Case Report **Open Access**

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The perils of protocols: acute phosphate nephropathy after intravenous phosphate replacement

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Abstract: Protocols are commonly used in the hospitals around the world and enable health care organizations to put evidence into practice and provide a framework for the management of the individual patient. Such standardization of practice is felt to reduce variations in practice and improve quality of care. However, the protocols have advantages and disadvantages. I present a case where activation of the protocols for "Electrolyte, phosphate and magnesium replacement" at the time of admission to the hospital, resulted in harm to the patient because of inappropriate timing of the test(s) with a resulting action to correct the expected laboratory abnormality. Timing of tests and administration of various medications including antibiotics in hospitalized dialysis patients is important, and both the physicians and the nursing staff require vigilance when requesting/performing tests and ordering/administering medications to dialysis patients.

Keywords: acute kidney injury; acute phosphate nephropathy; ethylene glycol intoxication; hemodialysis; hypophosphatemia; pitfalls of protocols; phosphate supplementation.

Introduction

> *"Protocols have a tendency not only to minimize failures, but in the process also eliminate genius … "*
> W. van Hooran, ENAM Presentation (September 1999)

Medical protocols (Table 1), commonly used in the hospitals around the world, enable the health care organizations to put evidence into practice and provide a framework for the management of the individual patient. Such standardization of practice is felt to reduce the variations in clinical practice and improve the quality of care most of the times but rarely may result in unintended consequences [1–3]. Acute phosphate nephropathy is often described after oral phosphate administration [4–6] but rarely described after intravenous phosphate therapy for hypophosphatemia [7]. I present a case where the administration of intravenous phosphate because of the activation of the protocol on admission, led to acute phosphate nephropathy and prolonged need for dialysis therapy in a patient who presented with intoxication.

Case presentation

A 47-year-old man with unremarkable past medical history was sent from a peripheral hospital, for an emergent CT scan of his head, when he was brought to hospital for ataxia. On arrival, he was noted to have decreasing level of consciousness and was taken to the emergency room, where the patient was intubated and received intravenous fluids and inotropes, for transient hypotension during intubation. A cursory neurological examination was non-focal. Once stabilized, a CT scan of the head was done that was negative for acute pathology or hemorrhage. No ancillary history was available, except that he was apparently well several days ago. A normal lumbar puncture ruled out meningitis and subarchanoid hemorrhage. He was admitted to the intensive care unit (ICU) where he received in addition to ventilatory support, intravenous fluids and antibiotics.

Laboratory data (Table 2) showed marked leukocytosis, evidence of kidney dysfunction, with anion gap metabolic acidosis with superimposed respiratory acidosis and an elevated osmolar gap of 36 with a slightly elevated serum lactate of 2.9. The blood toxicologic screen

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Table 1: Medical protocols: features and consequences.

Features	Consequences
– **Standardization**: enables all tasks to be undertaken in a well-defined predetermined step-by-step manner – **Framework**: provides framework for working in multidisciplinary teams – **Inter-operator independence**: any member should produce same result – **Safety**: enables all staff to perform tasks safely without relying on memory – **Consistent**: helps prevent errors by reducing variations in practice – **Promotes evidence-based practice**: helps use of best evidence in clinical practice	**Advantages**: – Enable audits – Allows tasks to be performed safely without background knowledge – May enable a less qualified staff to perform task **Pitfalls**: – Let staff work without thinking – Mindless working, may lead to lack of interest or de-motivation – Discourages innovation – May constraint clinical freedom

Table 2: A snap-shot of Laboratory data over 3-week period.

