Case Report

Fatal lactic acidosis possibly related to ganciclovir therapy in a renal transplant patient?

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Abstract

Ganciclovir is widely prescribed in renal transplant patients for the prevention or treatment of herpes and cytomegalovirus (CMV) infections. Side-effects are usually represented by hematological disorders, and particularly leucopenia. We report a case of severe and fatal lactic acidosis developing in a 76-year-old renal transplant woman, a few days after ganciclovir has been introduced to treat CMV pneumonia. Usual etiologies of lactic acidosis were ruled out. A high lactate/pyruvate molecular ratio was suggestive of a respiratory chain dysfunction. With the analogy to nucleoside analogues-related lactic acidosis, we suggest that ganciclovir may exceptionally be responsible for respiratory chain dysfunction and subsequent lactic acidosis, and we discuss potential risk factors in our patient.

Keywords: Ganciclovir, lactic acidosis, renal transplant

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.152772

Quick Response Code:

Introduction

Ganciclovir is frequently prescribed to prevent and cure viral infections after organ transplantation. Safety profile is mainly limited to an increased risk of leucopenia, but recent case observations suggest that ganciclovir could be exceptionally associated with lactic acidosis.[1] We would like to report an additional fatal case documented by blood lactate/pyruvate (L/P) ratio.

Case Report

A 76-year-old renal transplant woman was admitted to the Intensive Care Unit (ICU) for coma and respiratory distress. Current immunosuppressive therapy included methylprednisolone (4 mg/day), tacrolimus (1 mg/day) and mycophenolate mofetil (1000 mg/day); candesartan was also given for arterial hypertension. The recent serum creatinine concentration was 1.70 mg/dl (estimated glomerular filtration rate [GFR] 28 ml/min/1.73 m^2). Hepatitis B virus (HBV) reactivation (10^9 DNA copies/ml) has been documented for the last 18 months, but no specific treatment was started as liver tests remained within normal range. 12 days before, the patient had been first referred to the nephrology ward for progressive dyspnea. Chest X-ray and lung computed tomography (CT) revealed bilateral lung infiltrates. Quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) in plasma found 3130 copies/ml, and culture of the bronchoalveolar lavage supported the diagnosis of CMV pneumonia. Intravenous sodium ganciclovir was started at the initial daily dose of 200 mg, but was increased to 400 mg (4.2 mg/kg) by the second hospital day; CMV PCR became rapidly negative. The white blood cell count before ganciclovir therapy was 5080/mm^3, with a nadir at 3430/mm^3 after 10 days. During the hospital stay, renal function deteriorated (creatinine 2.67 mg/dl, estimated GFR declining from 26 to 17 ml/min/1.73 m^2) and, on day 12, the patient fell and was diagnosed with a hip fracture. Orthopedic surgery under epidural anesthesia was not complicated. A list detailing the medications given during the hospital stay and the perioperative procedure is provided in Table 1.

A few hours later, the patient developed altered consciousness and respiratory distress. Arterial blood

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gas analysis revealed: pH 6.79, pCO_2 54 mm Hg, bicarbonate 8 mmol/l, lactate 20 mmol/l (<2.0). The patient was intubated for mechanical ventilation and received intravenous 8.4% sodium bicarbonate and thiamine supplementation. Continuous venovenous hemofiltration was initiated. After 6 h of resuscitation, arterial pH rose progressively up to 7.31. The central venous oxygen saturation ($ScvO_2$) was 61.5%. Echocardiography showed a well preserved left ventricular function. There was no evidence for septic or hemorrhagic shock. Arterial lactate (L) was 27 mmol/l, pyruvate (P) 0.6 mmol/l, and the L/P molar ratio reached the value of 45. The patient experienced hypoglycemia despite the administration of dextrose 30%. Impaired glucose utilization was also suspected by the presence of biological signs of ketogenesis, with a high urinary excretion of 3-hydroxybutyrate (256.2 mmol/mol creatinine [Normal <10]) and of dicarboxylic acids. Ganciclovir therapy was discontinued from ICU admission, after an 11-day course. Further complications included rhabomyolysis and vasoplegia. Blood cultures were sterile, and abdominal CT did not show any sign of bowel ischemia. Hyperlactatemia persisted while liver tests were moderately disturbed, and the ammonia level was 109 μg/dl [Table 2]. The patient remained severely encephalopathic with normal brain CT. Fatality occurred on hospital day 14, after persisting hyperlactatemia (>25 mmol/l) and circulatory failure despite the progressive increase of vasopressors. Autopsy was not accepted by the relatives.

Table 1: List of the medications prescribed before the development of lactic acidosis

Methylprednisolone	Pantoprazole
Tacrolimus	Calcium
Mycophenolate	Escitalopram
Furosemide	Cefazoline
L-thyroxin	Candesartan
Bisoprolol	Alizapride
Atorvastatin	Paracetamol
Tramadol	Ganciclovir

Discussion

The possibility, that ganciclovir therapy could induce severe lactic acidosis, was recently suggested.[1] In a short series of three clinical cases, Kabat-Koperska *et al*. described nonrespiratory acidosis in kidney transplant recipients receiving anti-CMV therapy.[1] However, lactic acidosis was formally documented in two cases only, with a limited number of data points. In one case, the high lactate concentration was documented after that the patient had presented several episodes of generalized seizures.

