Bronopol allergic contact dermatitis

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Bronopol (2-bromo-2-nitropropane-1, 3-diol) is an antimicrobial compound widely used as a preservative, primarily in cosmetic formulations. Analysis of patch tests performed on our patients revealed an incidence of 12.5% relevant positive results to 0.5% and/or 0.25% bronopol. This result reflects a history of prolonged use of bronopol-containing lubricants in our referral population of patients with different types of severe, extensive dermatitis. Contact sensitization to bronopol in this population is probably facilitated by abnormal cutaneous barrier function. Our findings emphasize the need for further clinical study of the potential for bronopol to produce contact sensitivity, and suggest caution with regard to its use in patients with dermatitis.

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Bronopol (2-bromo-2-nitropropane-1, 3-diol) (Fig. 1) has been used as a preservative, most commonly in cosmetic product formulations. It is an odorless, colorless, crystalline solid that is soluble in water, alcohols, glycols and, to a lesser extent, oils (1). Bronopol has a wide range of antimicrobial properties and is active against gram-positive and gram-negative bacteria, fungi, and yeasts (1-4). Bronopol is particularly effective against Pseudomonas aeruginosa (5).

According to data disclosed by the Food and Drug Administration in 1981, bronopol is the 7th most commonly used preservative in cosmetic formulations, ranking behind methylparaben, propylparaben, imidazolidinyl urea, quaternium-15, formaldehyde and butylparaben (6). There are more than 300 cosmetic formulations containing bronopol (7). Most often, products contain bronopol in concentrations of less than 0.1%. The largest group consists of makeup bases, followed by hair conditioners, blushers, cleansing preparations, and eyebrow pencils. Many shampoos, moisturizers, and other cosmetics contain from 0.1% to 1% bronopol. Although bronopol is usually encountered in cosmetics, it has also been used as a preservative for milk samples (8), as a substitute for dichromate, and as an additive in simulated silage (9).

Despite the use of bronopol as a preservative in popular lubricants, there is relatively little information on the risk of developing contact sensitivity to bronopol in patients with dermatitis. Because a bronopol-containing lubricant was standardly prescribed in our practice, we decided to assess the potential for acquiring contact sensitivity to bronopol in the Mayo Clinic setting.

Material and Methods

From January to July, 1980, 129 patients received patch tests to a standard screening battery containing more than 30 commonly encountered allergens. The tests were administered according to the guidelines of the North American Contact Dermatitis Group, and the AI test method was used. Of the 129 patients, 57 were tested with 1% aqueous bronopol only. Testing with 3 concentrations was included in
the series in February, 1980, and 72 of the 129 patients had application of patches containing 1%, 0.5% and 0.25% bronopol. The patches were placed on the back and removed after 48 h. Readings were at 48 and 72 h in 58 patients and at 48, 72, and 96 h in another 71. The 96 h reading was omitted in 58 patients for practical reasons not related to the type of dermatitis or our study of bronopol. Results were scored on a scale of 1+ to 3+: 1+ macular erythema; 2+ an edematous or vesicular response; 3+ a spreading, bullous or ulcerative reaction. The clinical histories and positive results of other patch tests in the patients who had reactions to bronopol were then reviewed.

Results

Using the criterion that an irritant patch test reaction decreases in intensity or subsides with multiple readings, 23 patients showed irritant reactions to 1% bronopol. Because of our high rate of irritant reactions to the 1% concentration, as well as that reported in the literature, only those patients with positive reactions to 0.5% and/or 0.25% bronopol were further considered for clinical relevance. There were 3 irritant reactions to 0.5% bronopol and 2 to the 0.25% concentration.

Of the 72 patients tested to 0.5% and 0.25% bronopol, 12 (16.6%) showed non-irritant positive reactions. 9 of these 12 (representing 12.5% of the 72 patients) were considered clinically relevant in terms of use history of a bronopol-containing product in relationship to the type and course of their dermatitis. 5 out of 9 reacted only to 0.25% bronopol, and 4 out of 9 showed a response to both concentrations.

