CASE REPORT

A complication to be aware of: hyperkalaemia following propranolol therapy for an infant with intestinal haemangiomatosis

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SUMMARY

Infantile haemangiomas, benign vascular tumours seen in 4–10% of infants are characterised by their spontaneous remission following a 3–9 month period of dynamic growth. Propranolol has been reported to be used as a successful treatment of severe symptomatic infantile haemangiomas. Hyperkalaemia has not been recognised as a serious effect of propranolol since recently. Here, we would like to portray a 2-year-old male patient with intestinal haemangiomatosis who presented with severe hyperkalaemia and was successfully managed with hydration, loop diuretics, potassium binding granules, inhaler β -2 agonists and insulin. To date, this is the first case of intestinal haemangiomatosis complicated with severe hyperkalaemia. Our case suggested the idea of close monitorisation of potassium levels as well as haemodynamic status at the initialisation of the propranolol treatment.

BACKGROUND

Infantile haemangiomas, benign vascular tumours seen in 4–10% of infants are characterised by their spontaneous remission following a 3–9 months period of dynamic growth.¹ Propranolol has been reported to be used as a successful treatment of severe symptomatic infantile haemangiomas.^{2–3} Previously reported adverse events are bradycardia, hypotension, hypoglycaemia and bronchospasm.^{3–5} A step by step increase in propranolol dose and monitorisation of patient for haemodynamic changes are recommended at the initialisation of propranolol therapy.^{6–7} Hyperkalaemia has not been recognised as a serious effect of propranolol since recently it was reported in a 17-week-old female preterm infant who presented with a large, cutaneous-subcutaneous haemangioma of the thoracic wall during propranolol treatment.⁸ A further interesting finding of laboratory tumour lysis syndrome (TLS) with hyperkalaemia and hyperphosphataemia was reported in a 33-day-old patient with an ulcerated infantile haemangioma starting as an 8 mm lesion on the upper lip and later enlarged to cover the entire upper lip as an ulcerated lesion.⁹ Here, we would like to portray a 2-year-old male patient with intestinal haemangiomatosis who presented with severe hyperkalaemia and was successfully managed with hydration, loop diuretics, potassium binding granules, inhaler β -2 agonists and insulin. To date, this is the first case of intestinal haemangiomatosis complicated with severe

hyperkalaemia. Our case suggested the idea of close monitoring of potassium levels as well as haemodynamic status at the initialisation of the propranolol treatment.

CASE PRESENTATION

Eight-month-old male patient was admitted to our hospital with a 2-day history of melaena. He did not have fever, emesis, diarrhoea or bleeding from any other site. His history revealed three similar gastrointestinal (GI) bleeding episodes in the form of melaena and haematochezia two of which required packed red blood cell transfusion (PRBC). At the physical examination he was at the 25th centile for weight and height without any pathological finding other than bloody stool at rectal examination.

INVESTIGATIONS

Laboratory studies showed microcytic anaemia (haemoglobin (Hb): 7 g/dL, mean corpuscular volume: 60 fL), normal platelet count and coagulation parameters. On abdominal ultrasonography, a hypervascular mass with dimensions of 6×3×6 cm neighbouring the lower pole of the spleen was detected. Upper and lower GI endoscopy and Meckel scintigraphy were normal. Small intestinal passage graph revealed nodular thickenings in the bowel segments and narrowings secondary to those segments. In the CT angiography there was diffuse thickening and contrast enhancement involving ileal segments (figure 1).

DIFFERENTIAL DIAGNOSIS

He was investigated for bleeding diathesis and all haemostatic laboratory tests were normal. After ultrasonography-guided biopsy he was diagnosed with intestinal haemangiomatosis with positive CD34 and GLUT-1 positivity (figure 2).

