

Review Article

Persistent lactic acidosis after chronic topical application of silver sulfadiazine in a pediatric burn patient: a review of the literature

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Abstract: A 3-year old male who sustained 2nd and 3rd degree burns that covered approximately 60% TBSA presented to a large adult and pediatric verified burn center. On hospital day (HD) 26 of his stay, *Candida* fungemia was identified by blood culture, delaying operative management until HD 47. On HD 47, after his first operative intervention, the patient developed a persistent metabolic and lactic acidosis. On HD 66, a search for a cause of his osmol gap of 56 mOsm/kg revealed a potential source-propylene glycol. Previous studies have implicated the propylene glycol emulsifier in the silver sulfadiazine that was being applied to his skin as a rare cause of lactic acidosis in severely burned patients. Within 24 hours of stopping the silver sulfadiazine therapy, his lactic acidosis and osmol gap resolved; within 72 hours his metabolic acidosis resolved. Silver sulfadiazine is commonly used adjunct therapy in the treatment of 2nd and 3rd degree burns and generally has few adverse reactions. The absorption of propylene glycol systemically can rarely occur when applied to extensive burns, presumably due to the disruption of the skin barrier; the half-life of PG is 10 hours and can be prolonged with renal disease because ~50% of the sulfadiazine is excreted in the urine unchanged. When propylene glycol is present systemically, it is metabolized to lactic acid in the liver, which can cause a lactic acidosis. Several commonly used drugs also use propylene glycol as an emulsifier, including IV preparations of lorazepam, pentobarbital, phenobarbital, and phenytoin. In all of these clinical scenarios, including severe burn patients that are being treated with silver sulfadiazine, both lactic acid and propylene glycol levels should be measured to monitor for this rare, potentially serious co-morbidity.

Keywords: Burn, propylene glycol, silver sulfadiazine, metabolic acidosis, hyperosmolality

Introduction

Burn injuries involving greater than 30% total body surface areas (TBSA) result in severe cardiovascular, physiologic and immunologic derangements [1]. When there is a massive loss of free water, dramatic shifts in body fluid occurs. Additionally, there is an increase in the relative concentration of solutes. Hyperosmolality is produced by the alterations in the intake and losses of solutes and water and, particularly in the severely burned patient, hyperosmolality portends a poor prognosis [2]. In these patients, there is no discrepancy

between the serum osmolality and the normal serum constituents. There are rare clinical situations whereby burn patients have osmolality discrepancies due to exogenous chemicals. The use of silver sulfadiazine, a commonly used topical antibiotic in burn care, has been associated with the development of hyperosmolar states [3-5]. Propylene glycol (PG), a component of the cream-based silver sulfadiazine topical antibiotic, does not cross the intact skin barrier. However, transdermal absorption of PG from the topical application of silver sulfadiazine (and the associated signs and symptoms of PG toxicity) has been reported in patients

