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A Simple Cost Saving Measure: 2.5% Mafenide Acetate Solution

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Abstract

Objective—The optimal concentration of mafenide acetate solution for use in the treatment of burns is unknown. Despite data supporting the use of a 2.5% solution, 5% formulation is traditionally used, and has been the highest costing medication on formulary. The aim of the current study is to evaluate cost and patient outcomes associated with a new policy implementing the use of 2.5% solution in burn patients and restricting the 5% formulation to specific indications only.

Methods—A retrospective review of all patients receiving mafenide acetate solution at a single pediatric burn hospital was performed before and after the initiation of the new policy on the use of 5% versus 2.5% solution. Duration of therapy, adverse events, cost, incidence of wound infection and bacteremia were analysed.

Results—In 2009, 69 patients were treated with 5% mafenide acetate solution for a total cost of $125,000 ($1811/patient). In 2010, following the initiation of the policy, 48 patients were treated: 19 received 5% mafenide acetate solution with appropriate indication, while the remaining 29 received 2.5% solution for a total cost of $38,632 ($804/patient). There were no significant changes in the incidence of bacteremia or wound infection. No side effects of either solution were noted.

Conclusions—Under certain conditions, a 2.5% mafenide acetate solution appears sufficient. In this multinational pediatric burn hospital, the use of a 2.5% solution was not associated with increased bacteremia or wound infection and proved to be more cost-effective.

Introduction

Despite numerous advances in burn care over the past decades, wound infection continues to be a significant complication in the burn patient and may lead to systemic sepsis and death [1–3]. Topical antimicrobials have emerged as the traditional modality used to control bacterial load at the burn wound site [4–7]. They have been shown in numerous studies to limit bacterial colonization in the setting of an open burn wound or a widely meshed autograft,

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effectively reducing counts to less than 10^5 per gram of tissue [8–12]. Moreover, they were used over the years to avert the possibility of beta hemolytic *Streptococcus* infection [13–15].

Mafenide was introduced in 1966 as a topical Sulfonamide in the form of Mafenide Hydrochloride 10% ointment. With its bacteriostatic action, via inhibition of nucleotide synthesis [2,16–18], it was shown to reduce total bacterial counts in burn wounds to very low levels and thought to contribute to reduced mortality rates [18,19]. Side effects included significant discomfort/pain, due to its high osmolality and hypertonicity, especially when applied to superficial burns [5,20]. Additional side effects were rash, formation of neo-eschar [2,21], and acid-base imbalance (i.e. metabolic acidosis due to inhibition of carbonic anhydrase [22]). In an attempt to improve the safety profile of Mafenide, a 5% Aqueous Solution was created [7,23–25]. Favorable outcomes were observed with this new approach [26], however, metabolic acidosis and pain continued to be a disadvantage [20], as well as a very high cost (at our institution, Sulfamylon 5% Solution was the #1 cost drug on formulary in 2009 at $125,000 according to our 2010 Drug Usage Evaluation report). Table 1 illustrates the average costs of the most commonly used topical agents. In this regard, and based on an *in vitro* wet disc assay demonstrating comparable antimicrobial activity between a 2.5% and 4% solution of mafenide [27,28], a new policy was instituted in our burn center that restricted the 5% mafenide acetate solution to targeted indications only; otherwise, a 2.5% solution was utilized. The aim of this article is to present cost and patient outcome data associated with this new approach.

Methods

As part of a drug usage evaluation (DUE) and in an effort to ensure cost-effective use of Sulfamylon® Solution therapy while potentially reducing side effects, a new policy that restricted the use of 5% mafenide acetate solution to special situations was implemented in our institution. Beginning in 2010, a 2.5% mafenide acetate solution became the standard concentration unless otherwise indicated. Indications for the 5% Sulfamylon Solution included: (1) eschar + sepsis, (2) eschar + multidrug resistant organisms (MDROs), (3) eschar + foreign patient admission + unknown wound culture data, (4) sepsis + MDROs + suspected/probable silver nitrate failure, and/or (5) confirmed or suspected skin or skin structure infection with MDROs + suspected/probable silver nitrate failure.

We recorded total number of patients receiving Mafenide therapy (5% and 2.5% solutions), indications for 5% solution when used, duration of therapy, and any adverse events encountered (rash, metabolic acidosis, wound infection, bacteremia, sepsis). Total cost of Mafenide therapy and cost per patient were calculated.

Results

117 patients were included in this study. All were evaluated by an attending burn surgeon at the time of admission. In 2009, 69 patients were treated with 5% mafenide acetate solution for a total cost of $125,000 ($1,811/patient). In 2010, following the initiation of the new policy, 48 patients were treated: 19 receiving 5% solution, and 29 receiving 2.5% solution (Table 2). The duration of therapy for the 5% group ranged between 1 to 15 days with an

average of 4.5 days of treatment per individual compared to the 2.5% group where the range of therapy was between 1 to 27 days with an average of 6.4 days. The total cost (5% and 2.5% combined) in 2010, was $38,632 ($804/patient). The estimated cost savings, per 100 patients treated, is $100,700.