		Normal range	Day 0: Admission day			Day 1: next am	Day 7	Day 21
			In ER 07:10	In ICU 10:45	120 min during dialysis 18:10			
Biochemistry	Blood Urea	2.6–7.7 mmol/L	2.8	3.7	2.9	6.3	21.5	
	Serum creatinine	35–97 µmol/L	144	148	116	257	733	594
	Serum potassium	3.5–5.0 mmol/L	6.6	7.3	2.9	3.7	4.2	
	Serum bicarbonate	24–26 mmol/L	3	4	18			
	Serum calcium	2.02–2.60 mmol/L	2.51	2.45	2.22	1.99		
	Serum albumin	35–50 g/L	54				33	
	Serum phosphate	0.87–1.45 mmol/L		1.34	0.33	2.31	2.13	
	Serum uric acid	202–416 µmol/L		432	206			
	Serum Magnesium	0.70–1.05 mmol/L	1.05	1.11	0.67	0.60	0.84	
VBG	pH		6.85	6.85				
	pCO_2		19	25				
	Serum osmolality (measured)	285–295 mOsm/kg		320	299			
	Serum osmolality (calculated)			284	286			
	Osmolar gap	0–14		36	13			
	Serum lactate	<2.0 mmol/L		2.9				
	Anion gap	12±2	28	22				
CBC	WBC	$4.0–11.0\times10^9$/L	34.2	47.6	26.8	15.5	10.5	
	Hemoglobin	140–180 g/L	189	177	147	127	119	
	Platelets	$150–400\times10^9$/L	469	486	284	222	327	
Toxicology	Blood alcohol			<2.2				
	Blood salicylates			<0.10				
	Blood acetaminophen			<66				

Acute Hemodialysis x1 – 4 h (1552–1952 h), Bath: K1.0, Bicarbonate 35 mmol/L, calcium 1.25 mmol/L

Table 3: Approach to a patient with increased anion-gap and osmolar gap.

Increased anion-gap (causes)	Increased osmolar gap (causes)
"Mudpiles":	**Alcohols:**
– Methanol/metformin	– Methanol
– Uremia	– Ethylene glycol
– Diabetic ketoacidosis	– Ethanol
– Paraldehyde/phenformin/propylene glycol/pyroglutamic acid	– Isopropyl alcohol
– Iron/INH/infection	**Osmotic agents:**
– Lactic acidosis	– Mannitol
– Ethylene glycol	
– Salicylates	
Caveats:	
– Osmolar gap: is high only during the early phase of toxic alcohol ingestion. When these alcohols get metabolized, the osmolar gap decreases as their metabolites do not contribute to osmolar load, but then anion gap may increase	
– Lactate: one of the metabolites of ethylene glycol may cause false elevation of lactate	
– Urine calcium oxalate crystals: take time to form and may be absent early on after ethylene glycol ingestion	
– Serum calcium may be low in patients with ethylene glycol intoxication, because of calcium binding to oxalate to form crystals	

for aspirin, acetaminophen and alcohol was negative. A chest X-ray showed mild infiltrate in the right lower lobe.

Because of the increased anion gap metabolic acidosis, elevated osmolar gap, the possibilities of toxic alcohol ingestion was considered (Table 3). A urinalysis showed 3.0 g/L of protein, 1+ blood with 5–10 RBCs/hpf, 5–10 WBCs/hpf and oxalate crystals. The diagnosis of ethylene glycol intoxication was favored and he was started on fomipezol 1000 mg in 250 mL of normal saline to be given intravenously over 30 min, while the patient was being prepared for emergent hemodialysis. The patient underwent emergent hemodialysis for 4 h using a high-flux dialyzer with a dialysate comprising of bicarbonate35 mmol/L, potassium 1.0 mmol/L, calcium 1.25 mmol/L. The dialysis was completed at 19:52 hours on the same day. The patient tolerated dialysis well and his clinical condition stabilized, and he was extubated successfully the next morning. As per the hospital's electrolyte/phosphate replacement protocol that was activated on admission, a nurse did blood work and a blood sample was drawn during dialysis, 100 min before the completion of dialysis therapy. The serum potassium was normal but the serum phosphate was low at 0.33 mmol/L (it was normal before dialysis at 1.34 mmol/L, Table 1) and based on the protocol recommendations, the nurse called the intensive care physician and advised the physician of a low serum phosphate level, who advised her to give intravenous phosphate as per protocol. The patient received 30 mmol of sodium phosphate in 500 mL of normal saline intravenously over 4 h and the next morning the serum phosphate level was elevated at 2.31 mmol/L and remained elevated thereafter.

The patient remained anuric and the serum creatinine continued to increase and peaked at 1115 μmol/L, 9 days later and he required ongoing dialysis support. Although the possibility of ischemic/toxic acute tubular necrosis was high but as he remained anuric and dialysis dependent, a kidney biopsy was performed 2 weeks later, that showed resolving acute tubular necrosis but with calcium-phosphate deposits consistent with phosphate nephropathy. Instead of requiring possibly a single dialysis treatment for intoxication, he required dialysis for 3-months before he recovered renal function allowing him to come off dialysis.

