within one hour was safe and did not increase toxicity.¹¹⁻¹³ Whether the toxicity of lipid formulations of AmB depends on the infusion rate is unclear. In one animal study with rabbits, a single dose of 1.5 mg/kg C-AmB administered in five minutes was lethal due to cardiac toxicity while doses up to 10 mg/kg of L-AmB administered within the same time were tolerated well.¹⁴ Clinical trials comparing different infusion rate strategies of L-AmB are lacking.

Treatment and prevention

In general, treatment of AmB-related acute cardiac toxicity is aimed at the correction of the increased plasma potassium level. Cardiac toxicity can be antagonised by calcium gluconate via lowering the threshold potential of myocardial cells thereby normalising the difference between the membrane potential and the threshold potential.¹⁵ Administration of glucose/insulin and/or salbutamol may lower the plasma potassium level by promoting cellular influx. Haemodialysis is indicated in patients with renal failure. Our patient did not respond to either calcium gluconate and plasma potassium lowering medication. An explanation for this might be the ongoing and massive cellular potassium efflux.

Whether toxicity might be prevented by slower infusion rates is unclear. As noted above, the relationship between the infusion rate of AmB and the development of (cardiac) toxicity is not unequivocal. However, some authorities argue that infusion rates of four to eight hours are safe and probably without noticeable toxicity.¹⁶ Whether continuous infusion over 24 hours might further reduce toxicity is

unclear. Indeed, continuous infusion of C-AmB over 24 hours has shown to reduce (nephro)toxicity;^{17,18} however, efficacy may be decreased due to lower peak serum levels.¹⁹ Discontinuation of (liposomal) AmB should be considered when suspected related hyperkalaemic episodes have occurred provided that the fungus is susceptible to alternative antifungal drugs.

CONCLUSION

The acute onset of severe hyperkalaemia with concomitant cardiac arrhythmias is a rare but life-threatening side effect related to infusion of both C-AmB and L-AmB. Clinicians should be aware of this adverse reaction when prescribing this drug. Although higher infusion rates do not increase toxicity *per se*, slower administration over more than two hours might be considered. Discontinuation of (liposomal) AmB should be considered when suspected related hyperkalaemic episodes have occurred.

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