

THE EFFECT OF DIFFERENT FORMULATIONS OF EQUIVALENT ACTIVE INGREDIENTS ON THE PERFORMANCE OF TWO TOPICAL WOUND TREATMENT PRODUCTS

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Product selection for the management of pressure ulcers or perineal dermatitis is typically based on consideration of active ingredients, but a growing body of evidence suggests that delivery vehicles also may influence product safety and efficacy. A 10-day, randomized, controlled experimental study was conducted to compare the safety and efficacy of two prescription products used for the treatment of pressure ulcers and perineal dermatitis. Both products contain equivalent active ingredients (balsam of Peru, castor oil, and trypsin), but one product delivers these ingredients in an ointment base while the other uses an aerosol spray. Sixty healthy volunteers (> 65 years of age) underwent intentional creation of two equivalent skin wounds (approximately 6 mm in diameter) using an Erbium-YAG laser. Volunteers served as their own control. Wounds were randomized to treatment with one of the balsam of Peru products or saline. Wounds were evaluated every other day. Significant differences between treatments were observed for most outcome variables (edema, scabbing, erythema, epithelialization). Wounds managed with the ointment-based product had lower edema, scabbing, and erythema scores and higher epithelialization scores than the spray or saline managed wounds. The results of this study confirm that formulation of the vehicle base can have a significant effect on product safety and effectiveness.

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A pressure ulcer is a localized area of tissue necrosis that occurs when soft tissue is compressed between a bony prominence and an external surface.¹ This condition occurs most commonly in frail, elderly patients, but may occur in persons of any age with specific predisposing conditions, causing immobility and altered cutaneous sensation. Risk factors for pressure ulcers include compromised local circulation, inadequate nutrition, immobility, neurological deficits that reduce sensory awareness, and urinary or fecal incontinence.^{2,3} Many products have been developed to treat pressure ulcers and perineal dermatitis, but limited data exist concerning their safety and effectiveness.³⁻⁶

The term *perineal dermatitis* refers to erythema either alone or associated with erosion of the perineal skin due to urinary or fecal incontinence. The precise etiology of this condition is not known. Associated factors include occlusion of the skin with a containment device such as a pad or adult containment brief; increased acidity when the skin is exposed to urine or stool; excessive moisture from sweat, urine, or liquid stool; fecal enzymes in contact with skin as a result of fecal incontinence; and secondary infection.⁷ Reported prevalence rates for perineal dermatitis among aged patients vary from 23% to 41%; its incidence among frail elders is not known.³

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The reported prevalence of pressure ulcers among patients aged 65 years or older varies from 0.31% to 0.70%, and the annual incidence is reported as 0.18% to 3.36%.¹ Both prevalence and incidence increase with age; patients ≥ 80 years are four to 20 times more likely to develop a pressure ulcer than are persons 65 to 70 years.¹ Estimates of the total cost of pressure ulcers to the US healthcare system range from \$1.3 billion to as high as \$8.5 billion annually.¹

Selection of a pharmaceutical for the management of pressure ulcers or perineal dermatitis is usually based on consideration of active ingredients. Evidence suggests, however, that the delivery vehicle also can influence safety and efficacy.^{8,9} For example, Johnson et al¹⁰ demonstrated variable toxicity when four topical agents commonly used for wound cleaning were compared in an *in vitro* model using cultured human fibroblasts. Similarly, the frequency and severity of side effect profiles of multiple drugs have been altered while efficacy was preserved by reformulating the compounds in a sustained-release or transdermal delivery vehicle.^{11,12}

Two products currently available for the treatment of pressure ulcers and perineal dermatitis contain equivalent active ingredients in different base formulations. The ointment (BCT-O) is composed of balsam of Peru, castor oil, and trypsin. The spray formulation (BCT-S) is equivalent with respect to the active ingredients. In both products, balsam of Peru increases local circulation by dilating the cutaneous blood vessels; thus, increasing local blood flow to remove products of skin necrosis and to bring nutrients and oxygen needed for re-epithelialization.¹³ Trypsin provides proteolytic cleansing of the wound and a measure of antimicrobial action. The castor oil in both products is an emollient and is a constituent of the vehicle base.