Although a number of our patients gave histories of reactions to a variety of cosmetics, in most cases exposure to bronopol occurred through use of Eucerin® cream, a 50% water-in-oil emulsion containing petrolatum, mineral oil, mineral wax, wool wax alcohols and 0.05% of the preservative bronopol. This product was widely prescribed in our practice as a general lubricant for patients with a variety of dermatologic problems, in particular, allergic or irritant contact dermatitis. For example:

(i) A 76-year-old woman had dermatitis over the extensor aspects of both forearms in the areas where she had applied Eucerin® cream. Patch tests showed positive reactions to 0.5% and 0.25% concentrations of bronopol.

(ii) A 40-year-old man who had been applying Eucerin® cream to neurodermatitis of the lower extremities had patch test reactions to 0.5% and 0.25% bronopol, to Eucerin® cream and to wool wax alcohols.

(iii) A patient with ichthyosis vulgaris and chronic hand dermatitis had patch test reactions to both concentrations of bronopol (Fig. 2).

All of the 9 patients with relevant positive patch tests to bronopol showed patch test reactions to other antigens, including 3/9 (33%) who reacted to formaldehyde.

After these patch test data were revealed, we stopped routine use of Eucerin® cream and noted a marked decrease in the number of positive patch tests to bronopol. Compared with the period from January to June 1980, when we noted a 12.5% incidence of positive patch tests to 0.5% and/or 0.25% bronopol, from January to June 1981, the incidence decreased to 10.7% positive patch tests to 0.5% bronopol (7.8% to 0.25% bronopol), and further dropped to 2.3% positive reactions to 0.5% bronopol from January to June 1982 (2.0% to 0.25% bronopol).
Discussion

On the basis of the results of studies primarily with animals or normal human subjects, bronopol was thought to produce minimal contact sensitivity or irritancy at concentrations of less than 0.1%, and hence to be relatively safe for general use (7).

Irritancy has been assessed in animals by application of bronopol in different vehicles with and without occlusion to the non-abraded or abraded, clipped, and shaved skin of rabbits. Bronopol (0.5 g) contacting moistened abraded or unabraded rabbit skin for 24 h yielded a primary irritation score of 0.75 out of a possible high score of 8 (with less than 5 considered not to represent a primary irritant) (7). Croshaw et al. (1) found irritation from 2% bronopol after 1 application but not from 0.5% after 4 applications. Bryce et al. (10) showed that assessment of irritation is highly related to the vehicle and manner of testing: 1 application of 1% bronopol in acetone under occlusion or 5% bronopol in polyethylene glycol 300 under occlusion was not irritating, whereas 0.5% bronopol in acetone or in 2.5% aqueous methylcellulose on repeated application without occlusion was highly irritating. This result suggests that 1 product may safely contain more than 10 times the bronopol of another, if it is applied to the skin in the proper vehicle. Therefore, concentration is not the only factor in determining whether an irritant reaction to bronopol will develop in a patient. This is of particular concern since patients are exposed to bronopol in a wide variety of formulations.

Marbach (11) studied bronopol in yellow soft paraffin at 0.1%, 0.5%, 1%, 2.5%, and 5% concentrations applied daily under occlusion for 21 days to 8 normal subjects and concluded that the irritation threshold corresponded to 0.5% to 1% concentration. From this conclusion, a challenge concentration of 0.25% was adopted. When 120 normal subjects were given induction concentrations of 5%, irritant reac-

