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LETTER TO THE EDITOR

Silver absorption in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis treated with silver-impregnated dressings. A case series

To the Editor:

There is a lack of consensus for wound care in patients with Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Conventional dressings, such as gauze with petrolatum, have been the mainstay of treatment for the extensive epidermal wounds. Recent publications have demonstrated a trend towards the use of modern dressings for wound care in SJS/TEN, including silver-impregnated dressings, for the antimicrobial properties and improved patient comfort secondary to decreased frequency of dressing changes.[1–5] However, cytotoxic effects of silver have been demonstrated in human cell lines, including fibroblasts, keratinocytes, granulocytes, monocytes, and macrophages.[6,7] Animal and human studies addressing the possibility of silver toxicity from silver-coated dressings applied to burns have yielded conflicting results with regard to systemic silver absorption.[8–13] To our knowledge, this study would be the first retrospective chart review investigating silver absorption in SJS/TEN patients treated with silver nylon and silver foam dressings.

After obtaining approval from the University of South Florida Institutional Review Board, we performed a retrospective chart review using the Epic Electronic Medical Record to search for eligible patients. All patients from July 2016 to March 2017 who were diagnosed with SJS/TEN were considered for this study. Patients treated with silver-impregnated dressings met the inclusion criterion, which yielded a total of 14 patients. Those who did not have serum silver measurements drawn during their treatment period were excluded (8 patients). A total of 6 patients were selected for this review, which included 5 adults and 1 child. Serum silver levels had been ordered if the consulted Dermatology team suspected silver toxicity, suggested by argyria, acute leukopenia, and/or elevated transaminases.

The results of this retrospective study showed that 5 patients had elevated serum silver levels ranging from 9.9 to 110 μg/L (normal range < 5 μg/L). All 5 patients with elevated serum silver levels had a decrease in white blood cell counts compared with baseline. One patient with normal serum silver levels had a normal white blood cell count throughout admission but developed elevated transaminases. None of the patients developed argyria. Table 1 summarises the patient's characteristics.

One patient was treated with silver foam wound dressings (Mepilex Ag, Mölnlycke Health Care US, LLC, Norcross, GA). Four patients received silver nylon wound dressings (Silverlon, BWD, Argentum Medical, Geneva, IL). One patient received both dressings. The silver content of Mepilex Ag and Silverlon is 1.20 and 5.46 mg/cm^2, respectively.[14] Mepilex Ag is routinely changed every 6 to 7 days, whereas Silverlon is changed every 3 to 4 days. Four patients received IVIG during the hospitalisation, and 1 patient was managed with supportive care only Three patients had underlying haematological malignancies and also had 75% to 100% total body surface area involved, which was characterised by erythroderma and/or erythematous to dusky macules and patches, atypical target lesions, purpura, or areas of skin detachment. Their total body surface area with denuded skin and/or a positive Nikolsky sign was 5% to 25%.

Studies regarding the safety of silver-based dressings have yielded controversial results. in vitro studies have indicated that silver released from silver-coated commercial dressings is highly toxic to cultured keratinocytes, fibroblasts, and immune cells.[6,7] However, the exact mechanism for silver cytotoxicity remains unclear. It has been proposed that ionic silver can cause direct or indirect damage to human DNA. The latter may occur from the increase of reactive oxygen species production or from the decrease of ATP production, both of which damage mitochondria, ultimately reducing energy-dependent DNA repair mechanisms.[15–17]

In recent animal models of thermal and chemical burns treated with silver nylon dressings, silver ions were detected only in the wound bed but not in blood or other tissues.[5] The authors suggested that silver nylon dressings are a safer alternative than silver nitrate, nanocrystalline silver, or silver sulfadiazine, all of which have been associated with elevated levels of silver ion in blood, urine, and solid organs.[4,6,7] In major burn patients treated with a nanocrystalline silver dressing, a prospective study of 6 patients suggested that absorption of silver can occur; however, no systemic adverse effects were

TABLE 1 Patient characteristics and laboratory results at the time of serum silver measurement

Age	Sex	Co-morbidities	Score TEN	Total BSA involved (%)/ detachment (% BSA)	Causative drug	Systemic treatment	Reason for serum silver measurement	LOS (d)	Dressing type	Serum Ag (ref: <5 μg/L)	WBC baseline (ref: 4.6-10.210* 3/μL)	WBC when serum Ag measured	WBC at discharge or transfer
59	M	AML	4	100/25	TMP-SMX	IVIG	Leukopenia	10	Silver foam	74	4.68	2.42	1.11
67	F	MDS s/p alloSCT, acute GVHD	4	90/10	TMP-SMX	Infliximab, IVIG	Acute decrease in leukocyte counts	20	Silver nylon	64	7.03	4.84	0.26
74	M	COPD, T2DM, CAD, gout, CHF	2	80/8	Allopurinol	IVIG	AST = 55 and leukopenia	12	Silver nylon	55	5.42	2.56	6.43
34	M	ESRD on HD, anaemia, HTN	3	50/8	TMP-SMX or naproxen	Etanercept	Acute decrease in leukocyte counts	21	Silver nylon	9.9	3.28	2.5	9.14
2	F	Seizures, premature birth	1	75/5	Zonisamide	IVIG	ALT = 891 U/L AST = 595 U/L	15	Silver foam, silver nylon	2.2	7.59	8.06	10.73
72, deceased	M	MDS, lymphoma	4	90/20	Bumetanide or azithromyc in	None	Acute decrease in leukocyte counts	16	Silver nylon	110	2.93	1.63	1.38

alloSCT, allogenic stem cell transplant; ALT, alanine aminotransferase, AML, acute myeloid leukaemia; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end stage renal disease; HD, haemodialysis; HTN, hypertension; IVIG, intravenous immunoglobulin; LOS, length of stay; MDS, myelodysplatic syndrome; T2DM, type 2 diabetes mellitus; TMP-SMX, trimethoprim-sulfamethoxazole; WBC, white blood cell count.

noted.[7] In contrast, case reports associated systemic silver absorption with subsequent argyria, elevated transaminases, and leukopenia.[2,4] Our study indicates that silver nylon and silver foam dressings may lead to systemic silver absorption, similar to other silver compounds. Our study also highlights the need of larger research studies to investigate whether the observed leukopenia and elevated transaminases are a result of silver toxicity, an underlying haematological malignancy (as noted in 3 of our patients), or to SJS/TEN itself.

In this setting of controversial data with a low level of evidence, the UK guidelines for adult patients with SJS/TEN recommends, based on the expert opinion of the Guidelines Development Group, a conservative approach with bland greasy emollients over the entire epidermis with topical antimicrobial agents to sloughed areas only.[18] They recommend limited use of silver products if extensive areas are being treated due to the risk of absorption. In the United States, the American Burn Association recommends treating areas of denuded skin with biological, biosynthetic, silver-, or antibiotic-impregnated dressings and also indicates that silver-impregnated dressings offer the advantage of less-frequent dressing changes, which may prevent mechanical damage to the healing epidermis.[19]

Altogether, our findings support that further studies are needed to elucidate the pharmacokinetics and safety of silver dressings in patients with SJS/TEN and ultimately provide rigorous evidence for the development of wound care guidelines in this patient population.

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