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CASE REPORTS/CASE SERIES

Salbutamol to facilitate management of acute hyperkalemia in liver transplantation: a case report

Présentation de cas: le salbutamol utilisé pour faciliter la prise en charge de l'hyperkaliémie aiguë dans une transplantation hépatique

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Abstract

Purpose *Acute hyperkalemia is a frequent, potentially life-threatening complication in orthotopic liver transplantation (OLT). We describe a case of acute hyperkalemia during the pre-anhepatic stage that remained persistent despite conventional treatment, including calcium salts, insulin and glucose, sodium bicarbonate, and furosemide.*

Clinical features *A 50-yr-old man with end-stage hepatitis B liver cirrhosis underwent living donor liver transplantation, receiving a right lobe graft donated by his son. The initial serum potassium concentration was 4.6 mEq l^{-1}. Despite conventional management, the serum potassium concentration increased to 6.6 mEq l^{-1}, intraoperatively. Since about 90 min elapsed from the division of the hepatic artery and the portal vein to the clamping of the suprahepatic inferior vena cava, the persistent hyperkalemia may have resulted from loss of potassium from ischemic liver cells into the systemic circulation. After incorporating nebulized salbutamol, a selective β_2-agonist, into the combined therapeutic regimen (sodium bicarbonate and insulin with glucose), the serum potassium concentrations rapidly normalized.*

Conclusions *This case suggests that acute and relatively refractory hyperkalemia can develop when surgical interruption of hepatic inflow is prolonged during hepatectomy in patients undergoing OLT using the piggyback technique. In such situations, incorporating nebulized salbutamol with a conventional anti-hyperkalemia strategy can provide an effective therapeutic option to treat hyperkalemia, even during the anhepatic stage.*

Résumé

Objectif *L'hyperkaliémie aiguë est une complication fréquente et potentiellement fatale lors de transplantation hépatique orthotopique. Nous décrivons un cas d'hyperkaliémie aiguë pendant la phase pré-anhépatique qui a persisté malgré le traitement traditionnel, y compris les sels de calcium, l'insuline et le glucose, le bicarbonate de soude et le furosémide.*

Éléments cliniques *Un homme de 50 ans souffrant d'une cirrhose du foie par hépatite B en phase terminale a subi une transplantation hépatique d'un donneur vivant, recevant un greffon du lobe droit de son fils. La concentration sérique de potassium initiale était de 4,6 mEq·L^{-1}. Malgré une prise en charge conventionnelle, la concentration sérique de potassium s'est élevée à 6.6 mEq·L^{-1} pendant l'opération. Étant donné qu'environ 90 min s'étaient écoulées entre la division de l'artère hépatique et de la veine porte et le clampage suprahépatique de la veine cave inférieure, l'hyperkaliémie persistante résultait peut-être de la perte de potassium des cellules hépatiques ischémiques dans la circulation systémique. Après avoir incorporé du salbutamol nébulisé, un agoniste β_2 sélectif, au régime thérapeutique combiné (bicarbonate de soude et insuline*

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avec glucose), les concentrations sériques de potassium sont rapidement revenues à des taux normaux.

Conclusion *Ce cas suggère qu'une hyperkaliémie aiguë et relativement réfractaire peut se manifester lorsque l'interruption chirurgicale de l'apport hépatique est prolongée durant une hépatectomie chez des patients subissant une transplantation hépatique orthotopique avec la technique de perfusion jumelée. Dans de telles situations, l'incorporation de salbutamol nébulisé à une stratégie anti-hyperkaliémique traditionnelle peut constituer une option thérapeutique efficace pour le traitement de l'hyperkaliémie et ce, même durant la phase anhépatique.*

During orthotopic liver transplantation (OLT), hyperkalemia frequently follows massive transfusion, renal insufficiency, or a sudden release of potassium from the graft on reperfusion.[1,2] We describe a case of acute hyperkalemia that was provoked by acute hepatic necrosis during the pre-anhepatic stage in living donor liver transplantation (LDLT). Despite initial treatment, including calcium insulin and glucose, sodium bicarbonate, and furosemide,[3] hyperkalemia did not resolve until nebulized salbutamol was administered. The efficacy of a selective β_2-agonist, such as salbutamol, in lowering serum potassium has been established in normal volunteers[4] and in chronic renal failure patients.[5–9] However, there are no data regarding its potential efficacy as a treatment option for hyperkalemia as a result of OLT, especially during the anhepatic stage. We report the successful use of nebulized salbutamol in combination with conventional treatments to prevent a life-threatening increase in serum potassium during the pre-anhepatic stage in LDLT. The patient provided written consent for publication of this report.

