

Postoperative Use of Topical Antimicrobials

To the Editor:

A recent review by Sheth and Weitzul advocate the use of topical antimicrobials in the postoperative management of open wounds.¹ Unfortunately, the authors base this recommendation on studies in which the utility of topical antimicrobials is demonstrated in nonpostoperative settings (burns, ulcers, and artificially inoculated wounds) with vastly different endpoints of bacterial colonization and counts, rather than clinically infected wounds.

Due to concern for the development of contact dermatitis, the authors discourage the use of neomycin and instead encourage the use of bacitracin and mupirocin. Based on patch-testing studies by the North American Contact Dermatitis Group, the prevalence of allergic contact dermatitis (ACD) in the last 10 years from bacitracin (7.9–9.2%) is not much lower than that from neomycin (10.6–11.5%).² Furthermore, bacitracin is the most common topical antibiotic known to cause type I anaphylactic reactions.³ A previous randomized controlled trial comparing bacitracin ointment with white petrolatum in the postoperative setting demonstrated no benefit in terms of postoperative healing or infection rates; however, a higher incidence of ACD was demonstrated in the bacitracin group.⁴ Based on these data, the use of topical bacitracin carries risks not associated with the use of petrolatum, with no added benefit. Another randomized controlled trial using

mupirocin (which rarely causes ACD) demonstrated no benefit in terms of infection or healing.⁵

Thus far, to our knowledge, there is no compelling clinical study that demonstrates a clear benefit from using topical antimicrobials in the setting of clean postoperative wounds, whether open or closed. Furthermore, the use of topical antibiotics poses potential risks of ACD and anaphylaxis. Finally, white petrolatum has been shown to be equally efficacious and presents much less of a cost burden than topical antimicrobials.

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Multifocal Fixed Drug Eruption Due to Celecoxib

To the Editor:

Multifocal fixed drug eruption (MFDE) is a rare cutaneous disorder characterized by numerous lesions relapsing on multiple sites each time the causative drug or a chemically

related drug is taken.¹ A case of this drug reaction from celecoxib is reported.

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A 61-year-old nonatopic woman presented with 15 round, red-brown, edematous, moderately itching patches. Their size varied from 2 to 10 cm in diameter. The lesions, symmetrically distributed on the trunk and upper and lower limbs (Fig 1), appeared 3 hours after the ingestion of 200 mg of celecoxib for cervical pain caused by osteoarthritis. The drug had been previously taken on several occasions without any rash occurring. A clinical diagnosis of MFDE was suspected. Routine laboratory investigations were in the normal range. Celecoxib was discontinued, and the patient was treated with ebastine, tetracosactide hexa-acetate, and desoximetasone cream. After 1 week, only slight brownish black hyperpigmentation remained.

Two months after the resolution of the eruption, patch testing with celecoxib 10% in petrolatum and in dimethyl sulfoxide (DMSO 50% aqueous) was carried out on previously involved and uninvolved sites of the back with van der Bend square chambers (van der Bend BV, Brielle, Netherlands). Readings performed according to International Contact Dermatitis Research Group criteria revealed positive reactions in all patch sites, especially when the drug was in DMSO or when it was applied to the involved skin. The patch-test result with DMSO was negative. Because celecoxib is a sulfonamide-containing drug, some sulfonamide compounds in petrolatum (p-phenylenediamine [1%], sulfonamide mix [5%], furosemide [5%], sulfamethoxazole [10%], and glibenclamide [10%]) were patch tested. No positive cross-reactions were observed.

To our knowledge, this is the first case of MFDE reported in the literature. Only one case of celecoxib-induced fixed drug eruption (in a woman with two typical clinical lesions and with a positive oral rechallenge test result) has been published.²

Celecoxib, a nonsteroidal antiinflammatory drug (NSAID) belonging to the cyclooxygenase-2 (COX-2) inhibitors, is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent. Celecoxib is well tolerated in patients suffering from acetylsalicylic acid-induced asthma, chronic idiopathic urticaria, and adverse skin reactions to NSAIDs,^{3,4} but it should be avoided in subjects with "sulfa" allergy. Sulfonamides are classified into two different groups: (1) aromatic amines (sulfonamide antimicrobials), with a -NH₂ group at the N₄ position of the benzene ring, and (2) nonaromatic amines, without this group (such as furosemide, thiazide diuretics, sulfonyleureas, and celecoxib).⁵ In addition, the latter compounds do not contain a methylated heterocyclic ring at the N₁ position (which is present in arylamine sulfonamides). Therefore, cross-reactions between celecoxib and sulfonamide antimicrobials should not be frequent.



