RESEARCH POINTERS

Improvement in cholesterol emboli syndrome after iloprost therapy

Iloprost therapy improved distal extremity lesions and renal function in patients with cholesterol emboli syndrome

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Cholesterol emboli syndrome is a disorder in which multiple cholesterol crystals dislodge from atherosclerotic plaques, either spontaneously or after vascular interventions, treatment with anticoagulation, or thrombolytic treatment. The syndrome typically presents with painful ischaemic skin lesions, livedo reticularis, and acute renal failure. Treatments such as aspirin, statins, discontinuation of anticoagulation, and surgical correction of the embolic source are of limited efficacy.[1 2] We report four cases of cholesterol emboli in which treatment with iloprost, a prostacyclin analogue,[3] improved both ischaemia of the distal extremities and renal failure.

Patients and results

Four patients who had had a myocardial infarction and underwent procedures including coronary angiography, coronary bypass grafting surgery, and intra-aortic balloon pump implantation (table) presented within a month with cholesterol emboli syndrome. They had bilateral painful cyanotic ischaemic lesions of the toes with concomitant livedo reticularis in the presence of normal peripheral leg pulses. Skin biopsy from one of the ischaemic toe lesions showed cholesterol clefts. Despite treatment with aspirin, simvastatin, and dipyridamole and discontinuation of warfarin and heparin, pain intensity remained severe, new lesions appeared, and (in case 4) serum creatinine concentrations rose to 330 µmol/l.

Intravenous iloprost was administered continuously in gradually increasing doses up to 2 ng/kg/min for 10-14 days, followed by eight hour long infusions three times a week for an additional two to three weeks, and, thereafter, once a week. The rationale was to promote wound healing of the gangrenous lesions. At 30 days' follow up ischaemic lesions had entirely resolved and only those skin lesions featuring gangrenous changes at presentation did not improve. No new ischaemic lesions appeared in the toes. The pain in the extremities gradually resolved, as assessed by the need for narcotics and visual pain scale.

The fourth patient presented with cardiogenic shock, and an intra-aortic balloon pump was implanted. Serum creatinine concentrations rose from 105 µmol/l to 240 µmol/l during the first 10 days and then started to fall to 190 µmol/l on day 13. Then, in the absence of haemodynamic changes, it rose to 330 µmol/l on day 16, associated with ischaemic skin lesions and livido reticularis, cholesterol cleft on skin biopsy, eosinophilia, eosinophiluria, and hypocomplementaemia, all suggesting that the renal failure was related to cholesterol emboli. Iloprost therapy was started, and after 30 days of follow up the creatinine concentration was 240 µmol/l and remained so during long term follow up.

Side effects included transient drop in blood pressure in one patient, reversed by slowing of the infusion rate, and nausea, which necessitated discontinuation of iloprost therapy in two patients. After two days without iloprost the third patient developed new ischaemic lesions of the distal legs. Treatment was resumed at a slower rate and no new lesions were observed.

Comment

Patients suffering from cholesterol emboli syndrome, a progressive disease unresponsive to therapy, may

Table 1 Patients' characteristics, clinical presentation, treatments and response to iloprost

	Patient 1	Patient 2	Patient 3	Patient 4
Age	57	75	76	80
Sex	Male	Female	Female	Female
Medical history	Non-Q wave myocardial infarction, congestive heart failure, hypertension	Non-Q wave myocardial infarction, atrial fibrillation, hypothyroidism	Non-Q wave myocardial infarction, hypertension	Anterior wall myocardial infarction, congestive heart failure, hypertension, diabetes mellitus
Precipitating factors	Coronary angiography	Coronary angiography, warfarin	Coronary angiography, coronary artery bypass graft	Intra-aortic balloon pump, heparin
Clinical presentation	Leg ulcers	Leg ulcers	Leg ulcers, livido reticularis	Livido reticularis, acute renal failure
Laboratory data	Eosinophilia	None	Eosinophilia, raised erythrocyte sedimentation rate	Eosinophilia, eosinophiluria, low C3 complement
Cholesterol clefts	+	+	+	+
Treatment before iloprost	Aspirin, simvastatin	Aspirin, dipyridamole, cessation of wafarin	Aspirin, dipyridamole, simvastatin	Aspirin, dipyridamole, simvastatin, cessation of heparin
Pain intensity after iloprost	Decrease	Decrease	Decrease	Decrease
Degree of pain (visual scale)			10 to 4	4 to 0
Narcotic use	Stopped	Stopped	Decreased	Stopped
Status of leg ulcers	Two toes amputated	Improved	Improved, one necrotic toe	Improved
Renal function	NA	NA	NA	Improved

benefit from iloprost. Administered to four patients suffering from multiple cholesterol emboli, iloprost caused the disappearance of most cyanotic lesions, with a dramatic relief of pain, and, in at least one patient, stabilised and subsequently improved renal function. These cases suggest that the drug should be initiated early to stabilise, and even reverse, the clinical syndrome, but only randomised controlled trials can provide firm evidence of a beneficial effect of iloprost in this syndrome.