The two products differ in their mode of delivery and consequently in their physical characteristics. Balsam of Peru, castor oil, and trypsin spray is an aerosol designed to be sprayed onto the lesion. Balsam of Peru, castor oil, and trypsin ointment is applied to the lesion; therefore, BCT-S utilizes a liquid aerosol base containing an emulsifier as an inactive ingredient and propellants and BCT-O utilizes a topical ointment base containing

safflower oil and aluminum magnesium hydroxide stearate as inactive ingredients. A portion of the castor oil in BCT-O is hydrogenated, which provides a cosmetically elegant ointment base.

The dissimilarity in the vehicle bases of BCT-O and BCT-S, with equivalent active ingredients, raises the important question of whether the difference in the formulation base could affect the performance of the two products. The following study was conducted to compare the safety and efficacy of two products on experimentally induced cutaneous wounds in healthy adult volunteers.

Materials and Methods

The data reported here are drawn from a subset of participants in a larger study that also included comparisons of hydrocolloid and saline. In the current controlled experimental trial, 30 participants were enrolled to determine the efficacy and safety of BCT-O (Xenaderm™ Ointment, Healthpoint, Ltd., Fort Worth, Texas) versus BCT-S (Granulex® Spray, Bertek Pharmaceuticals Inc., Sugar Land, Texas) in the treatment of experimentally induced skin wounds. In additional arms of the study, another 15 participants compared BCT-O versus saline and 15 additional participants compared BCT-S versus saline. Each study arm was composed of a unique set of participants who received both treatments and served as their own control. The other arms of the larger study also included a direct comparison of treatments, each with its own unique participant population. These data are unrelated to this study and are planned for publication at a later date.

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KEY POINTS

- In wound and skin care, it is generally believed that product safety and effectiveness profiles are similar for dressings within the same “categories” of products and for products that have the same active ingredients.
- Studying the effects of two products with similar active ingredients but with different delivery systems (ointment versus aerosol spray) on acute wounds, researchers observed significant differences between the two treatments.
- Additional research confirming the findings while controlling for other variables is warranted. In the meantime, clinicians clearly should not assume therapeutic equivalency based on product active ingredients.

TABLE I
WOUND EVALUATION SCORES: BALSAM OF PERU, CASTOR OIL, AND TRYPSIN OINTMENT (BCT-O) (N=29) VERSUS BALSAM OF PERU, CASTOR OIL, AND TRYPSIN SPRAY (BCT-S) (N=29)

Observation/ Treatment	Day 1	Day 3	Day 5	Day 7	Day 9
Erythema [†]					
BCT-O	4.36	4.09*	4.26*	4.00*	3.41*
BCT-S	4.71	6.59	6.88	6.78	5.98
Edema [†]					
BCT-O	0.07*	0.24*	0.12*	0.14*	0.14
BCT-S	1.24	1.00	0.74	0.62	0.24
Scabbing [†]					
BCT-O	0.10*	0.26*	0.64*	0.38*	0.45*
BCT-S	1.02	3.31	5.10	5.60	5.43
Re-epithelialization [‡]					
BCT-O	0.93	2.97*	4.07*	6.03*	8.14*
BCT-S	0.60	1.29	1.97	2.91	4.34

* Statistically significant ($P < 0.05$)

[†] Erythema, edema, scabbing 10-point analog scale with 0 = none, 10 = severe. A lower score indicates less irritation.

[‡] Re-epithelialization, 10-point analog scale with 0 = no healing, 10 = complete healing

Participants were at least 65 years old and in general good health. Participants were excluded from the study if they were taking medications or vitamin preparations with the potential to affect blood coagulation (eg, warfarin sodium, heparin, vitamin E) or platelet aggregation (aspirin >650 mg/day).

Additional exclusion criteria included any disease or condition of the skin likely to interfere with evaluation of the test material and irritation, scars, cuts, or any form of dermatitis affecting the thighs.

Participants were randomly assigned to one of the following treatment groups: BCT-O ointment versus BCT-S spray (N = 30), BCT-O ointment versus saline (N = 15), or BCT-S spray versus saline (N = 15).

Written informed consent conforming to 21 Code of Federal Regulations 50.25 was obtained from each participant before enrollment in the study, and all research procedures were approved by IntegReview Institutional Review Board.