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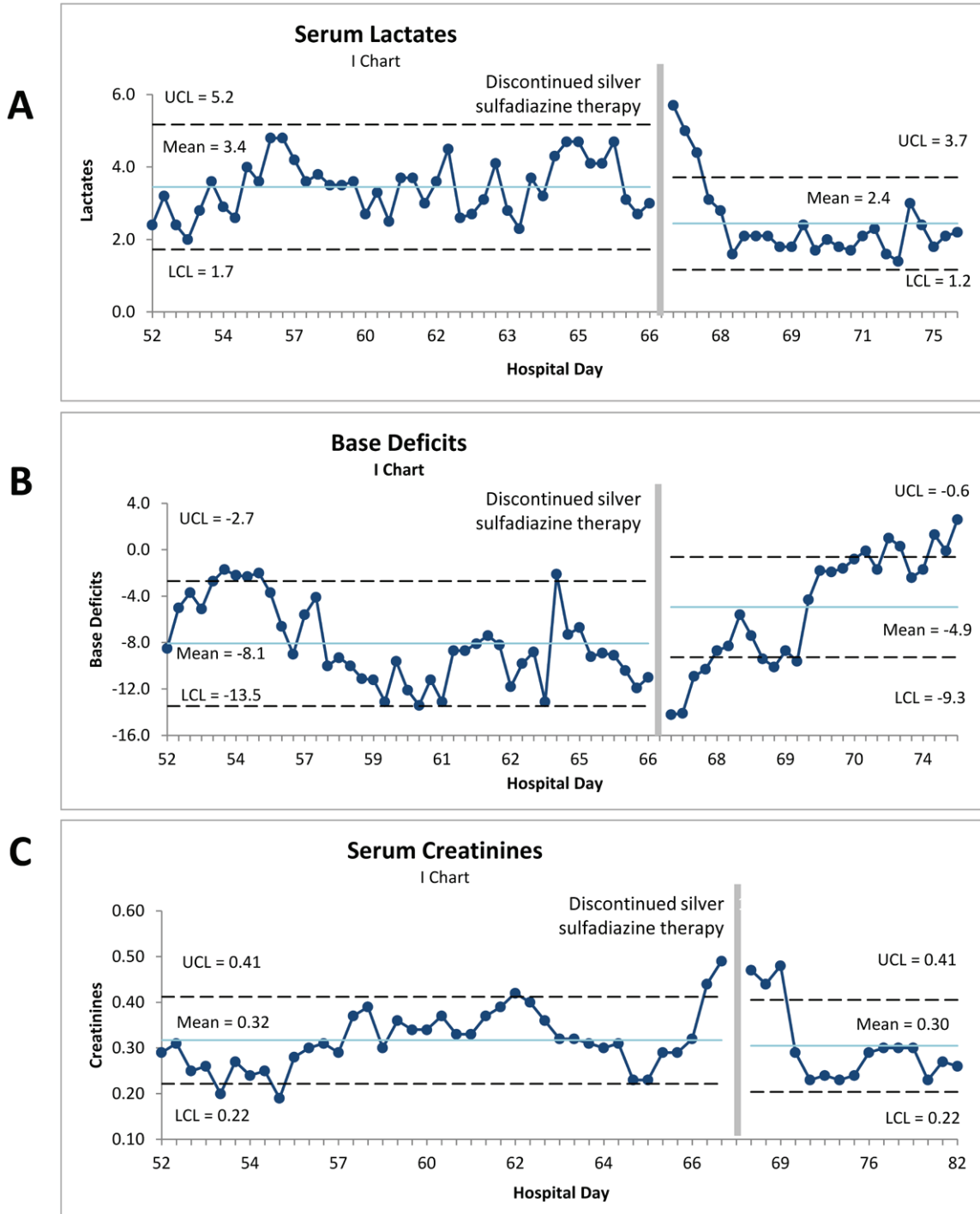


Figure 1. The resolution of lactic acidosis occurs after the silver sulfadiazine application on HD 47 in the present study. A. Lactic acid control chart both prior and after the stopping of silver sulfadiazine topical treatment. B. Resolution of base deficits parallel changes decreases in lactic acid. C. Increases in serum creatinine may be related to these changes as at least 50% of PG is excreted unchanged in the kidneys. Statistical process control methods (SPC) [24, 25], as shown here, are commonly applied methodologies to statistically analyze quality control methods in hospital settings such as the clinical laboratories or patient safety applications [26-31]. The data were presented in a Shewhart control chart with upper and lower control limits to assist in discerning between common cause and special cause variation. Common cause variation is the variation inherent in a stable system without statistically significant changes over time. Special cause variation is unnatural, occurring as a result of changes or circumstances outside of the stable system. Special cause variation signals a statistical change and is detected according

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to specific rules in SPC related to trends above or below the mean or points above or below the control limits. These special causes should be investigated for a source if not related to a known intervention when using in real time or to analyze a process over time. In this case, an intervention (elimination of topical agent with PG) was linked to the special cause variations seen in the laboratory studies. Traditional tests of significance also reveal a statistical difference post-intervention (see text); however, the cyclical patterns of serum lactates levels before and after dressing changes would not have surfaced in real time using this method alone.

