

Interaction of Topical Sulfacetamide and Topical Dapsone With Benzoyl Peroxide

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Background: A recent study demonstrated evidence of a yellow-orange discoloration of the skin and hair when topical dapsone gel was combined with benzoyl peroxide. This phenomenon had previously been observed by one of us (A.B.F.) when sulfasalazine was combined with benzoyl peroxide. To investigate these interaction phenomena, topical dapsone gel and sulfacetamide sodium lotion were combined with various topical acne treatments, including benzoyl peroxides, clindamycin phosphate, and retinoids.

Observations: Products containing benzoyl peroxide produced an orange-brown discoloration when mixed with either sulfacetamide or dapsone.

Conclusions: Knowledge of the chemical reaction between benzoyl peroxide and sulfacetamide and dapsone will help minimize the occurrence of this interaction on our patients' skin.

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ACNE IS ONE OF THE MOST common reasons for visits to dermatologists in the United States.¹ It is caused by abnormalities of the pilosebaceous unit such as increased sebum production, bacterial overgrowth, hyperkeratinization, and inflammation.² Combination treatment of acne vulgaris is often implemented to address each of these abnormalities. Treatment with multiple medications is more effective and works more quickly than treatment with single agents.² Therefore, it is vital to understand possible reactions among topical acne medications to minimize adverse events and to maximize safety and efficacy.

One such reaction is the oxidation and inactivation of tretinoin by benzoyl peroxide. This reaction is accelerated when the medications are exposed to light.^{3,4} Another reaction was discovered in a recent study that evaluated the efficacy of dapsone gel, 5%, in combination with other topical acne medications.⁵ In that study, 7 of 100 patients (7%) in the dapsone gel and benzoyl peroxide group noted a temporary yellow to orange discoloration of the skin and/or facial hair after application of both medications 10 minutes apart. The discoloration lasted between 4 and 57 days, resolved after discontinuation of treatment, and caused 2 of the 7 patients to discontinue the clinical trial.⁵ According to the authors, the patients also complained that the products stained their clothing and that the stains were difficult to remove. To our knowledge, this reaction has not been previously reported in the literature. The phe-

nomenon had previously been observed by one of us (A.B.F.) when sulfasalazine was combined with benzoyl peroxide.

Dapsone gel (**Figure 1A**), a synthetic sulfone, was recently approved by the Food and Drug Administration in a topical aqueous gel form to treat acne vulgaris.^{6,7} The anti-inflammatory and antimicrobial properties of dapsone have previously been implemented in an oral form to treat dermatitis herpetiformis, Hansen disease, and, more historically, severe acne.⁸⁻¹⁰ Systemic dapsone is typically reserved for the treatment of severe nodular acne due to a dose-dependent hematologic toxic reaction.¹¹ The topical form was developed with hopes of minimizing this adverse effect and of attaining efficacy in the treatment of acne vulgaris.

Sulfacetamide sodium (**Figure 1B**), a sulfonamide, demonstrates bacteriostatic activity against both gram-negative and gram-positive organisms. It competitively antagonizes para-aminobenzoic acid, causing interference with bacterial DNA synthesis.¹² Benzoyl peroxide (**Figure 1C**), an organic peroxide, is one of the most commonly prescribed acne medications because of its antibacterial, antikeratolytic, and comedolytic actions.¹³ It is converted to benzoic acid in the skin and primarily targets the pilosebaceous units.¹⁴ The bactericidal action of benzoyl peroxide against *Propionibacterium acnes* is thought to involve the release of free-radical oxygen through the degradation of bacterial proteins and interaction with microbial cell components.¹⁴ The labile O-O bond is the source of these free radicals, which are the active intermediary and the cause of many of benzoyl per-

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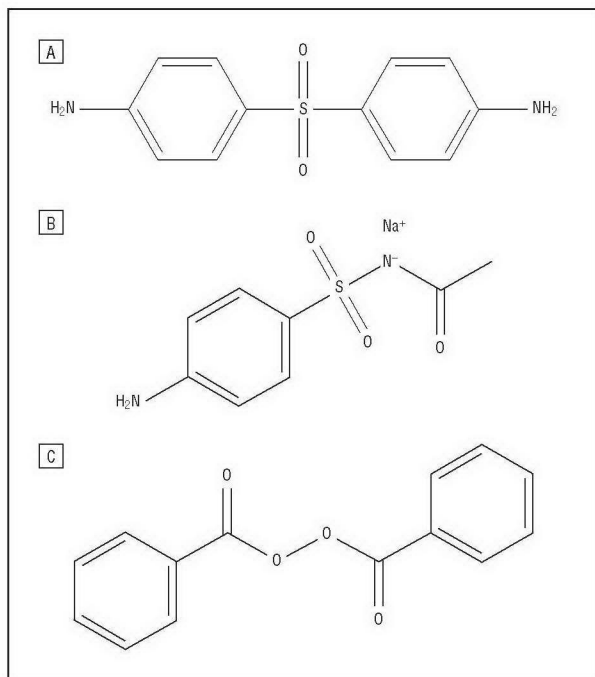


