Heparin Induced Hyperkalemia

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INTRODUCTION

Heparin induced hyperkalemia (HIH) is infrequently reported.[1-9] We outline the risk factors for development of this adverse event and describe a case of HIH which was successfully managed using conservative means while the patient continued to receive heparin therapy.

CASE

A 65 year-old male with severe chest pain, haemoptysis, right lower lobe pneumonia, and a right lower lobe mass was transferred to this hospital following a complicated two-week stay in a peripheral hospital. The patient was admitted to cardiology, and on day five, after concluding that his chest pain was not of cardiac origin, he was transferred to the chest service for investigation of the pulmonary mass.

His past medical history was extensive and included chronic obstructive pulmonary disease, ischemic heart disease with a coronary artery bypass graft, congestive heart failure, a left cerebral vascular accident, bilateral carotid endarterectomy, pacemaker insertion, benign prostrate hypertrophy, renal calculus, and a non-functioning left kidney with insertion of a ureter stent. He was a 50 pack-year smoker who quit smoking six weeks prior to admission to hospital. His family history was remarkable for diabetes mellitus.

On admission to the ward, his medications included acetylsalicylic acid 650 mg po daily; nitroglycerin 0.3 mg SL prn; and salbutamol and ipratropium metered dose inhalers, 2 puffs qid; diltiazem 90 mg po bid; cotrimoxazole DS po bid; prednisone 15 mg po daily to be decreased by 5 mg q2d and discontinued; and milk of magnesia, docusate sodium and Maalox® prn. He had been receiving heparin 5000 units sc q12h which was discontinued on transfer to our ward.

On examination, the patient was in no apparent distress. His blood pressure was 140/86 mm Hg; heart rate 80 beats per minute and regular; and respiratory rate 18 per minute. Head and neck examination was remarkable for upper and lower lid xanthelasma. Chest examination revealed diminished breath sounds throughout, with basilar crackles more prominent on the right, and dullness to percussion at the right base. Cardiovascular examination was unremarkable. Femoral bruits were noted, the left being louder than the right. Dorsalis pedis pulses were absent. The abdomen was obese and distended, but bowel sounds were normal. The rest of the examination was unremarkable.

Pertinent laboratory values included serum sodium 144 mmol/L (133-148 mmol/L), potassium 4.5 mmol/L (3.5-5.5 mmol/L), urea 18.4 mmol/L (2.5 - 7.0 mmol/L), serum creatinine 187 μmol/L (55 - 120 μmol/L); blood glucose 6.6 mmol/L (3.6 - 6.1 mmol/L), alkaline phosphatase 235 U/L (20 - 94 U/L), lactic acid dehydrogenase 418 U/L (88 - 177 U/L), white blood cell count 25.4 x 10^9/L,(4-10 x 10^9) haemoglobin 125 g/L (135-180 g/L) and haematocrit .381 (.4-.54). Blood gases on room air were: PO_2 57 mm Hg, pH 7.44 with a PCO_2 31 mm Hg.

The clinical impression was that of a lung cancer and possible pulmonary embolus, in a man with multiple problems. Therefore, the plan was to perform a needle biopsy of the lung lesion, obtain a bone scan and urology consult and, in view of the hypoxemia and chest pain, rule out a pulmonary embolus.

On day eight the patient was noted to have a swollen right leg and a deep venous thrombosis was diagnosed. Heparin therapy was initiated with a bolus of 5,000 units of heparin followed by an infusion of 1,000 units hourly. The heparin infusion was continued at a dosage of approximately 1400 units/hr to maintain the PTT within the range of 50 - 55 seconds (control 34 seconds). Laboratory values on day 10 included: sodium 134 mmol/L, potassium 4.8 mmol/L, creatinine 133 μmol/L, PTT 50 seconds and PT 11.3 seconds. Warfarin therapy was initiated on day 18 and heparin therapy was discontinued on day 24.

On day 27, a deep venous thrombosis developed in the left leg despite adequate warfarin therapy. A haematologist was consulted, and subsequently the patient's warfarin was discontinued, and heparin therapy was resumed with increased intensity to maintain the PTT in the range of 80 - 90 seconds. With this increase, there was slow improvement in the symptoms of leg swelling and tenderness. Eleven days following the increase in heparin dose, after a total of 30 days of heparin therapy, the patient was noted to be hyperkalemic (potassium 5.8 mmol/L) necessitating the administration of sodium polystyrene 30 g. Two further doses

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Acknowledgements: The authors would like to acknowledge Mrs. Jan Butler for her preparation of the manuscript.

of sodium polysterene 30 g were administered and all intravenous solutions were switched to normal saline. His serum creatinine was 114 μmol/L, his pH 7.4 and the only changes to his admission medications had been the addition of warfarin and heparin as noted, and the discontinuation of cotrimoxazole. At the time, the patient was not receiving potassium or any agents other than the heparin known to increase serum potassium and it was felt that the hyperkalemia was secondary to heparin. It was not considered feasible to switch to warfarin at this time as the patient was awaiting further surgery related to the lung lesion.