Table 1. Measured serum osmolality of patient described during hospital stay

Serum osmolality (mOsm/kg)	Hospital Day
355	66*
304	67
306	68
298	73
300	74
297	75

*Date of last silver sulfadiazine dressing.

with extensive burns [4-6]. Here we review a case involving a 3-year old with extensive burn trauma that demonstrated classic laboratory values indicating serum PG toxicity. We discuss the differential diagnosis of this patient and illustrate the biochemistry and metabolism of PG in the context of his clinical course. We will also review the diagnostic options available to diagnose this situation should it be necessary given the critical role that silver sulfadiazine plays in the treatment of burn patients.

Case study

A 3-year old male who sustained 2nd and 3rd degree burns covering approximately 60% TBSA-including circumferential trunk, back and bilateral lower extremities with upper extremity burns confined to his elbows-presented to a large adult and pediatric verified burn center for treatment. He was hemodynamically unstable with significant respiratory compromise, requiring intubation for airway protection. He remained hemodynamically labile throughout his nine-month hospital course. It was suspected that part of his hemodynamic instability was due to *Candida* fungemia, which was identified by blood culture on HD 26. Operative management of his wounds was delayed until HD 47, due to concerns surrounding his hemodynamic instability and sepsis. While awaiting operative management, his wounds were managed with topical application of a mixture of silver sulfadiazine and nystatin. On HD 47, 5% of his

wounds were excised and covered with porcine xenograft, whereas his remaining unexcised wounds remained dressed with a mixture of silver sulfadiazine (Thermazene®, Silvadene®, SSD Cream®) and nystatin. From HD 47 until HD 68 he had a persistent metabolic and lactic acidosis (see **Figure 1A, 1B**) initially attributed to sepsis or diabetes insipidus. Sepsis was suspected in the context of hemodynamic instability requiring pressor support, history of *Candida* fungemia and laboratory tests consistent with disseminated intravascular coagulation (elevated prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) and thrombocytopenia). Diabetes insipidus was suspected in light of the elevated serum osmolality and high urine output but, in light of a serum sodium that was either below or within reference range, this diagnosis was eliminated. A measured serum osmolality on HD 66 was 355 mOsm/kg. A concomitantly drawn basic metabolic panel demonstrated a serum sodium, blood urea nitrogen and glucose of 144 mmol/L, 5 mg/dL and 159 mg/dL, respectively. This resulted in a calculated osmolality of 299 mOsm/kg. Continued investigation to identify the source of this 56 mOsm/kg osmol gap (355 – 299 mOsm/kg) was initiated and upon close review of his medications, it was discovered that the patient was on two medications containing PG-a potential cause of an osmol gap metabolic acidosis-lorazepam and silver sulfadiazine [3, 7-10]. During this investigation a cyclical nature to the elevated serum lactates was also identified; peaking 6 hours after dressing change, while reaching a nadir immediately prior to dressing change. With this information, a systematic approach to the determination of his acidosis was undertaken beginning with modification of the dressing change regimen on HD 67 from silver sulfadiazine and nystatin to a mixture solution of mafenide acetate and amphotericin. Within 24 hours of stopping the silver sulfadiazine treatment the lactic acidosis and osmol gap resolved (**Table 1**). His metabolic acidosis resolved within 72 hours. Given the expeditious resolution of his labora-

tory abnormalities, his clinical condition was attributed to PG toxicity secondary to transdermal absorption of PG contained within the silver sulfadiazine. He remained in the hospital an additional 7 months, during which his operative management was completed, and was subsequently discharged home in good condition.