Figure 1. Chemical structures of dapsone, sulfacetamide sodium, and benzoyl peroxide. A, Dapsone, International Union for Pure and Applied Chemistry (IUPAC) name: 4,4'-sulfonylbisbenzenamine; molecular formula: $C_{12}H_{12}N_2O_2S$. B, Sulfacetamide sodium, IUPAC name: *N*-acetyl-4-aminobenzenesulfonamide sodium; molecular formula: $C_9H_9N_2NaO_3S$. C, Benzoyl peroxide, IUPAC name: dibenzoylperoxide; molecular formula: $C_{14}H_{10}O_4$.

oxide's biologic effects.^{15,16} The effectiveness of benzoyl peroxide can be enhanced if the molecule gains access to a tertiary amine for electron transfer. For example, when benzoyl peroxide is combined with antibiotics or antifungal agents containing tertiary amines, such as erythromycin, clindamycin phosphate, terbinafine, and butenifine, therapeutic results are improved.^{15,17,18} Detrimental effects can also result from the use of these free radicals. When tertiary amine-containing topical anesthetic agents were applied to skin that was pretreated with benzoyl peroxide, the anesthetic effect diminished by 75%.¹⁹ The aims of this study were to further investigate the discoloration reaction between dapsone gel and benzoyl peroxide and to evaluate whether or not a similar reaction would occur with sulfacetamide and benzoyl peroxide.

METHODS

A half a pea-sized amount of sulfacetamide solution, 10%, was applied to 8 different sections of a white cotton dinner napkin. Then, another half a pea-sized amount of each of the following was added to the sulfacetamide and the ingredients were mixed together: creamy benzoyl peroxide wash, 8%; clindamycin, 1%, plus benzoyl peroxide gel, 5% (BenzaClin, gel 1); clindamycin, 1%, plus benzoyl peroxide gel, 5% (Duac, gel 2); topical clindamycin gel, 1%; tretinoin gel, 0.05%; tazarotene cream, 0.1%; and adapalene gel, 0.3%. One of the sulfacetamide applications served as the control, as no additional product was mixed. The same application process was repeated with dapsone gel, 5%, mixing it with each of the additional topical medications and leaving 1 area of dapsone gel to serve as the control. Then, photography was performed at 30-minute intervals for 6 hours and at 12 hours. Finally, the napkin was washed and dried with a nonbleach de-

tergent in a warm/cold cycle to determine whether the product residue was easily removable. All photographs are original, without color correction, but were taken in a room with natural and fluorescent lighting, which varied over the course of the day.

RESULTS

In all groups containing sulfacetamide, including the control, a faint orange ring was visible at 30 minutes and remained at 12 hours (**Figure 2**). A yellow tint was present in the sulfacetamide plus benzoyl peroxide group at 3 hours, followed by a similar yellow tint in both sulfacetamide plus benzoyl peroxide and clindamycin plus benzoyl peroxide groups at 4 hours. These yellow tints gradually developed into an orange-brown color by 12 hours. Aside from the faint orange ring, there was no color change in the sulfacetamide control or in the sulfacetamide plus clindamycin, sulfacetamide plus tretinoin, sulfacetamide plus tazarotene, or sulfacetamide plus adapalene groups.

In the groups containing dapsone gel, an orange change occurred in the dapsone gel plus benzoyl peroxide group at 1 hour, followed by both dapsone plus clindamycin and dapsone plus benzoyl peroxide groups at around 2 hours. At 6 hours, these 3 groups were brown. A faint yellow color change was noted in the dapsone gel control, dapsone gel plus clindamycin, dapsone gel plus tretinoin, dapsone gel plus tazarotene, and dapsone gel plus adapalene groups at 5 hours; it persisted for 12 hours. After the napkin was washed and dried, no product remained in any of the groups containing sulfacetamide. In the dapsone gel-containing groups—the dapsone plus benzoyl peroxide and the 2 combination dapsone gel plus clindamycin and benzoyl peroxide products—brown stains remained despite washing. Also, a pale-yellow residue was noticeable in all other dapsone gel-containing groups.