In cholesterol emboli syndrome cholesterol crystals obstruct small arterioles, causing local ischaemia and end organ damage. Iloprost, a prostacyclin stable analogue used for treating critical leg ischaemia, Raynaud's syndrome, and pulmonary hypertension,[3] is a potent vasodilator and antiplatelet aggregant, which stabilises endothelial integrity and has cytoprotective properties. This might explain our clinical observations in these four patients.

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Challenges in managing profound hypokalaemia

Potentially life threatening profound hypokalaemia with metabolic acidosis may not be adequately dealt with by current treatment recommendations

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Abnormalities of serum potassium are associated with well described clinical features: lassitude when potassium <3.5 mmol/l, possible muscle necrosis at <2.5 mmol/l, and a flaccid paralysis with respiratory compromise at <2 mmol/l.[1] World wide, hypokalaemia is most often caused by diarrhoea, although specific treatment of hypokalaemia is not mentioned in international guidelines for managing gastroenteritis.[2] Furthermore, a recent case made us concerned that the potassium replacement recommended in medical texts (a maximum rate of infusion of 0.3-0.5 mmol/kg/hour and a maximum daily replacement of 3-5 mmol/kg) may be inadequate for profound hypokalaemia (≤ 1.5 mmol/l).

Patients, methods, and results

The patient (case 1, table) was an 8 month old child with gastroenteritis who was too weak to respond appropriately to pain, with reduced respiratory effort, metabolic acidosis, intermittent sinoatrial block, and an inappropriately low heart rate (72 beats/min) given the degree of dehydration. The risk of inadequate treatment seemed to outweigh the risk of aggressive fluid and potassium replacement as mechanical ventilation and inotropic support were not available. The maximum recommended administration rate and total daily dose for intravenous potassium were therefore exceeded by at least 4 and 3 fold respectively without adverse effects.

We identified further cases with potassium concentrations ≤ 1.5 mmol/l (614 Na^+/K^+ Analyser, Chiron Diagnostics) from paediatric admissions to the high dependency unit of Kilifi District Hospital in1993-2000. Data were extracted from the case records and examined for blood gas and potassium values at 4-8 hours and 18-30 hours after admission (early and late resuscitation phases). The maximum and average hourly rates and total of potassium infusion during resuscitation were calculated.

Thirteen patients, seven of whom died, were identified (table). In four death was too rapid to allow evaluation, and in one survivor data were inadequate. Strikingly, nine out of 11 patients with data on blood gases on admission were markedly acidotic. Although acidosis was persistent (possibly confounding potassium measurements) and continued stool losses could not be measured, there was a significant correlation between the late phase change in potassium and the average rate of potassium replacement over 24 hours (Spearman's τ 0.78, $P=0.02$). The only child developing a potassium value >5.6 mmol/l during admission was a child with a Gram negative septicaemia (case 8): potassium rose to 6.6 mmol/l (pH 6.99, base excess –23.9 mmol) at 48 hours, shortly before death.

Comment

Current guidelines for potassium replacement may not deal adequately with the rare but life threatening situation of profound hypokalaemia (≤ 1.5 mmol/l) associated with metabolic acidosis seen in our developing country setting. Furthermore, recent prospective data suggest that half the children admitted with gastroenteritis have a base excess ≤ -10 mmol and 7% a potassium <2 mmol/l (PS, unpublished data) even though acidosis would normally be expected to increase potassium concentrations (due to efflux of intracellular potassium in exchange for extracellular hydrogen). About 500 children with gastroenteritis and 300 with severe malnutrition are admitted to our hospital annually, so the problem of hypokalaemia with acidosis is important.

Globally, lack of resources makes it likely that such hypokalaemia is rarely recognised. Paradoxically, therefore, children with severe gastroenteritis, perhaps at highest risk of hypokalaemia, may receive intravenous fluids[2] with little or no potassium (0.9% saline, Ringer's lactate, or Hartmann's). In fact by ameliorating any associated acidosis through correcting hypovolaemia or direct alkalinisation (by lactate) cells may import potassium in exchange for intracellular hydrogen ions, further lowering serum