Results

The laboratory results obtained immediately after the first attempt at covering a small percentage of his wounds, in retrospect, demonstrated many of the classic laboratory findings described in PG toxicity, most notably just prior to the discontinuation of the silver sulfadiazine (**Figure 1**). This patient's arterial blood gases demonstrated a profound metabolic acidosis (base deficit nadir of -14.2) with a concomitant lactic acidosis (serum lactate peak 5.7) (**Figure 1A, 1B**). Furthermore, the patient had a measured serum osmolality of 355 mOsm/kg (with a concomitantly calculated osmolality of 299 mOsm/kg), a white cell count of $4.8 \times 10^9/L$ (range $5.5\text{-}15.5 \times 10^9/L$) and doubling of serum creatinine from a baseline of 0.19 mg/dL to 0.49 mg/dL on HD 66 (**Figure 1C**). The changes in lactate and base deficit were statistically significant using both statistical process charts (**Figure 1** legend for explanation), and with traditional statistical methods (second-order autoregressive model). The changes in lactate and base deficit met statistical significance ($p = .009$ and $p = .015$, respectively). The changes in creatinine, however, were not statistically significant ($p = .093$). In addition, repeated blood cultures did not identify a bacterial or fungal etiology for the lactic acidosis.

Discussion

Propylene glycol in silver sulfadiazine

Silver sulfadiazine (Thermazene[®], Silvadene[®], SSD Cream[®]) is used as an adjunct in the treatment of second and third degree burns to prevent infection. It is usually applied once or twice daily to a thickness of 1/16 inch to the affected burned areas. Multiple adverse reactions have been reported, including dermatologic (e.g. itching, rash), hematologic (e.g. hemolytic anemia, leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia), hepatitis, local pain and burning, interstitial nephritis, and serum hyperosmolality, due to the transdermal

absorption of the PG component in the cream [6]. The transdermal absorption of PG during topical application of silver sulfadiazine can occur when applied to extensive burns, presumably due to the disruption of the skin barrier. The half-life of silver sulfadiazine is 10 hours and can be prolonged with renal disease [6]. This occurs because approximately 50% of the sulfadiazine is excreted in the urine unchanged [11]. The time to peak concentration of sulfadiazine has been reported to be 3-11 days with continuous topical therapy [11]. In the present case, no evidence for PG toxicity was identified prior to HD 47. The exact reason for this delay is unknown, but may be related to the patient's decline in renal function, evidenced by a doubling in serum creatinine (**Figure 1C**).

Silver sulfadiazine, propylene glycol toxicity, and burn patients

While the identification of hyperosmolality and lactic acidosis related to treatment with silver sulfadiazine in burn patients is rare, it has been reported by at least 5 groups since 1970. Ecklund, et al. first demonstrated the presence of hyperosmolality in burn patients treated with silver sulfadiazine in 1970 [12]. They identified that 15 of 74 patients (16%) had hyperosmolality; of these 15 patients, the reported osmolality approximated the calculated osmolality in 6 patients (Group A), leaving 9 patients (60%) that did not have a known reason for the hyperosmolality (Group B) [12]. Patients with hyperosmolality that could be accounted for had burn surface areas of 15-50% (avg. 33%), while Group B had 35-90% burn surface areas (avg. 65%). The reported osmolality in Group A was 330 (calculated 333; discrepancy = -3). Group B had an osmolality of 404 (calculated 320; discrepancy 84). The authors of this study analyzed several patient serums by gas chromatography estimated PG concentrations of 0.04 M (40 mOsm) to 0.101 M (100 mOsm/kg) [12]. Group A patients without discrepancies did not have appreciable amounts of PG detected in their serum [12]. Since there were large differences in the average surface area affected in Group A (33%) compared to those in Group B (65%), the increased total surface area affected by severe burns may be one reason that PG leaked into the systemic circulation.

Bekeris, et al. identified two severely burned patients that had a marked hyperosmolality

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Table 2. Selected agents used in critical care suspended in propylene glycol and implicated in propylene glycol toxicity