Figure 1. Red-brown edematous patches on the patient's trunk.

For these data and the results of our diagnostic tests, further investigations on cross-reactivity among COX-2 inhibitors, sulfonamides, and p-amino compounds are required.

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Formaldehyde, Aspartame, Migraines: A Possible Connection

To the Editor:

The following comments relate to the Jacob and Stechschulte case study in which the authors speculate that aspartame consumption may be associated with migraine and recurrent dermatitis (published in the May/June 2008 issue of *Dermatitis*).¹ The authors ignored the fact that aspartame metabolites bring nothing new to the human body and are in fact constituents of many common foods we consume daily. The aspartame molecule is simply a dipeptide of aspartic acid and the methyl ester of phenylalanine, (not the methyl ester of aspartic acid, as suggested by the authors). It is completely hydrolyzed in the gastrointestinal tract to the amino acids, aspartic acid, and phenylalanine, plus a small amount of methanol.² These amino acids are found in all protein-containing foods, such as dairy and meat products, and are absorbed and metabolized by the body like amino acids from any other protein-based food. Methanol is similarly present in many foods, such as fresh fruits, vegetables, and juices.³ Methanol is also a normal constituent in blood, urine, saliva, and expired air.⁴ Formaldehyde, a methanol metabolite, is produced during the demethylation of many substances, including many foods and drugs.⁵ For example, fruit juices, coffee, and alcoholic beverages produce significantly greater quantities of formaldehyde than aspartame-containing products.⁶ Thus, it would be impossible to distinguish clinically relevant patch-test reactions to formaldehyde from aspartame from such reactions in which the formaldehyde was derived from the host of other dietary sources of formaldehyde.

In their discussion, Jacob and Stechschulte raised concerns that formaldehyde may form adducts that are difficult to remove by normal metabolic pathways and that may result in their accumulation in tissues. Dietary methanol is oxidized in the liver to formaldehyde and formic acid. The metabolism of methanol to formic acid is very rapid, with formaldehyde having a half-life of 1 to 2 minutes.⁵ Hence, there is no accumulation of formaldehyde after even high doses of methanol.⁷ It is estimated that more than 50,000 mg of formaldehyde are produced and metabolized each day in a human adult and that the liver can metabolize 22 mg of formaldehyde per minute.⁸ Furthermore, formic acid, a metabolite of formaldehyde, is an essential one-carbon-pool intermediary substrate for amino acid and purine nucleotide synthesis via folate-dependent metabolism.⁷

The authors' suggestion of the development of migraine after consumption of aspartame-containing products ignored results in earlier peer-reviewed publications. Schiffman and colleagues and Leon and colleagues reported on randomized double-blind placebo-controlled studies that involved larger sample sizes (40 and 108 subjects, respectively) and evaluated the association of headache and administration of aspartame (capsules) at doses of 30 mg/kg of body weight and 75 mg/kg of body weight (the equivalent of an adult drinking 4 L and 10 L, respectively, of beverage sweetened with 100% aspartame). In both studies, the headache incidence rate in the aspartame group was not significantly different from that of the placebo group.^{9,10} As to the report of dermatitis flares after consumption of aspartame, Geha and colleagues investigated allergic-type symptoms such as urticaria and angioedema in a multicenter randomized double-blind placebo-controlled crossover clinical study of 21 subjects who received capsules containing 25 mg or 300 mg of aspartame, capsules containing 7.5 mg of diketopiperazine (DKP) and 3.75 mg of β -aspartame (conversion products of aspartame). The authors concluded that there was no statistically significant difference in the incidence of allergic-type reactions between aspartame and placebo challenges.¹¹

Although Jacob and Stechschulte commented on the limitation of their study and their drawing conclusions from their small sample, they ignored the large quantities

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