At the first study visit (Test Day 0), the study investigator examined the skin of the outer aspect of the upper thighs and, if acceptable, used an Erbium-

YAG laser to create partial-thickness wounds on the right and left thigh that were approximately 6 mm in diameter. Based on the randomization scheme described above, each wound was treated with BCT-O, BCT-S, or saline. The same treatment was applied repeatedly to that wound throughout data collection, each subject serving as his/her own control.

Participants in the BCT-O treatment group were instructed to apply a small amount of BCT-O or saline to the center of an adhesive bandage each morning and evening and then apply that bandage to the wound. A protocol deviation occurred for participants in the BCT-S arm. The original protocol instructions called for application of the BCT-S directly onto the supplied adhesive bandages in order to keep the application protocols the same. The clinical investigator deviated from the protocol and instead sprayed the BCT-S directly onto the wounds and (due to the size of the spray area), covered the wounds with a 4" x 4" gauze pad, and taped the edges. Participants in the BCT-S treatment group also were instructed to spray BCT-S on the wound each morning and evening and cover the wound with a 4" x 4" gauze pad and tape the edges.

Participants returned to the clinic for evaluation on Test Days 1, 3, 5, 7, and 9. At each visit, the wound site was clinically graded for either irritation or wound healing. Erythema, scabbing, edema (irritation markers), and re-epithelialization (wound healing marker) were scored using a 10-point analog scale. At each visit, the wound site was clinically graded for either irritation (0 = none; 10 = severe) or healing (0 = no healing; 10 = complete healing). Thus, lower irritation scores mean less irritation, and conversely, a higher healing score means a greater positive impact on healing. The participant removed the bandage before the investigator rated each wound so the examining dermatologist was blinded as to the identity of the treatment applied to the wounds. Participants were instructed to remove the bandages by pulling the tape from a different side each time to minimize any irritation from the adhesive.

Mean rating scores for each of the primary outcome variables (erythema, edema, scabbing, and re-epithelialization) were compared between treatment groups using a paired *t*-test; a *P* value ≤ 0.05 was defined as statistically significant.

Clinical Grading for Erythema

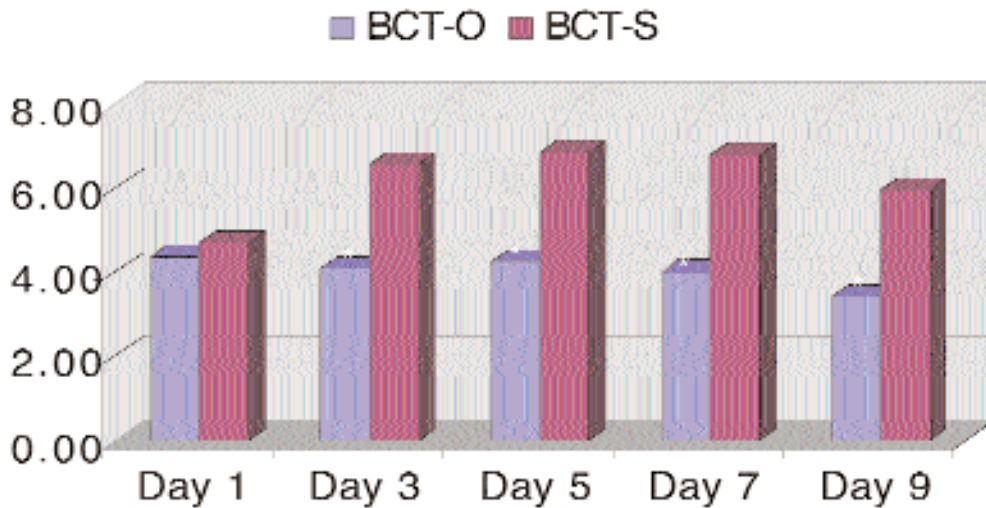


Figure 1

Erythema: BCT-O versus BCT-S^{*}

^{*} $P < 0.05$; 10-point analog scale with 0 = none, 10 = severe

[†] Balsam of Peru, castor oil, and trypsin ointment versus balsam of Peru, castor oil, and trypsin spray