Our case is documented by serial determination of lactate concentration, but also by the calculation of the L/P molar ratio. The L/P molar ratio, in the absence of a clear etiology of shock and hypoperfusion, was very high. In a recent series of patients admitted with either septic or cardiogenic shock, the L/P ratio before resuscitation never exceeded 34 in the nonsurvivors.[2] The blood L/P molar ratio reflects the equilibrium between product and substrate of the reaction catalyzed by lactate dehydrogenase. Usually, a L/P molar ratio >25 is suggestive of a primary or secondary respiratory chain dysfunction.[3]

Our patient also experienced significant episodes of hypoglycemia, and administration of hypertonic dextrose was required to prevent these events. Together with the presence of biological signs of ketogenesis, this is indicative of impaired glucose utilization. The limitation of our observation is the absence of the determination of free fatty acids in the plasma which could have indicated the activation of anaerobic glycolysis. No postmortem examination was possible; therefore, the occurrence of liver steatosis could not be explored.

Table 2: Evolution of laboratory data during ICU stay

	ICU							
	Hospital day 12				Hospital day 13			Hospital day 14
	5 h 00	9 h 00	13 h 00	18 h 00	0 h 00	6 h 00	14 h 00	0 h 00
Arterial pH	6.79	7.33	7.27	7.37	7.36	7.21	7.11	7.23
pCO_2 (mmHg)	54	28	31	32	26	28	50	50
Bicarbonate (mmol/l)	8	14	14	18	14	11	16	20
Lactate (mmol/l) (<2.0)	20	21	22	17	17	19	19	25
Serum creatinine (mg/dl) (0.60-1.30)	4.49			2.59		1.87		
ASAT (IU/l) (<50)	142					1169		
ALAT (IU/l) (<50)	69					443		
INR (0.80-1.30)	1.73					2.46		
Glucose (mg/dl) (60-90)	87	109	50	195	143	124	82	105
Dextrose 5%	X	X						
Dextrose 30%			X	X	X	X	X	X
Sodium bicarbonate (mmol) (cumulative dose)	300	1300	1400	1700	1830	2005	2385	3245

ICU: Intensive care unit; ALAT: Alanine aminotransferase; ASAT: Aspartate aminotransferase

There are numerous causes of lactic acidosis in ICU patients. Lactic acidosis caused by oxygen deficits is generally termed type A and is the most common form in ICU patients. In the present observation, cardiogenic shock, septic shock (and worsening of pneumonia), bowel ischemia and severe liver failure were ruled out. By contrast, type B lactic acidosis is related to impaired gluconeogenesis. This condition is often associated with thiamine deficiency or to side-effects of drugs impairing mitochondrial respiratory chain. With reference to nucleoside analogues used to treat HIV infection, we postulated that ganciclovir could have interfered with the activity of enzymes of the mitochondrial respiratory chain. Inhibition of mitochondrial DNA synthesis interrupts the mitochondrial respiratory chain, resulting in the activation of anaerobic glycolysis and overproduction of lactic acid.[4] There is limited experimental evidence showing a potential damage of rat hepatocyte mitochondria exposed to ganciclovir in the presence of thymidine kinase produced by herpes simplex virus.[5,6]

Since a recent large survey of the safety of various antiviral medications failed to identify a specific signal for ganciclovir or valganciclovir toxicity, several additional factors could have contributed to the development of ganciclovir-related lactic acidosis in our patient.[7] First, we cannot exclude that lactate hepatic clearance was somewhat impaired in the context of chronic HBV reactivation. Second, as the major excretion pathway for ganciclovir is renal, potential systemic accumulation of the drug could have contributed to the development of mitochondrial toxicity. In patients with chronic kidney disease and/or acute modifications of renal function during the hospital stay, careful adaptation of drug dosage is required, and further reduction is advocated for maintenance once induction has been achieved.[8] Finally, our patient was on tacrolimus, a medication suspected to have promoted lactic acidosis in a patient on antiretroviral therapy.[9] However, since ganciclovir is not metabolized through the cytochrome P450 system or by P-glycoprotein, the potential detrimental role of tacrolimus in our patient is unlikely.

Altogether, the severe and refractory lactic acidosis, associated with a significantly increased L/P ratio and an inhibition of neoglucogenesis, in the absence of any other medication interfering with the mitochondrial respiratory chain, suggests a critical role for ganciclovir in the development of lactic acidosis in the present case. A call for caution is warranted in solid organ recipient treated with intravenous ganciclovir, and regular lactate monitoring could be recommended in high risk patients, including those with underlying hepatic disease and renal insufficiency.

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How to cite this article: Wittebole X, Morelle J, Vincent MF, Hantson P. Fatal lactic acidosis possibly related to ganciclovir therapy in a renal transplant patient? Indian J Crit Care Med 2015;19:177-9.

Source of Support: Nil, **Conflict of Interest:** None declared.