Case report

A 50-yr-old man (177 cm, 83 kg) suffering from end-stage hepatitis B liver cirrhosis was admitted for LDLT. He had a history of four transarterial chemoembolizations and an ethanol injection for the recurrence of hepatocellular carcinoma. There was no evidence of hepatorenal syndrome and no history of diabetic mellitus or renal dysfunction. His serum potassium concentration was normal (4.4 mEq l^{-1}) one day before surgery, as were his blood urea nitrogen (BUN; 20.5 mg dl^{-1}) and creatinine (1.3 mg dl^{-1}) levels. The model for end-stage liver disease score at OLT was 19. He had not taken any medication known to cause hyperkalemia within the previous two weeks.

Anesthesia was induced with fentanyl 100 μg i.v., thiopental sodium 250 mg i.v., and vecuronium 8 mg i.v., and was maintained with oxygen, air, and desflurane. Neuromuscular block was maintained with atracurium. Hemodynamic monitoring included right radial and femoral artery, central venous, pulmonary artery, and capillary wedge pressures, as well as cardiac output measurements. The surgery proceeded by way of the piggyback technique, with preservation of caval flow. Blood samples were taken from a catheter in the right radial artery. The initial serum potassium concentration was 4.6 mEq l^{-1} (Table 1). At the mid-point of the hepatectomy, the concentration increased to 5.9 mEq l^{-1} (Table 1) and then further increased to 6.6 mEq l^{-1} (Table 1), despite the administration of calcium gluconate (1 g i.v.) and an infusion of sodium bicarbonate (40 mEq) and dextrose (50%, 50 ml) with 10 U of regular insulin. At this stage, the electrocardiogram (ECG) monitor showed tall T waves, absent P waves, and a normal QRS complex. Although hourly urine output remained 80–100 ml h^{-1}, furosemide 10 mg i.v. was administered. Subsequently, the administration of dextrose (50%, 50 ml i.v.) with 10 U of regular insulin was repeated. Approximately 2 h after the initial anti-hyperkalemic interventions, hyperkalemia persisted. At this point, neither potassium-containing fluids nor packed red blood cells had been administered, nor was there evidence of significant metabolic acidosis (Table 1). The cause of the hyperkalemia was unclear, but it was thought to have been related to the surgical procedure. Due to anatomic factors (a caudate lobe wrapping around the IVC), about 90 min had elapsed from the division of the hepatic artery and the portal vein to the clamping of the suprahepatic inferior vena cava (IVC), and it was presumed that the persistent hyperkalemia resulted from loss of potassium from ischemic liver cells into the systemic circulation.

We decided to incorporate nebulized β_2-agonist therapy into the combined regimen of insulin, glucose, and sodium bicarbonate, and we determined that hemodialysis would have to be considered if hyperkalemia did not resolve after one more therapeutic cycle of this combined therapy. Thus, we changed the anesthetic machine to one with a different ventilator (Savina, Drager Medical, Lübeck, Schleswig-Holstein, Germany), which enabled the nebulized treatment to be administered during positive pressure ventilation. Nebulized salbutamol (10 mg in 3 ml of normal saline) was administered over 20 min. During this period, the desflurane anesthesia was supplemented with intermittent bolus injections of propofol and fentanyl, and the infusion of dextrose (50%, 50 ml) with 10 U of insulin and sodium bicarbonate (40 mEq) was continued. Except for transient tachycardia at the initiation of the salbutamol treatment, no complication was observed. As there was little time at this point to reperfuse the liver graft, we simultaneously mobilized the necessary personnel and equipment for possible hemodialysis. However, within

Table 1 Arterial blood gases, and potassium, ionized calcium, and glucose concentrations during liver transplantation