Agent	Reference
Barbiturate (pentobarbital and phenobarbital)	Yorgin, et al. [16]
Bactrim	Zar, et al. [32]
Benzodiazepines (diazepam and lorazepam)	Parker, et al. [22] Arroliga, et al. [18] Seay, et al. [15] Wilson, et al. [17] Wilson, et al. [9] Tayar, et al. [19] Cawley, et al. [20] Zosel, et al. [21] Zar, et al. [7]
Phenytoin	Zosel, et al. [21] Louis, et al. [14]
Etomidate	Bledsoe, et al. [8] Bedichek, et al. [33]
Silver sulfadiazine	Moore, FD [2] Kulick, et al. [3] Kulick, et al. [6] Lockhart, et al. [11] Eklund, et al. [12] Bekeris, et al. [5] Fligner, et al. [4] Peleg, et al. [13]
Paracetamol	Allegaert et al. [34]
Nitroglycerin	Demey [23]

while being treated with silver sulfadiazine [5]. These patients had 80% and 90% TBSA burns and had peak serum osmolalities of 420 mosm/kg and 493 mosm/kg, respectively [5]. When both patients' sera were analyzed by gas chromatography, PG was identified in both patients at levels that could account for the differences between the actual and calculated serum osmolalities. Both patients died due to the sequelae of gram-negative septicemia.

Ten years later, Kulick, et al. reported that in 262 hospitalized burn patients hyperosmolality was a relatively common finding secondary to exposure to silver sulfadiazine [3]. When they investigated these 262 patients, they looked for hyperosmolality by defining it as at least 2 osmolality values >310 mOsm/kg. They identified 15 of these patients (6%) met this definition of hyperosmolality. Nine of which were found to have an osmol discrepancy, found to be a volatile substance by freezing point depression and vapor point analysis. Further analysis by gas chromatography demonstrated that PG as the agent accounted for most of the

osmol gap, secondary to exposure to their topical silver sulfadiazine utilized in their treatments [3]. A clinically interesting observation is that each of these patients had a TBSA > 35%, indicating that PG levels causing hyperosmolality did not seem to occur in patients with smaller burn surface areas. This is consistent with the relative impermeability that intact skin has to PG, which is decreased after burns violate the integrity of this barrier [3].

In 1985, Fligner, et al. reported hyperosmolality in an 8 month-old patient with 78% TBSA burn due to PG [4]. The peak PG concentration identified in the patient was 1,059 mg/dL. The increased osmol gap could be attributed to an elevated PG level; the patient exhibited either a zero-order elimination at a rate of 13.5 mg/dL/hr or first-order elimination of 16.9 hours [4]. The authors propose that the transdermal absorption of PG may have contributed to their subsequent cardiac arrest.

While PG toxicity is seen when silver sulfadiazine preparations are applied to burn patients with a higher percentage of TBSA, premature babies may be more sensitive to PG toxicity, as demonstrated in a recent case study. Peleg, et al. reported a premature infant that experienced propylene glycol intoxication. The patient was 1200 g at 29 weeks gestation and was accidentally overheated on a heating pad causing second degree burns on the buttocks covering an area less than 5% TBSA [13]. The burns were treated with gauze dressing of 0.2% nitrofurazone dissolved in PG 96.8% [13]. On day 4 of life, the baby became apneic, lethargic and had a metabolic acidosis before going into a coma [13]. Cerebral spinal fluid and blood cultures were negative and electrolytes were normal; urinary excretion of lactate and 2-ketoglutarate was slightly elevated [13]. There was an exceptionally high peak of PG in the urine chromatogram (~3000 mg/dL); plasma osmolality and PG levels were not performed [13]. The topical treatment was stopped and full recovery occurred within 48 hours. The infant was discharged at 2 months of age without subsequent problems, demonstrating normal growth and development at 5 months of age [13].

Propylene glycol metabolism and laboratory testing

In contrast to ethylene glycol, which can cause acute toxicity in humans, PG is "generally rec-

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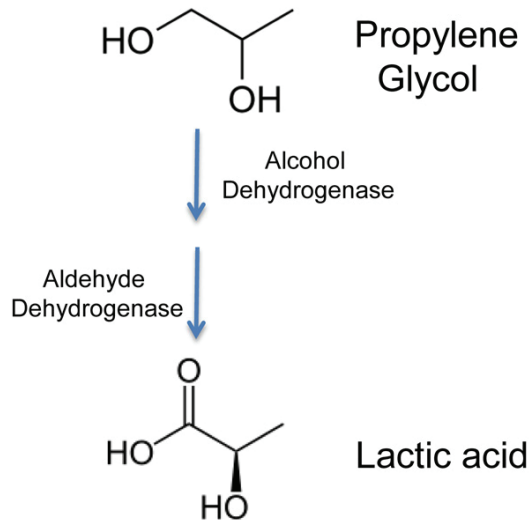