The patient remained in hospital for several weeks during which time a diagnosis of a non small cell lung cancer was made. Following surgery, his heparin therapy was replaced with warfarin on day 50, and he was discharged approximately three months after his original presentation.

Addendum

Approximately one month after his original discharge from hospital, the patient was readmitted with bilateral deep vein thrombosis. Warfarin was discontinued, and heparin therapy commenced. His potassium on admission was 4.4 mmol/L which increased to 5.3 mmol/L over the next two days. His serum creatinine was 136 μmol/L and glucose 6.4 mmol/L. He was not receiving any exogenous potassium or potassium sparing medications at this time. Sodium polystyrene 30 g po daily was commenced to control hyperkalemia, and he was discharged from the hospital on day nine, receiving heparin SC and sodium polystyrene. His serum potassium was 4.4 mmol/L.

DISCUSSION

Administration of heparin has been shown to decrease aldosterone production by the zona glomerulosa of the adrenal gland. This occurs in all patients as early as four days after initiation of heparin therapy and may increase with time,[5] but is rarely of any clinical consequence. Normally, there is partial compensation with increased renin production by the juxtaglomerular apparatus of the kidney resulting in stimulation of the renin-angiotensin-aldosterone axis which limits the extent of hypoaldosteronism and hyperkalemia.[5] Heparin induced hyperkalemia likely occurs in those patients who cannot adequately compensate by increasing aldosterone levels. In some cases, hyponatremia and hypotension may also occur.[3-5]

Three groups of patients would seem to be at risk for the development of HIH: diabetics, patients with renal insufficiency, and patients on long-term heparin therapy. Diabetics are known to have juxtaglomerular sclerosis and low renin levels, and those diabetics with mild to moderate renal insufficiency seem to be particularly prone to hyporeninemic-hypoaldosteronism and HIH.[5] Nine of fifteen reported cases of HIH have involved diabetic patients.[1,2,4,5,6,8] In patients with impaired potassium excretion due to renal failure, the effect of heparin on aldosterone synthesis may be sufficient to result in hyperkalemia.[6] There have been five reports of HIH in non-diabetic patients with mild to moderate renal failure[3,6,7,9] with the mean serum creatinine in the cases reported being 1.7 mg/dl (approximately 150 μmol/L), ranging from 1 - 3.2 mg/dl (88-283 μmol/L). HIH has not been reported in patients with severe renal failure, perhaps only because hyperkalemia is an expected and unreported event in such patients. Finally, patients on long term heparin therapy also may be at risk for the development of HIH.[3,4]

The time to onset of HIH in the reported cases has ranged from 5 - 66 days (mean 23.6 days) excluding one diabetic who developed irreversible HIH after two years of heparin therapy. Atrophy of the zona glomerulosa was found in this patient.[4] One other case of irreversible HIH after 66 days of heparin therapy has been reported. In the latter patient, the zona glomerulosa was found to be normal at autopsy.[3] In animals, narrowing of the zona glomerulosa has been shown to occur after two weeks of heparin therapy with a marked, thinning after four weeks of therapy.[10] This may contribute to reduced aldosterone synthesis and the development of HIH in patients on prolonged heparin therapy. Serum sodium has decreased in most patients with one patient developing severe hyponatremia (Na 111 mmol/L).[4] The dose and route of heparin administration do not seem to be important in the development of HIH. While our patient and two others[5,7] developed hyperkalemia with continuous infusions of therapeutic doses, most cases occurred in patients receiving low-dose heparin subcutaneously. Of interest, the highest potassium concentration occurred in our patient during the highest intensity anticoagulation (potassium 5.8 mmol/L, PPT>120 sec).

A prospective study has shown HIH to occur in 8.4% of patients receiving heparin. This developed after 5 - 21 days with those at risk of HIH including patients with diabetes mellitus, those receiving potassium as well as patients with metabolic acidosis (a factor known to contribute to hyperkalemia on its own).[13] In most cases, hyperkalemia resolves within days after discontinuation of heparin.[1,2,5-9] However, it may be irreversible as reported in two cases.[3,4] In our patient, discontinuation was not deemed appropriate initially, and hyperkalemia was managed by the occasional use of sodium polystyrene, and by avoidance of hyperkalemia-inducing agents. It would seem prudent that if heparin can be discontinued, and alternate anticoagulation instituted, that this should be done. When this

is not possible, frequent monitoring of potassium and intermittent therapy with sodium polystyrene would be useful. If this therapy cannot control potassium and/or the patient becomes symptomatic, either due to hyperkalemia, hyponatremia or hypotension, alternate therapies should again be pursued.

Patients with diabetes mellitus, mild to moderate renal insufficiency, or those receiving prolonged heparin therapy would appear to be at greatest risk of HIH, and pharmacists should monitor for this adverse event in this sub-population. Considering the consequences of hyperkalemia and the reported time to onset of HIH (5 - 66 days), it might be reasonable to monitor serum potassium in those at risk for the development of HIH at the onset of therapy and once weekly for the first ten weeks of therapy.

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