Fig. 2. Patch tests 29, 33, and 34 show positive reactions to 1%, 0.5%, and 0.25% bronopol, respectively.
tions sometimes developed. Of the 93 subjects in whom challenge testing was performed with 0.25% bronopol, none had reactions. Bryce et al. (10), who gave 10 human volunteers closed patch tests with bronopol at concentrations of 0.5%, 1% and 2% in soft paraffin and 0.05%, 0.1% and 0.25% in water, found that 1% bronopol in pet. produced slight irritation in 2 persons and that 0.25% aqueous bronopol produced slight irritation in 1 person. They also looked at 149 patients from a contact dermatitis clinic who received a patch test battery that included 0.25% bronopol in soft paraffin; 3 had slight transient erythema. They found no sensitization to bronopol. The North American Contact Dermatitis Group (1975-1976) found that 13.2% of 190 patients had reactions to 1% aqueous bronopol (12). The conclusion was that 1% bronopol is an obvious irritant, and revision of the concentration in standard patch testing was recommended.

On the basis of these studies, we patch tested patients to 3 concentrations of bronopol. We also found a significant rate of irritant reactions to 1% concentration, and thus focused on the 2 lower patch test concentrations for further study. Our findings of 12.5% relevant positive patch tests to 0.5% and/or 0.25% bronopol would suggest a significant potential for contact sensitivity to this preservative. It must be kept in mind, however, that our patient population, based at a tertiary care center, is not representative of a local outpatient clinic or a population of normal individuals.

Our patients had various types of either localized or generalized dermatitis; the large % of positive results of patch tests to bronopol may be correlated with the wide use of the bronopol-containing product Eucerin®. Before the results of this study were available, Eucerin® was routinely prescribed - as a lubricant for regular general whole-body application - in our hospital service of 40 to 60 patients. Our hospital pharmacy estimated that about 2,500 pounds of Eucerin® were prescribed each year. This lubricant was applied frequently to large areas of the body, usually on the skin with abnormal barrier function. Because of these data showing a high potential for bronopol sensitivity, we stopped routinely prescribing Eucerin® cream for our patients, and have since noted a significant decrease in the % of positive patch tests to bronopol. Compared with our study population described above (patch tested from January to June 1980), we found 10.7% positive patch test to 0.5% bronopol from January to June 1981 (7.8% to 0.25% bronopol), and only 2.3% positive patch tests to 0.5% bronopol from January to June 1982 (2.0% to 0.25% bronopol).

The ability of bronopol in concentrations suitable for preservative use to cause contact sensitization is probably primarily a result of the altered barrier function in patients with dermatitis and the large surface in contact with the preparation. In contrast, patients with normal skin often are exposed to preparations, such as shampoos, on smaller surfaces for brief periods. Hence, we may have identified a population at risk for contact with this preservative rather than a general problem with its use.

1/3 of our patients with relevant positive reactions to bronopol also reacted to the formaldehyde patch test included in the standard series. Breakdown of bronopol results in formation of formaldehyde and bromonitroethanol (Fig. 3), a process which is accelerated by increased pH and/or temperature; e.g., the half life is more than 5 years at pH 4 but drops to 2 months at pH 8 (4, 10). Multiple positive results of patch tests with formaldehyde in our bronopol reactive group lead to concern because of the undefined risk of decomposition of bronopol to formaldehyde in topical preparations and the risk of exposure of bronopol leading to

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Brotonpol

\[2\text{-Hydroxymethyl-2-nitro-1,3-propanediol}\]

Formaldehyde and bromonitroethanol

Nitrile

Fig. 3. Breakdown products of bronopol.
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broadened sensitivity to related compounds, particularly formaldehyde. Bryce et al. (10) found no cross-sensitization with formaldehyde in 149 patients from a contact dermatitis clinic. However, Fisher (13) found that 3 out of 4 formaldehyde-sensitive patients had positive patch tests to bronopol. Special caution should be exercised in the use of bronopol-containing products by formalin-sensitive patients.

Because of the frequency of patch test reactivity in combination with a history of bronopol exposure, caution should be exercised in the prolonged and widespread use of preparations containing bronopol by patients with dermatitis. If flare-ups occur or dermatitis is difficult to control in such patients during use of bronopol-containing products, contact sensitivity to the preservative bronopol should be considered.

References


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