Figure 2. The metabolism of propylene glycol in humans involves both alcohol dehydrogenase and aldehyde dehydrogenase to form lactic acid. While at least 50% of PG is excreted unchanged in the kidney, the remaining is metabolized in the liver to lactic acid if it is present in the systemic circulation.

ognized as safe” as an additive to medications and foods. It is used as an emulsifying agent, as an FDA-approved additive for military dietary rations (Agency for Toxic Substances and Disease Registry 1997), and as an emulsifying agent in a number of commonly used medications—a fact not commonly recognized (**Table 2**). No adverse health effects are likely to occur when people are exposed to PG. However, heavy use of these products has caused been reported to induce excess levels of PG in the body, including extensive topical application on compromised skin [13-17].

Propylene glycol is rapidly converted lactic acid through the actions of alcohol dehydrogenase and aldehyde dehydrogenase in the liver (**Figure 2**) [9, 18-20]. Lactic acid is then converted to pyruvate and metabolized through the Krebs cycle [21], which is then metabolized to carbon dioxide and water. The elimination half-life of PG is about 4 hours; with 12-45% of the absorbed PG excreted by the kidneys unchanged or as the glucuronide conjugate [9, 18-20]. While it is “generally recognized as safe,” toxicity due to PG should be considered in any patient receiving a medication that contains PG as a solvent in which hyperosmolality, lactic acidosis, or a clinical presentation similar to sepsis develops as in the present case. Signs

and symptoms of sepsis overlap with PG toxicity, so it is critical to be able to discern between these two entities based not only using clinical signs and symptoms, but also laboratory testing (**Table 3**). When determining the PG contribution to the osmol gap and toxicity, it has been shown that serum PG concentrations correlate with an osmol gap at 48 hours [18] and the PG levels can be divided by 7.6 to estimate the osmolar effect [22].

Propylene glycol is a small molecular weight alcohol that does not bind tightly to serum proteins and is highly water soluble, so it is cleared quickly by hemodialysis [17, 22]. Intermittent hemodialysis has been suggested as the preferred method of treatment as it lowers levels quickly [22]. Previous studies have also reported the use of fomepizole as it inhibits alcohol dehydrogenase to prevent the formation of lactic acid [21-23].

Laboratory testing for lactic acid levels and for PG itself should be performed in patients exposed to medications suspended in PG, if an osmol gap is identified (**Table 2**). This will require a greater appreciation for the potential toxicity that occurs in these preparations due to the emulsant PG. Lactic acid testing is a routine test run in most clinical laboratories with a turn-around time of 5 minutes. Propylene glycol can be measured using gas chromatography from urine or serum. However, not all facilities have the ability to test for PG, requiring it to be sent out for analysis. When gas chromatography is available to detect PG, it generally takes about 2 hours (1 hour, if ordered as an emergent test).

Summary

In this case, we illustrate the potential toxicity of the generally harmless emulsification agent PG used in many medications, including silver sulfadiazine. The exact reason for the patient’s sensitivity to the silver sulfadiazine on HD 47 of treatment is not clear, but it is evident that the lactic acidosis resolved immediately upon removal of the treatment. Since up to 50% of lactic acid is cleared by the kidneys, one possible reason may be the patient’s worsening kidney function at the time the lactic acidosis. When using drugs with PG, including silver sulfadiazine, it is prudent to be aware of the adverse symptoms that may occur including hematologic (e.g. hemolytic anemia, leukope-

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Table 3. Signs and symptoms of propylene glycol toxicity and sepsis