COMMENT

All benzoyl peroxide products used in this study, including the benzoyl peroxide creamy wash, 8%, and 2 different clindamycin, 1%, plus benzoyl peroxide gel, 5%, products produced a discoloration reaction when mixed with either sulfacetamide or dapsone gel. Based on these results, both sulfacetamide and dapsone gel share a similar reaction with benzoyl peroxide, although the exact chemical reaction is unclear.

Because topical medications are frequently used in combination for the treatment of acne, these results are useful in understanding the possible reactions caused by the use of various topical acne medications. In these cases, it would be beneficial to use the medications at different times of the day and to encourage patients to completely wash off the benzoyl peroxide before applying other topical agents. Educating patients by warning them about the discoloration and inactivation reactions may help stress adherence to the designated treatment plan. Emphasizing the possibility of clothing stains would also deter patients from drifting from the prescribed regimen. Dapsone alone, at least on cloth, can impart a slight color. Unlike cloth, skin does not appear to be discolored by dapsone gel monotherapy or by dapsone in combination with non-benzoyl peroxide-containing prod-

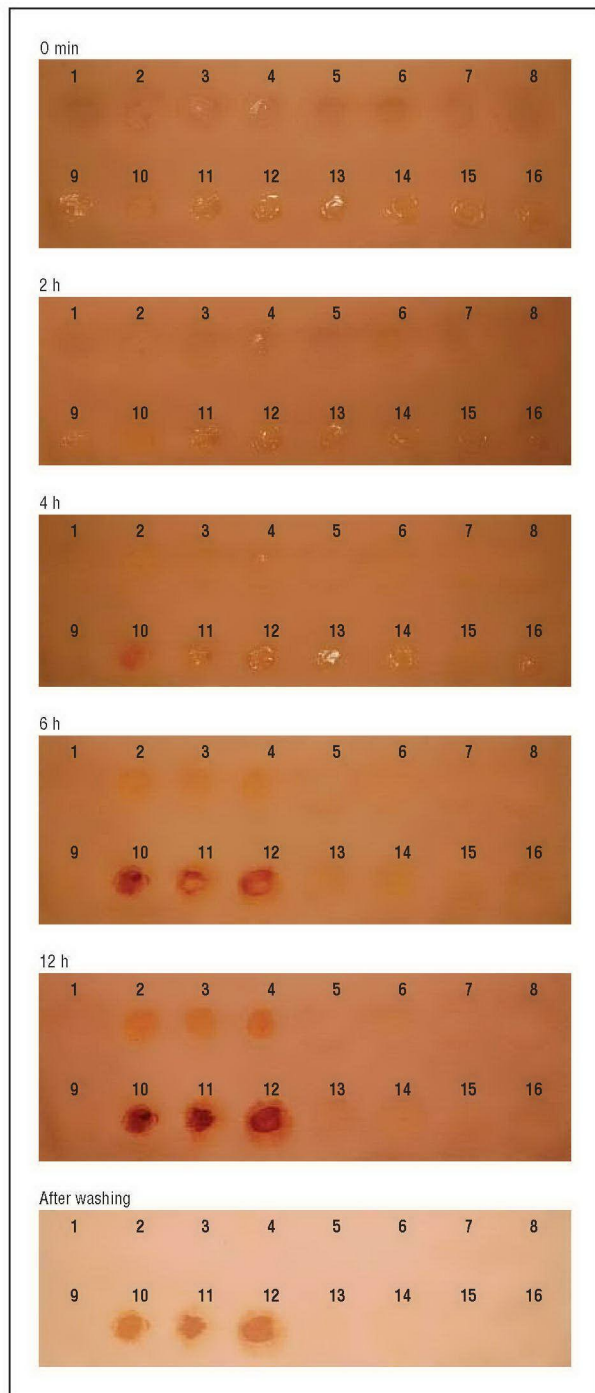


Figure 2. Photographs of sulfacetamide sodium and dapsone combined with different acne medications on a white cotton napkin at 0 minutes and at 2, 4, 6, and 12 hours after application and after the napkin is washed.

ucts.⁵ The colored precipitate that does occur on skin with benzoyl products is easily wiped away and does not stain skin. Dapsone gel has recently been marketed in the United States for the treatment of acne, and sulfacetamide is already being prescribed. It is important for dermatologists and other physicians to understand the possible reactions when they are developing treatment plans for their patients.

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