Clinical Grading for Edema

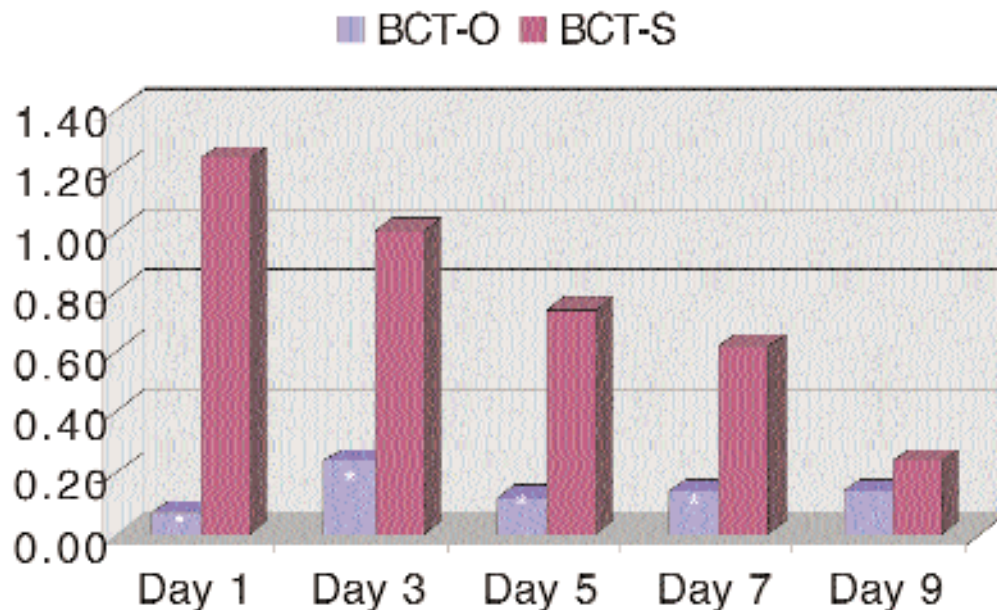


Figure 2

Edema: BCT-O versus BCT-S^{*}

^{*} $P < 0.05$; 10-point analog scale with 0 = none, 10 = severe

[†] Balsam of Peru, castor oil, and trypsin ointment versus balsam of Peru, castor oil, and trypsin spray

Results

BCT-O versus BCT-S. The effectiveness of treatment with BCT-O or BCT-S was compared on the basis of erythema, edema, scabbing, and re-epithelialization (see Table 1). Wounds managed with BCT-O ointment were associated with less erythema at the wound site than those managed with saline or BCT-S (see Figure 1). At Day 3, erythema was significantly lower in BCT-O-treated wounds and continued to be significantly lower throughout the course of the study ($P < 0.05$).

Edema was significantly lower ($P < 0.05$) at wound sites treated with BCT-O than wounds treated with BCT-S at Day 1 and continued to be lower through Day 7 of the study (see Figure 2). By Day 9, the degree of edema was similar in the two treatment groups.

Scabbing was significantly reduced ($P < 0.05$) at Day 1 in wounds treated with BCT-O and continued to be so throughout the course of the study (see Figure 3). In sharp contrast to the