Propylene Glycol Toxicity	Sepsis/Septic Shock
Hypotension	Hypotension
Tachypnea	Tachypnea
Tachycardia	Tachycardia
Cardiovascular collapse	Cardiovascular collapse
Normothermic**	Hyperthermic/Hypothermic**
Metabolic (Lactic) Acidosis	Metabolic (+/- Lactic) Acidosis
Osmolar Gap/Hyperosmolality**	Non-Gap Acidosis**
Leukopenia/Leukocyte count normal	Leukopenia/Leukocytosis
No evidence of infection (Negative bodily fluid culture, Negative radiographic findings)**	+/- Evidence of infection (Negative bodily fluid culture, Negative radiographic findings)**
Thrombocytopenia/Normal platelet count	Thrombocytopenia
Coagulopathy (Intravascular Hemolysis)	Coagulopathy
+/-Hepatic Dysfunction	+/-Hepatic Dysfunction

The use of propylene glycol based drugs can be confused with sepsis as it can clinically mimic it [19]. **indicates key symptoms and signs differentiating the two clinical entities.

nia, agranulocytosis, aplastic anemia, thrombocytopenia), hepatitis, and interstitial nephritis and follow the serum osmol gap. With discrepancies in osmol gap, it is most efficient to monitor serum lactate, identify medications containing PG, and remove the PG medication to reverse any toxicity that can occur. While rare, PG toxicity is a potential serious co-morbidity in burn patients, especially those with a large burn.

Conflict of interest statement

The authors do not have any conflicts of interest to disclose.

Abbreviations

PG, propylene glycol; TBSA, total body surface area; SPC, Statistical process control.

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References

[1] Kramer G, Lund T and Beckum OK. Pathophysiology of Burn Shock and Burn Edema. In: Herndon DN, editors. *Total Burn Care*. 3rd. Philadelphia: Saunders Elsevier; 2007. p. 93-103.

[2] Moore FD. Hypertonicity disorders in the burned patient. In: editors. *Transactions 2nd International Congress on Research in Burns*. Edinburgh and London: E. & S. Livingstone; 1965. p. 349-363.

[3] Kulick MI, Lewis NS, Bansal V and Warpeha R. Hyperosmolality in the burn patient: analysis of an osmolal discrepancy. *J Trauma* 1980; 20: 223-228.

[4] Fligner CL, Jack R, Twiggs GA and Raisys VA. Hyperosmolality induced by propylene glycol. A complication of silver sulfadiazine therapy. *JAMA* 1985; 253: 1606-1609.

[5] Bekeris L, Baker C, Fenton J, Kimball D and Bermes E. Propylene glycol as a cause of an elevated serum osmolality. *Am J Clin Pathol* 1979; 72: 633-636.

[6] Kulick MI, Wong R, Okarma TB, Falces E and Berkowitz RL. Prospective study of side effects associated with the use of silver sulfadiazine in severely burned patients. *Ann Plast Surg* 1985; 14: 407-419.

[7] Zar T, Yusufzai I, Sullivan A and Graeber C. Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam. *Nat Clin Pract Nephrol* 2007; 3: 515-520.

[8] Bledsoe KA and Kramer AH. Propylene glycol toxicity complicating use of barbiturate coma. *Neurocrit Care* 2008; 9: 122-124.

[9] Wilson KC, Reardon C, Theodore AC and Farber HW. Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest* 2005; 128: 1674-1681.

[10] Kraut JA and Xing SX. Approach to the evaluation of a patient with an increased serum os-