	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	HCO_3^-	Base excess (mEq l^{-1})	K^+ (mEq l^{-1})	Ca^{2+} (mEq l^{-1})	Glucose (mg dl^{-1})
ⓐ 10 min after anesthesia	7.42	35.6	232.9	23.4	−0.2	4.6	1.0	152
ⓑ 4 h after anesthesia	7.38	38.5	290.6	23.3	−1.0	5.9	1.2	135
ⓒ 5 h 30 min after anesthesia	7.40	37.7	286.9	23.4	−0.6	6.6	1.5	218
ⓓ 7 h 10 min after anesthesia	7.42	37.0	261.8	24.1	0.4	4.7	1.2	240
ⓔ 8 h 20 min after anesthesia	7.41	36.8	262.2	23.4	−0.4	5.8	1.3	108
ⓕ 9 h 20 min after anesthesia	7.43	35.4	258.6	23.5	0.0	4.6	1.4	185

$PaCO_2$, PaO_2 (mmHg); HCO_3^-, base excess, K^+, Ca^{2+} (mEq l^{-1}); glucose (mg dl^{-1})

20 min of receiving the combined therapy (10 min before reperfusion), serum potassium had decreased to 4.7 mEq l^{-1} (Table 1). The liver graft was vigorously flushed with 5% albumin (250 ml) via the portal vein before the reperfusion. Five minutes after the administration of calcium gluconate 1 g i.v., the liver graft was reperfused, and postreperfusion syndrome did not develop.

Two hours after the initiation of salbutamol treatment, serum potassium gradually increased to 5.8 mEq l^{-1} (Table 1), and a gradual peaking of the T wave was observed again on the ECG monitor. The patient was treated once again with insulin and nebulized salbutamol 10 mg i.v., and serum potassium again normalized to 4.6 mEq l^{-1} (Table 1). Further surgery was completed uneventfully, and the serum potassium concentration remained within the normal range. The operation lasted 12 hr15 min, and the anhepatic stage lasted 110 min. The estimated blood loss was 1800 ml; 2 U of packed red blood cells were administered during the surgery.

Discussion

Although hyperkalemic episodes are most common and important immediately after graft reperfusion, they can also develop at the pre-anhepatic stage during OLT.[2,10] Xia et al.[2] found that 10.2% of the patients develop hyperkalemia (≥5.5 mEq l^{-1}) in the pre-reperfusion period and that an increased baseline potassium concentration and red cell transfusion were independent predictors of hyperkalemia in this period. The preoperative or intraoperative administration of several medications, including angiotensin converting enzyme inhibitors, spironolactone, trimethoprim, succinylcholine, heparin, and epsilon-aminocaproic acid has also been identified as a risk factor for intraoperative hyperkalemia.[11,12] However, in the present case, the patient had not received any of these medications or a blood transfusion before the development of hyperkalemia, and his preoperative serum potassium concentration was normal. Furthermore, the development of hyperkalemia cannot be explained by either an excessive input of potassium or a primary failure of renal potassium excretion.

When considering the events of this case and the time course of the hyperkalemia (during the late hepatic dissection period), extensive cellular potassium loss as a result of surgical manipulation was the most likely cause. At the critical point of the hyperkalemic response, the hepatic artery and portal vein had already been divided, but the clamping of the suprahepatic IVC had been delayed for about 90 min because the caudate lobe was firmly wrapped around the IVC. Therefore, it is likely that progressive ischemic hepatic necrosis ensued during the interruption of hepatic flow and that a quantity of potassium was released from the necrotic liver cells and entered the systemic circulation. Ischemic liver cells can release large amounts of intracellular potassium,[13] and the potassium concentration in the systemic circulation is known to increase when the hepatic circulation is interrupted for periods longer than 20 min.[14,15] Moreover, hyperkalemia is more marked during longer periods of hepatic ischemia[16] and can be sustained for 2 h, even when circulation is restored.[15,16]

A similar episode of severe hyperkalemia has been reported in the setting of LDLT, in which the piggyback technique was used.[10] The piggyback technique, with preservation of the native IVC and direct anastomosis between the donor's IVC and the recipient's hepatic vein, avoids retrocaval and adrenal dissection, thereby leading to reduced bleeding and a shortened anhepatic stage. Furthermore, it offers the advantages of a low incidence of renal impairment and improved hemodynamic stability during the anhepatic stage without the use of venovenous bypass.[17] However, anatomical challenges, such as intensive inflammatory adhesions or a caudate lobe wrapped tightly around the IVC, often limit its use.[17] In such cases, the anesthesiologist should remain vigilant to prevent hepatic flow interruption longer than 20–30 min and to monitor closely for the possible development of hyperkalemia.