Appropriate indications for use of the 5% solution were noted in all instances. These are summarized in Table 3. No adverse events were documented in either group, and there were no significant changes in the incidence of bacteremia or wound infection when comparing 2010 to 2009.

Discussion

Shortly after the introduction of the original 10% Mafenide cream in burn clinical practice, drastic mortality benefits were observed with a marked reduction in the rate of invasive burn wound infections, particularly in patients with TBSA ranging from 20% to 79% [1,4,18,29]. Mafenide has a wide range of antibacterial activity against both gram (+) and gram (−) organisms as well as anaerobes, but with no fungal coverage [30–33]. Its broad anti-bacterial spectrum, effective even in the presence of blood and pus, and its ability to penetrate under the wound surface in both viable and nonviable tissue, extended its use in non-burn wounds (blast injuries, open fractures, synergistic gangrene, and necrotizing fasciitis) [34–38]. Moreover, it was recently shown to have excellent antimicrobial activity against MDROs [16]. Side effects were however noted: discomfort and pain (especially when applied on superficial burns, due to a high osmolality and hypertonicity [5,20]), rash, formation of neo-eschar [2,23], and acid-base imbalance; mafenide is converted to *p*-carboxybenzenesulfonamide by monoamide oxidase, a carbonic anhydrase inhibitor, causing metabolic acidosis [22]. In burn patients with inhalation injury and a concomitant respiratory acidosis, the use of mafenide acetate over a large burn surface area or the repeated application of this compound can be fatal [39]. Mafenide acetate has also be shown to decrease the breaking strength of healed wounds and may delay healing [40]. It is worth mentioning that the 10% cream formulation was particularly beneficial on burn wounds before the era of early excision as it penetrates eschar well and is easily applied [39,41]

Starting in the late 1960s, many studies were conducted to find an alternative agent devoid of these side effects. A study performed in the 1970s revealed that Mafenide (Sulfamylon) solution-soaked dressings resulted in cleaner wounds than saline dressings[6]. This led to the use of a new form of Mafenide, Sulfamylon Aqueous Solution. In 1972 Harrison *et al*. [21], based on their previous work on the use of the cream [23], performed a study on both human and animals using Sulfamylon 5% Aqueous solution. No sepsis or mortality events were noted and the 5% aqueous solution was shown to be equivalent to that of the 11.2% cream. It was concluded that Sulfamylon aqueous solution had excellent absorption in burned skin, is effective for debridement, granulation tissue protection and preparation, and bacterial control. Furthermore, dressings were comfortable when in place and the wounds always appeared clean [42–44].

Until the early to mid-1980's, the use of the 5% mafenide acetate solution was mostly limited to later stages of burn wound therapy: chronic granulating wounds before grafting or

as adjunctive treatment after grafting [7,20,25]. In 1983 Murphy *et al* [26] once again confirmed the efficacy of the 5% solution, with respect to the 11.2% cream; and since then, its use has expanded to all phases of burn wound management (acute, intermediate and chronic, and after surgical debridement, and over freshly applied meshed STSG) [35]. This formulation appeared to be effective, safe, and versatile with clearly less side effects than the cream form [42]. The main disadvantage was fungal colonization of the wounds due its lack of antifungal activity (Nystatin may beadded to the solution [45,46]) and pain or discomfort when the solution is applied to superficial burns [20]. The latter has been attributed to potential cytotoxic and injurious effects of mafenide to keratinocytes [47,48]. Nevertheless, after 26 years as an investigative agent, mafenide was approved by the US Food and Drug Administration in the mid-1990's as a 5% topical solution. Indications are limited to soaks treating meshed split-thickness autografts after excision of second-degree and third-degree burns [11,35].

Since the introduction of the 5% solution into clinical practice, no clinical trials have evaluated the effectiveness of a more diluted preparation. The 5% solution was obtained as a consequence of preparation and dilution simplicity. 5% Sulfamylon solution is prepared by reconstituting 50g of sterile mafenide acetate powder in 1000 ml of sterile water, producing a 5% clear and colorless solution with an osmolarity of 380 mOsm/L and a pH of 6.5–6.8. It can be applied to wounds in the same fashion as is normal saline and used at regular intervals (6–8 hours)in order to prevent wound dessication and maintain antibacterial activity [7,20,34,35]. In 1990 an *in vitro* wet disc assay, allowing testing of microorganisms for susceptibility and resistance to anti-microbial solutions, was used to examine varying concentrations of mafenide hydrochloride (1%, 2.5%, and 4%) [28]. The 2.5% mafenide solution was shown to be as efficacious as the 5.0% solution. In this regard, and in an effort to reduce the side effects of Sulfamylon® Solution therapy and ensure cost-effectiveness of this drug, a policy was instituted such that the 5% solution was restricted to critical cases; otherwise the 2.5 % solution was utilized. In this small cohort of international pediatric burn patients, this new policy resulted in a significant reduction in health-care cost, with no change in the rates of bacteremia or wound infection.