Clinical Grading for Scabbing

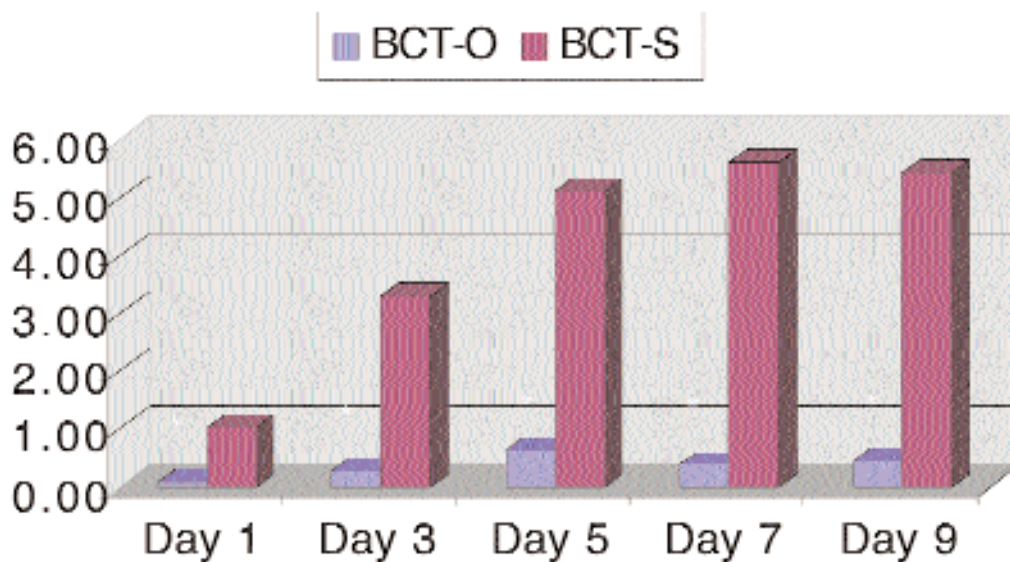


Figure 3

Scabbing: BCT-O versus BCT-S[†]

* $P < 0.05$; 10-point analog scale with 0 = none, 10 = severe

[†] Balsam of Peru, castor oil, and trypsin ointment versus balsam of Peru, castor oil, and trypsin spray

Clinical Grading for Epithelialization

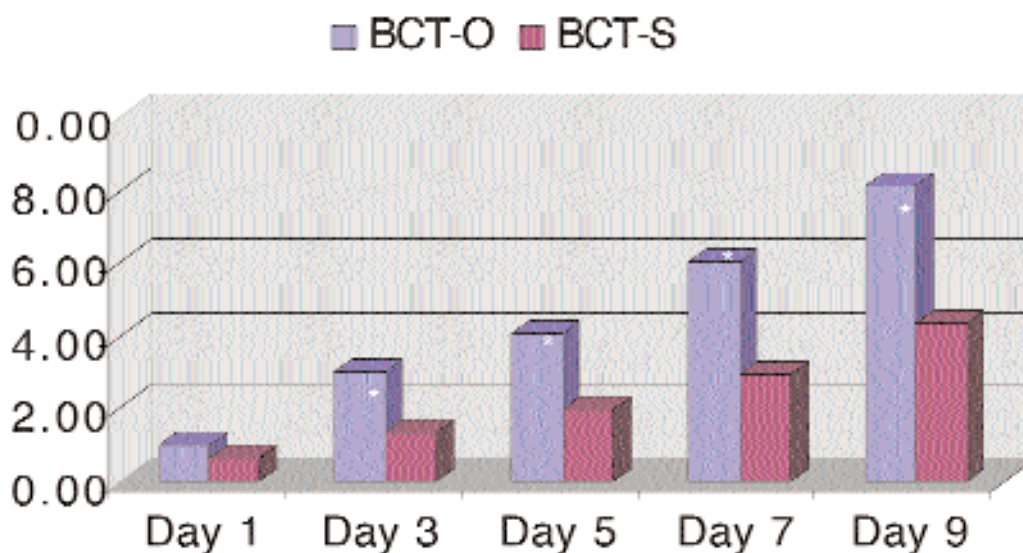


Figure 4

Epithelialization: BCT-O versus BCT-S[†]

* $P < 0.05$; 10-point analog scale with 0 = none, 10 = severe

[†] Balsam of Peru, castor oil, and trypsin ointment versus balsam of Peru, castor oil, and trypsin spray

findings in wounds treated with BCT-O, the degree of scabbing increased in wounds treated with BCT-S from Day 1 (mean score 1.02) to Day 3 (mean score 3.31) to Day 5 (mean score 5.10) and continued at that level to the end of the study. The degree of scabbing in wounds treated with BCT-O increased slightly from Day 1 (0.10) to Day 9 (0.45).

Re-epithelialization of the wound was greater in wounds treated with BCT-O than with BCT-S (see Figure 4). At Day 1, the degree of re-epithelialization was equivalent in the two treatment groups. By Day 3, however, the difference in favor of treatment with BCT-O was significant (mean 2.97 versus 1.29, $P < 0.05$). At successive observation days, the differences continued to favor BCT-O by a widening margin (Day 5, 4.07 versus 1.97, $P < 0.05$; Day 7, 6.03 versus 2.91, $P < 0.05$; Day 9, 8.34 versus 4.34, $P < 0.05$).