TREATMENT

During follow-up he had massive GI bleeding that required PRBC transfusion (Hb: 3 g/dL). Propranolol was begun at a dose of 0.5 and gradually increased to 2 mg/kg/day. He was discharged with propranolol full dose treatment. At the sixth month of his discharge he was symptom free and the control ultrasonography revealed the haemangiomatous area to be 3×2×3 cm. He was readmitted with GI bleeding again when he was 18 months old. It was learned that the family discontinued propranolol 6 months ago as they thought their

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Figure 1 CT angiography showing diffuse thickening and contrast enhancement involving ileal segments.

child was well. The ultrasonography at this last admission revealed a $3 \times 2 \times 3$ cm haemangiomatous area and after management of acute bleeding propranolol was restarted at a dose of 2 mg/kg/day. The family was not adherent to follow-up due to socioeconomic problems and admitted for routine control 6 months later. The patient was asymptomatic with normal vital signs. The laboratory tests revealed K^+ : 6.5 mmol/L, (control: 8.2 mmol/L) with other biochemical tests to be normal according to our laboratory cut-off levels (blood urea nitrogen: 11 mg/dL, creatinine: 0.23 mg/dL, lactate dehydrogenase: 310 IU/dL, Ca^{+2} : 10 mg/dL, P: 5.28 mg/dL, uric acid: 5 mg/dL, Na: 140 mmol/L). ECG was normal. The ultrasonography at this last admission revealed a $3 \times 2 \times 3$ cm haemangiomatous area again. Propranolol was discontinued. He was hospitalised for hyperkalaemia, and hydration of 3000 cc/m²/day, alkalinisation, furosemide 2 mg/kg/day and 0.15 mg/kg/dose 6 doses/day inhaler salbutamol were started on the first day of hospitalisation. He was monitored for cardiac effects of hyperkalemia. The patient was restricted for potassium containing diet as well. The patient was adherent to dietary restrictions during his hospitalisation. Sufficient diuresis was achieved and there were no ECG changes during follow-up. Control potassium levels were monitored every 8 h. Four days later as effective decrease of potassium levels cannot be achieved (control K^+ : 6 mmol/L) antipotassium granule (1 mg/kg/dose 2 doses/day) was added to the treatment. Two days later the K^+ level was still 5.44 mmol/L and insulin +glucose infusion was started; however, it was stopped due to

Figure 2 CD34 positivity in pathological examination.

hypoglycaemia. At the end of first week of follow-up an attempt to decrease furosemide caused an increase in K^+ level; therefore, furosemide was planned to be decreased very slowly (0.2 mg/kg/day every 4 days). At the second week of his hospitalisation, K^+ was found to be 3.85 mmol/L and propranolol was started at a dose of 0.5 mg/kg/day.

OUTCOME AND FOLLOW-UP

During a further 2 weeks of follow-up propranolol was gradually increased to a dose of 2 mg/kg/day and a stepwise cessation of salbutamol, furosemide and hydration was managed, antipotassium was continued one more week after discharge and was stopped as K^+ level remained stable (figure 3). The control abdominal ultrasonography showed the resolution of the haemangiomatosis at discharge and he did not have any GI bleeding and hyperkalaemia again during the 1 month ambulatory follow-up. Propranolol was discontinued 3 months later after a second normal ultrasonography. The patient has not had any symptoms for 6 months now.