For the management of acute intraoperative hyperkalemia, regardless of the underlying cause, three main approaches have been recommended: 1) to oppose the direct

toxic effects of hyperkalemia on cell membranes by infusing calcium salts; 2) to promote cellular uptake of potassium using insulin with glucose, a β_2-agonist, or possibly sodium bicarbonate, either alone or in combination; and 3) to remove potassium from the body using diuretics or hemodialysis.[3,12]

In this case, we administered relatively small doses of sodium bicarbonate and furosemide (80 mEq and 10 mg, respectively) for intractable hyperkalemia, because the patient had satisfactory urine output and no documented metabolic acidosis. The potassium-lowering effects of insulin have been demonstrated in the setting of OLT.[18] Insulin effectively decreases the serum potassium concentration within 15 min, and its effect lasts for at least 60 min, even in the anhepatic phase. However, the initial treatment, which included bicarbonate, insulin, and furosemide, failed to normalize the serum potassium concentration. During the initial uncontrolled hyperkalemic episode, the potassium influx into the systemic circulation may have exceeded the patient's renal excreting ability and the transcellular shifting capacities of the administered insulin (initial: 20 U, total: 40 U) and sodium bicarbonate. Ultimately, persistent hyperkalemia resolved after administering nebulized salbutamol. We believe that the patient's hyperkalemia was relatively refractory to the conventional treatments, but resolved only after the introduction of multimodal therapy incorporating the effects of nebulized salbutamol with initial therapy.

Generally, treatment with nebulized salbutamol for hyperkalemia requires a dose of 10–20 mg delivered over 10–30 min.[3,5] The onset of action is usually within 15–30 min, with a peak effect between 30 and 60 min, and its effect lasts for 4–6 h.[3,5,12] The onset time and the duration of its hypokalemic effect are similar to those of insulin and sodium bicarbonate.[12] In this case, we administered a total of 20 g of nebulized salbutamol over two cycles. The hypokalemic response is dependent on the dose administered, as greater efficacy was reported in patients receiving 20 mg vs. 10 mg of nebulized salbutamol.[9]

Salbutamol stimulates β_2-adrenergic receptors in muscles and the liver, and then it enhances cellular uptake of potassium with direct activation of Na^+–K^+ ATPase via a rise in the cyclic AMP system; its effect is independent of insulin. Although the anhepatic stage of OLT excludes any hepatic function, in the present case, nebulized salbutamol reliably reduced the serum potassium concentration even in the anhepatic stage, possibly by an extrahepatic transcellular potassium shift. Moreover, insulin and β_2-agonists are known to exert additive hypokalemic effects through different intracellular signalling mechanisms.[7] When sodium bicarbonate is combined with insulin or a β_2-agonist, it also has a synergistic effect in lowering the serum potassium concentration.[8,19] Previous studies found that 20 mg of nebulized salbutamol lowered serum potassium by 1.21 ± 0.19 mEq l^{-1} in tandem with the administration of insulin 10 U i.v., while nebulized salbutamol 15 mg lowered serum potassium by 0.96 mEq l^{-1} when given after sodium bicarbonate (2 mEq kg^{-1} i.v.).[8,20] In our case, despite a sustained influx of intracellular potassium to the systemic circulation, our triple combined therapeutic regimen reduced serum potassium by 2 mEq l^{-1}. Therefore, it is efficacious to use a regimen combining these three agents, particularly for acute, severe hyperkalemia.

A major concern regarding the use of salbutamol is a paradoxical elevation in serum potassium concentrations in the first minutes following nebulization.[5,21] Although this response is minor (0.15 mEq l^{-1})[5] or transient (less than 3 min),[5,21] in cases of excessive hyperkalemia, it is prudent to administer calcium salts immediately before initiating nebulized salbutamol.