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- molal gap and high-anion-gap metabolic acidosis. *Am J Kidney Dis* 2011; 58: 480-484.
- [11] Lockhart SP, Rushworth A, Azmy AA and Raine PA. Topical silver sulphadiazine: side effects and urinary excretion. *Burns Incl Therm Inj* 1983; 10: 9-12.
- [12] Eklund J. Studies on renal function in burns. 3. Hyperosmolal states in burned patients related to renal osmolal regulation. *Acta Chir Scand* 1970; 136: 741-751.
- [13] Peleg O, Bar-Oz B and Arad I. Coma in a premature infant associated with the transdermal absorption of propylene glycol. *Acta Paediatr* 1998; 87: 1195-1196.
- [14] Louis S, Kutt H and McDowell F. The cardiocirculatory changes caused by intravenous Dilantin and its solvent. *Am Heart J* 1967; 74: 523-529.
- [15] Seay RE, Graves PJ and Wilkin MK. Comment: possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; 31: 647-648.
- [16] Yorgin PD, Theodorou AA, Al-Uzri A, Davenport K, Boyer-Hassen LV and Johnson MI. Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis* 1997; 30: 134-139.
- [17] Wilson KC, Reardon C and Farber HW. Propylene glycol toxicity in a patient receiving intravenous diazepam. *N Engl J Med* 2000; 343: 815.
- [18] Arroliga AC, Shehab N, McCarthy K and Gonzales JP. Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* 2004; 32: 1709-1714.
- [19] Tayar J, Jabbour G and Saggi SJ. Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002; 346: 1253-1254.
- [20] Cawley MJ. Short-term lorazepam infusion and concern for propylene glycol toxicity: case report and review. *Pharmacotherapy* 2001; 21: 1140-1144.
- [21] Zosel A, Egelhoff E and Heard K. Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy* 2010; 30: 219.
- [22] Parker MG, Fraser GL, Watson DM and Riker RR. Removal of propylene glycol and correction of increased osmolar gap by hemodialysis in a patient on high dose lorazepam infusion therapy. *Intensive Care Med* 2002; 28: 81-84.
- [23] Demey HE, Daelemans RA, Verpooten GA, De Broe ME, Van Campenhout CM, Lakiere FV, Schepens PJ and Bossaert LL. Propylene glycol-induced side effects during intravenous nitroglycerin therapy. *Intensive Care Med* 1988; 14: 221-226.
- [24] Benneyan JC, Lloyd RC and Plsek PE. Statistical process control as a tool for research and healthcare improvement. *Qual Saf Health Care* 2003; 12: 458-464.
- [25] Provost LP MS. *The Health Care Data Guide: Learning from Data for Improvement*. San Francisco: Jossey-Bass, 2011.
- [26] Wilson A, Roberts WL, Pavlov I, Fontenot J and Jackson B. Patient result median monitoring for clinical laboratory quality control. *Clin Chim Acta* 2011; 412: 1441-1446.
- [27] Schoenmakers CH, Naus AJ, Vermeer HJ, van Loon D and Steen G. Practical application of Sigma Metrics QC procedures in clinical chemistry. *Clin Chem Lab Med* 2011; 49: 1837-1843.
- [28] Perla RJ, Provost LP and Murray SK. The run chart: a simple analytical tool for learning from variation in healthcare processes. *BMJ Qual Saf* 2011; 20: 46-51.
- [29] Canel C, Mahar S, Rosen D and Taylor J. Quality control methods at a hospital. *Int J Health Care Qual Assur* 2010; 23: 59-71.
- [30] Mohammed MA, Worthington P and Woodall WH. Plotting basic control charts: tutorial notes for healthcare practitioners. *Qual Saf Health Care* 2008; 17: 137-145.
- [31] Kirkland KB, Homa KA, Lasky RA, Ptak JA, Taylor EA and Splaine ME. Impact of a hospital-wide hand hygiene initiative on healthcare-associated infections: results of an interrupted time series. *BMJ Qual Saf* 2012; 21: 1019-1026.
- [32] Zar T, Graeber C and Perazella MA. Recognition, treatment, and prevention of propylene glycol toxicity. *Semin Dial* 2007; 20: 217-219.
- [33] Bedichek E and Kirschbaum B. A case of propylene glycol toxic reaction associated with etomidate infusion. *Arch Intern Med* 1991; 151: 2297-2298.
- [34] Allegaert K, Vanhaesebrouck S, Kulo A, Coesaert K, Verbesselt R, Debeer A and de Hoon J. Prospective assessment of short-term propylene glycol tolerance in neonates. *Arch Dis Child* 2010; 95: 1054-1058.