DISCUSSION

Systemic corticosteroids were the first-line therapy for complicated haemangiomas of infants until recently; however, unresponsiveness of a 6–31% to corticosteroids has led to a decrease in their usage.^{10 11} Propranolol has been recently introduced in the use of infantile haemangiomas by Leaute Labreze *et al* in 2008 and is widely used thereafter.^{2 4 5} As β -blockers decrease heart rate and depress myocardial activity, it is recommended for the patients at the initialisation of propranolol therapy to be monitored for hypotension, bradycardia and congestive heart disease. Other expected side effects are digestive system disorders, shortness of breath, nausea and vomiting, paraesthesia, purpura, thrombocytopenia, fatigue and cold extremities.¹² Hyperkalaemia as a complication of propranolol therapy was first reported by Pavlakovic *et al*⁸ in a 17-week-old female preterm infant who presented with a large, cutaneous-subcutaneous haemangioma of the thoracic wall. Severe hyperkalaemia without any pathological findings was observed 4 days into propranolol therapy. The absolute start of hyperkalaemia of our patient is not known as it could have been any time in the 6 month period during his propranolol therapy as the family did not bring him for control during this period. However, it is known that hyperkalaemia or other side effects were not seen when he was hospitalised for 2 days at initiation of propranolol when he had GI bleeding episodes. Propranolol has a wide use in paediatric cardiology; however, hyperkalaemia as a complication of propranolol had not been documented in cardiology studies previously.^{13 14} The interstitial and endothelial cells have been shown to divide and multiply under the effect of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in the dynamic growth phase of haemangiomas.^{15–17} At the involution phase bFGF and VEGF are reduced. It is established that hypoxaemia leads to increased expression of VEGF through hypoxia-inducible factor 1 α causing proliferation in relatively hypoxic medium of haemangioma.¹⁸ Hypoxia and noradrenergic stimulation have been shown to have the potential to stimulate VEGF.¹⁹ In the involution phase of haemangiomas there is increased apoptosis.²⁰ The effect of propranolol on infantile haemangiomas has been assigned to its effects on vasoconstriction, decreased expression FGF and VEGF genes, decreased angiogenesis and induction of apoptosis.³ Hyperkalaemia has not been a known complication of propranolol therapy since recently; however, as it induces apoptosis of cells in haemangioma, hyperkalaemia is attributed to the potassium content released by apoptotic haemangioma cells similar to TLS after cytotoxic therapy of

Figure 3 Serum potassium levels during follow-up.

haematological malignancies by Pavlakovic *et al.*⁸ However, it was thought to be in contrast to high phosphorous and uric acid content of malignant cells, the lysis of haemangiomas did not lead to TLS but only hyperkalemia.⁸ A recent report by Cavalli *et al.*⁹ established laboratory tumour lysis with hyperkalaemia and hyperphosphataemia with normal creatinine and uric acid levels. In this report a 33-day-old newborn was presented with an 8 mm haemangioma of the upper lip and it grew large to occupy the whole upper lip with ulceration. Whether the hyperkalaemia side effect is dependent on the size of the lesion is not known, however the large intestinal haemangioma area may have contributed to hyperkalaemia. Our patient only presented with hyperkalaemia; however, it took 2 months for potassium levels to be completely normalised resembling the previous case.⁹ Our patient was restricted for potassium containing foods after the detection of hyperkalaemia. The mechanism of propranolol to cause hyperkalaemia has been reported to impair β -2 receptors interfering with potassium into the cells as renal potassium excretion remains intact.²¹ It has been shown that potassium infusion following β -receptor blockade caused increased potassium levels compared to potassium alone by impairment of Na-K pump reuptake of extracellular potassium.²² The reason for lack of cardiac symptoms due to hyperkalaemia in our patient and previously reported two cases may be attributed to the inhibition of Na-K pump at myocardial cells as well. Our patient was treated with intravenous hydration, furosemide and inhaled β -2 agonists as in case of the previous reports.^{8, 9} Despite adequate decrease in potassium levels, antipotassium granule was added as a further treatment modality and has been successful together with other drugs. We recommend its usage in case of intractable hyperkalaemia as a complication of propranolol. After the vanishing of the intestinal haemangiomatosis our patient did not have hyperkalaemia again and rebound haemangioma was not observed after 6 months of cessation of therapy. To date, this is the first case of intestinal haemangiomatosis complicated with severe hyperkalaemia.

Learning points

- Hyperkalaemia should be kept in mind at the initialisation of propranolol therapy.
- Close monitoring of potassium levels as well as haemodynamic status at the initialisation of the propranolol treatment is necessary.
- Furosemide, hydration, salbutamol and antipotassium granule can be used in treatment of hyperkalaemia due to propranolol.

Contributors BB followed up with the patient and wrote the manuscript. AO revised the manuscript and controlled the latest version, followed up with the patient and took the images. BD followed up with the patient and revised the manuscript at the point of gastroenterology.

Competing interests None.

Patient consent Obtained.

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