Table 4: Risk factors for acute kidney injury after phosphate use [8].

1. Lower baseline kidney function (chronic kidney disease)
2. Use of ACEIs or ARBs (angiotensin converting enzyme inhibitors or angiotensin receptor blockers)
3. Age > 65 years
4. Congestive heart failure
5. Hypertension
6. Diabetes
7. Diuretic use

Discussion

Acute phosphate nephropathy is well described with oral phosphate solutions used for bowel preparation, especially in high-risk individuals (Table 4) with an incidence of 1–4% in the general population. Since 2008, these

agents has been prohibited [9], but are still used, though rarely, for catharsis [6]. The acute phosphate load after ingestion leads to a rapid increase in serum phosphate that stimulates parathyroid hormone (PTH) release that inhibits proximal tubular phosphate reabsorption resulting in an increase in urinary phosphate excretion. In addition, it suppresses 1,25-OH vitamin D3 synthesis, thereby inhibiting further intestinal phosphate absorption and normalization of serum phosphate [10]. The urinary calcium excretion increases initially because of the accompanying sodium load that suppresses calcium reabsorption in the proximal tubule. The high concentration of phosphate and calcium in the urine results in precipitation of calcium-phosphate crystals that flow downstream to the distal tubules and collecting ducts and bind to the epithelial cells, where these undergo internalization, triggering an inflammatory reaction and cellular damage [11].

Intravenous phosphate, in the present case, was administered to correct the apparent but expected hypophosphatemia during/after hemodialysis, secondary to inappropriate timing of the test because of an activated protocol, that resulted in acute kidney injury and prolonging the need for dialysis. It is possible that the initial passage of oxalate crystals secondary to ethylene glycol ingestion might have contributed but no oxalate crystals were reported in the biopsy.

Acute kidney injury (AKI) is common in the ICU patients with an overall incidence of 20%–50% [12]. It is often attributed to sepsis, hypotension and other co-morbidities [13]. Hypophosphatemia is common in ICU patients. Renal replacement therapy, in addition to sepsis and malnutrition are the common causes of hypophosphatemia in the ICU [14]. Intravenous administration of phosphate is used commonly in ICUs and can result in similar damage [7], though it is not recognized in the recent publications. Previous studies evaluating the efficacy and safety of intravenous phosphate supplementation described this intervention to be safe [15], but these studies did not evaluate the possibility of phosphate-induced kidney dysfunction.

Both AKI and hypophosphatemia are common in ICU patients and many patients receive intravenous phosphate supplementation, however, the use of phosphate supplementation with possibly resulting phosphate nephropathy as a contributing factor to AKI in ICU patients is almost never considered in the differential diagnosis of these individuals with AKI. As most of these patients do not undergo kidney biopsy, the underlying cause of AKI often remains speculative. At present, there are no data as this issue has not been studied in ICU patients receiving phosphate supplementation but, I feel, it is prudent to consider the possibility of acute phosphate nephropathy as a contributing cause of AKI, especially in the at-risk patients. However, further studies are required to evaluate this issue prospectively. Meanwhile, though serum phosphate can increase in patients with decreased kidney function of any cause, but a sudden elevation of phosphate levels with hypocalcemia and possibly hypomagnesemia in the ICU patients with AKI, should raise the suspicion of APN, especially in those patients who are receiving phosphate supplements, either oraly or intravenously.

This clinical vignette highlights the perils of a standard protocol, activated at the time of admission. As dialysis will remove potassium and phosphate, therefore electrolytes and phosphate should not be tested until at least 2-h after hemodialysis when these levels would be possibly equilibrated. The protocol activation in this patient led to the test at an inappropriate time (about 100 min before the end of diaylsis) that as expected resulted in inappropriate action/supplementation of phosphate for an expected low result during or immediately after dialysis. A second possibility is that the diagnosis of hyopphosphatemia was erroneous, due to the blood being drawn too close to the site of the dialysis venous return.

Timing of tests and administration of various medications including antibiotics in hospitalized hemodialysis patients is important. The time of hemodialysis in these individuals should be considered when writing admitting and ongoing interventions. Both the physicians and nursing staff should be vigilant and should consider the timing of these interventions when requested/performing tests and ordering/administering medications to hemodialysis patients. Ideally, to be safer, patients receiving dialysis should be excluded from such electrolytes/ phosphate replacement protocols.

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