Conclusion

Under certain conditions, a 2.5% mafenide acetate solution may be sufficient. In this small cohort of patients, the use of the 2.5% solution was not associated with increased bacteremia or wound infection. Restriction of the 5% solution, for use only with specific indications, provided significant cost savings. Although the 5% mafenide acetate solution has become the standard in practice, our data suggest that lower concentrations may be equally efficacious and significantly less costly. Burn centers may consider this simple strategy to decrease pharmacy expenditures.

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Table 1

Cost Breakdown for Commonly Used Topical Agents.

Cost Breakdown for Topical Agents						
Product	**Form & Concentration**	**Unit/cost**	**BSA covered by unit**	**Cost/m^2**	**Frequency per day**	**Cost/m^2/day**
Mafenide acetate	5% Solution	Bottle (1L)/122.5$	50cm × 50cm	490$	2	980$
	2.5% Solution	Bottle (1L)/61.25$	50cm × 50cm	245$	2	490$
	8.5% Cream	Tube (56.7g)/27.08$	35cm × 35cm	216.64$	2	433.28$
		Jar (454g)/186.54$	100cm × 100cm	186.54$	2	373.08$
Silver Nitrate (in H_2O)	0.5% Solution	Bottle (1L)/17.69$	50cm × 50cm	70.76$	4	283.04$
Sodium Hypochlorite or Dakin (in NS)	0.125% Solution (½ strength)	Bottle (473mL)/8.24$	35cm × 35cm	65.92$	3	197.76$
	0.025% Solution (¼ strength)	Bottle (473mL)/1.65$	35cm × 35cm	13.2$	3	39.6$
Bacitracin	Ointment:500U/g	Tube (30g)/1.44$	25cm × 25cm	21.6$	2	43.2$
		Jar (454g)/37.4$	100cm × 100cm	37.4$	2	74.8$
Silver sulfadiazine	1% Cream	Tube (50g)/9.32$	33cm × 33cm	74.56$	2	149.12$
		Jar (400g)/40.22$	95cm × 95cm	45.64$	2	91.28$
Mupirocin	2% Ointment	Tube (22g)/6.47$	22cm × 22cm	133.51$	2	267.02$

H_2O: sterile water; NS: Normal Saline 0.9%.

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Table 2

Sulfamylon Use

Treatment with 5% vs. 2.5% Mafenide Acetate			
Patients	***2010 (48 patients)***		***2009 (69 patients)***
	5% Mafenide Acetate *(n=19)*	**2.5% Mafenide Acetate *(n=29)***	**5% Mafenide Acetate *(n=69)***
Age	Avg: 8.86Y Range: 18M-17Y	Avg: 7.82Y Range: 22M-17Y	Avg: 6.59Y Range: 13M-17Y
TBSA	Avg: 53.32%/P Range: 32–88%	Avg: 40%/P Range: 8–87%	Avg: 30.71%/P Range: 2–95%
Treated BSA	Total BSA: 627% Avg: 33%/P Range: 2–65%	Total BSA: 897% Avg: 30.93%/P Range: 1–60%	Total BSA: 1182% Avg: 17.13%/P Range: 1–80%
Cumulative duration of treatment	Avg: 6.31 days/P Range: 1–17 days	Avg: 15.03 days/P Range: 4–58 days	Avg: 12.6 days/P Range: 1–82 days
Length of in-patient stay	Avg.: 43.26 days/P	Avg.: 38.68 days/P	Avg.: 22.39 days/P
Total Cost	$20, 768 (236 L)	$17,864 (406 L)	$125,000 (1470 L)
	$38, 632		
Average Cost per Patient	$1093	$616	$1811
	$804		

MDROs Multidrug Resistant Organisms; AgNO3 Silver Nitrate; Avg: average; Y: years; M: months; P: patient; L: liters

Table 3

Indications for use of 5% Mafenide Acetate

Indications of use for 5% Mafenide Acetate
❖ Eschar + Sepsis
❖ Eschar + MDROs
❖ Eschar + Foreign patient admission + Unknown wound culture data
❖ Sepsis + MDROs + suspected/probable AgNO3 failure
❖ Confirmed or suspected skin or skin structure infection with MDROs + suspected/probable AgNO3 failure