In summary, this case suggests that a delay in clamping the suprahepatic IVC for a significant period after the interruption of both the hepatic artery and the portal vein can cause the development of acute severe hyperkalemia in patients undergoing OLT using the piggyback technique. In such situations, careful intraoperative ECG monitoring with frequent measurements of serum potassium are important. During liver transplantation, treatment with nebulized salbutamol, insulin, and sodium bicarbonate is an effective therapeutic combination to treat hyperkalemia.

Conflicts of interest None declared.

References

1. *Perkins JD*. Hyperkalemia and liver transplantation. Liver Transpl 2008; 14: 252–3.
2. *Xia VW, Ghobrial RM, Du B, et al*. Predictors of hyperkalemia in the prereperfusion, early postreperfusion, and late postreperfusion periods during adult liver transplantation. Anesth Analg 2007; 105: 780–5.
3. *Kim HJ, Han SW*. Therapeutic approach to hyperkalemia. Nephron 2002; 92: 33–40.
4. *Smith SR, Ryder C, Kendall MJ, Holder R*. Cardiovascular and biochemical responses to nebulised salbutamol in normal subjects. Br J Clin Pharmacol 1984; 18: 641–4.
5. *Mandelberg A, Krupnik Z, Houri S, et al*. Salbutamol metered-dose inhaler with spacer for hyperkalemia: how fast? How safe? Chest 1999; 115: 617–22.
6. *Liou HH, Chiang SS, Wu SC, et al*. Hypokalemic effects of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure: comparative study. Am J Kidney Dis 1994; 23: 266–71.
7. *Lens XM, Montoliu J, Cases A, Campistol JM, Revert L*. Treatment of hyperkalaemia in renal failure: salbutamol v. insulin. Nephrol Dial Transpl 1989; 4: 228–32.
8. *Kim HJ*. Acute therapy for hyperkalemia with the combined regimen of bicarbonate and beta(2)-adrenergic agonist (salbutamol) in chronic renal failure patients. J Korean Med Sci 1997; 12: 111–6.
9. *Allon M, Dunlay R, Copkney C*. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. Ann Intern Med 1989; 110: 426–9.

10. *Kaku R, Matsumi M, Fujii H, et al*. A case of severe acute hyperkalemia during pre-anhepatic stage in living-related liver transplantation (Japanese). Masui 2002; 51: 1003–6.
11. *Perazella MA, Biswas P*. Acute hyperkalemia associated with intravenous epsilon-aminocaproic acid therapy. Am J Kidney Dis 1999; 33: 782–5.
12. *Alfonzo AV, Isles C, Geddes C, Deighan C*. Potassium disorders-clinical spectrum and emergency management. Resuscitation 2006; 70: 10–25.
13. *Abouna GM, Skillen A, Hull CJ, Hodson A, Kirkley JR*. A comparison of the effects of warm ischemia and hypothermia on liver glycogen, electrolytes, pH, and subsequent function during perfusion. Br J Surg 1969; 56: 382–3.
14. *Jolly PC, Foster JH*. Hepatic inflow stasis. Surgery 1963; 54: 45–55.
15. *Bengmark S, Hafstrom L, Hultin H, Jagenburg R, Vosmik J*. Serum potassium during and following short-term splanchnic ischaemia, short-term hepatic ischaemia, permanent hepatic ischaemia, and total hepatectomy in pigs. Br J Surg 1969; 56: 693–4.
16. *Hall RR*. Hyperkalaemia following temporary occlusion of the portal vein and hepatic artery. Br J Surg 1972; 59: 125–8.
17. *Busque S, Esquivel CO, Concepcion W, So SK*. Experience with the piggyback technique without caval occlusion in adult orthotopic liver transplantation. Transplantation 1998; 65: 77–82.
18. *Li Q, Zhou MT, Wang Y, et al*. Effect of insulin on hyperkalemia during anhepatic stage of liver transplantation. World J Gastroenterol 2004; 10: 2427–9.
19. *Kim HJ*. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron 1996; 72: 476–82.
20. *Allon M, Copkney C*. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int 1990; 38: 869–72.
21. *Du Plooy WJ, Hay L, Kahler CP, Schutte PJ, Brandt HD*. The dose-related hyper- and hypokalaemic effects of salbutamol and its arrhythmogenic potential. Br J Pharmacol 1994; 111: 73–6.