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Review

Hyperosmolar metabolic acidosis in burn patients exposed to glycol based topical antimicrobials—A systematic review

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ARTICLE INFO

Article history:
Accepted 24 June 2017
Available online xxx

Keywords:
Hyperosmolar metabolic acidosis
Burn patients
Glycol-based topical antimicrobials
Propylene glycol
Polyethylene glycol

ABSTRACT

Background: The well documented susceptibility of burn patients to acquired infections via damaged skin mandates application of antimicrobial agents. These agents are dissolved in various vehicles that augment skin absorption thus allowing greater efficacy. Polyethylene glycol (PEG) and Propylene glycol (PropG) are among the most commonly used vehicles, and both have been used in numerous medications and cosmetic products over the past few decades. Rarely, burn patients treated with agents containing these glycols present with a life threatening systemic toxidrome of hyperosmolar metabolic acidosis. We present a systematic review of outcomes in burn patients treated with similar agents.

Methods: Relevant studies were identified through systematic searches conducted in MEDLINE (Ovid), Embase (Ovid), CENTRAL (Ovid), and Web of Science (Thomson Reuters), from database inception to August 4th, 2016. All publications of clinical burn patient studies included at least one arm receiving a glycol based topical therapy.

Results: A total of 61 studies involving 10,282 patients and 4 different antimicrobial medications fulfilled the inclusion criteria. Nine burn patients (0.09%) were documented to present with hyperosmolar metabolic acidosis during topical silver sulfadiazine treatment. Propylene glycol isolated from their blood accounted for the high osmole gap.

Conclusion: This first systematic review found very few cases of documented hyperosmolar metabolic acidosis, all within one study that had set to specifically explore this toxidrome. High index of suspicion with frequent osmolar gap monitoring may help identify future toxicities in a timely manner.

Contents

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http://dx.doi.org/10.1016/j.burns.2017.06.006
0305-4179/

1. Introduction

Two commonly used glycol vehicles in topical products prescribed for prevention and treatment of skin infections are polyethylene glycol (PEG) and propylene glycol (PropG). Their presence in the antimicrobial ointment, cream or gel allows rapid penetration into skin and subcutaneous tissues [1]. Unlike toxic glycol ethers such as ethylene glycol (EG) and diethylene glycol (DEG), these two vehicles are considered benign; PEG is a macromolecule which no human enzyme can metabolize and PropG is metabolized into citric acid cycle constituents that are further metabolized into water and carbon dioxide, and therefore both are present in numerous pharmaceutical and cosmetic topical products [2–4].

Burn patients are extremely susceptible to acquired infections via their damaged skin, and the probability for such infections is higher as the involved percentage of total body surface area (%TBSA) is larger [5]. It has been the standard of care for several decades now to apply topical antimicrobials to the damaged skin of hospitalized burn patients on admission. This practice had resulted in significant reduction of mortality and various complications, mainly sepsis and prolonged hospital stay [6–8].

Clinical and laboratory follow up of burn patients published almost half a century ago had revealed a risk for developing lethal combination of acidosis and hyperosmolarity during burn unit stay [9,10]. Later publications had referred to these phenomena as potential adverse drug reactions to their topical therapy, however, no connection was established between any of the active antimicrobial ingredients and those severe metabolic insults [11,12].

Reports on isolation of abnormally high levels of PropG [13] and EG [14,15] from tissues of lethally intoxicated burn patients who were treated with topical products containing PropG and PEG, respectively, had begun to emerge 3–4 decades ago. Currently available Medline via PubMed data (Accessed November 15, 2016) regarding this toxidrome implicates silver sulfadiazine and nitrofurazone products (Table 1). However, a broader analysis of products marketed for burns, reveals several others which are glycol based (Table 2).

The objective of the study was to systematically identify all reports on systemic outcomes (mortality, adverse clinical course while on therapy, and appearance of hyperosmolar metabolic acidosis) of burn patients who were treated with a topical glycol based antimicrobial agent.

2. Methods

2.1. Systematic review

This research presents a structured literature review, done according to the *PRISMA guidelines*, as well as a synthesis of the findings and how they affect existing knowledge [16]. The study protocol had been submitted to PROSPERO and was published on their website. Registration number: CRD42016048459.

Table 1 – Published case reports of lethally intoxicated burn patients who were treated with topical products containing PropG and PEG.

	Topical antimicrobial product exposure	Exposed burn patients presenting with glycol toxidrome	%TBSA of exposed burn patients (range)	Exposed burn patients mortality N (%)	Exposed burn patients surviving with late sequelae N (%)	Toxin isolated from patients' tissues (blood or urine)
Bekeris et al. [13]	Nitrofurazone	2	80-90	2 (100)	N/A	Propylene glycol
Kulick et al. [15]	Silver sulfadiazine	2	90	2 (100)	N/A	Propylene glycol
Bruns et al. [14]	Silver sulfadiazine	3	20-56	3 (100)	N/A	Ethylene glycol
Flinger et al. [17]	Silver sulfadiazine	1	78	0	1 (100)	Propylene glycol
Peleg et al. [18]	Nitrofurazone	1	5	0	0	Propylene glycol
Willis [19]	Silver sulfadiazine	1	60	0	0	Propylene glycol
Summary		11	5-90	7 (63.6%)	1 (25%)	

Please cite this article in press as: T. Leibson, et al., Hyperosmolar metabolic acidosis in burn patients exposed to glycol based topical antimicrobials—A systematic review, Burns (2017), http://dx.doi.org/10.1016/j.burns.2017.06.006