BCT-O versus saline. Wounds treated with BCT-O demonstrated greater rate and

TABLE 2A
WOUND EVALUATION SCORES: BALSAM OF PERU, CASTOR OIL, AND TRYPSIN OINTMENT (BCT-O) VERSUS SALINE. BCT-O (N=14) VERSUS SALINE (N=14)

Observation/ Treatment	Day 1	Day 3	Day 5	Day 7	Day 9
Erythema [†]					
BCT-O	3.96	3.64*	3.86*	3.46*	3.00*
Saline	4.61	5.25	5.46	4.93	3.79
Edema [†]					
BCT-O	0.00	0.00*	0.00	0.00	0.07
Saline	0.43	0.43	0.14	0.11	0.00
Scabbing [†]					
BCT-O	0.07	0.18*	0.21*	0.21*	0.29*
Saline	0.21	1.50	2.04	1.93	2.25
Re-epithelialization [‡]					
BCT-O	1.14	3.14*	4.36*	7.25*	8.68*
Saline	0.79	1.61	3.14	5.61	7.86

* Statistically significant ($P < 0.05$)

[†] Erythema, edema, scabbing 10-point analog scale with 0 = none, 10 = severe

[‡] Re-epithelialization, 10-point analog scale with 0 = no healing, 10 = complete healing

TABLE 2B
WOUND EVALUATION SCORES: BALSAM OF PERU, CASTOR OIL, AND TRYPSIN SPRAY (BCT-S) (N=14) VERSUS SALINE (N=14)

Observation/ Treatment	Day 1	Day 3	Day 5	Day 7	Day 9
Erythema [†]					
BCT-S	4.07*	5.71	6.68	6.93	5.89
Saline	5.50	5.21	5.50	4.50*	3.89*
Edema [†]					
BCT-S	1.11	1.14	0.79	0.93	0.21
Saline	0.29	0.43*	0.21*	0.07*	0.00
Scabbing [†]					
BCT-S	0.75	2.29	3.07	4.21	5.00
Saline	0.29	1.14*	1.89	2.14*	1.75*
Re-epithelialization [‡]					
BCT-S	1.07	1.79	2.18	3.25	4.89
Saline	0.86	2.21	3.00*	5.61*	7.75*

* Statistically significant ($P < 0.05$)

[†] Erythema, edema, scabbing 10-point analog scale with 0 = none, 10 = severe

[‡] Re-epithelialization, 10-point analog scale with 0 = no healing, 10 = complete healing

degree of healing than those treated with saline based on the outcome variables erythema, scabbing, and re-epithelialization (see Table 2A). This difference was significant on Days 3, 5, 7, and 9. Edema at the wound site was ranked as minimal for both treatment groups.

BCT-S versus saline. Wounds treated with BCT-S showed reduced erythema compared with those treated with saline at Day 1 (see Table 2B). Edema was significantly greater around the wounds treated with BCT-S than around those managed with saline on Days 3, 5, and 7. Wounds treated with saline showed significantly decreased scabbing on days 3, 7, and 9 compared to those managed with the BCT-S. Wounds treated with saline showed significantly increased re-epithelialization on Days 5, 7, and 9.

Safety. Adverse events were reported in six subjects in this arm of the study — five involving wound sites treated with BCT-S and one involving saline. Four of the 5 adverse events were reported for the BCT-S-treated wounds in participants treated with BCT-S and BCT-O, one adverse event was reported for the BCT-S-treated wound in a participant treated with BCT-S and saline, and one adverse event was reported for a saline-treated wound in a participant treated with BCT-O and saline. The adverse events reported were insufficient wound healing by Day 3, 7, or 9, with little re-epithelialization, bleeding when the bandage was removed, and erythema around the wound site.

Discussion

The safety and efficacy of BCT-O have been demonstrated for the treatment of injured skin in a previous study.¹³ The present study confirms those findings and demonstrates greater efficacy combined with fewer adverse side effects when compared with BCT-S, a product containing equivalent active ingredients but using a different delivery vehicle and mode of application. In the formulation of BCT-O, part of the castor oil is hydrogenated and used to form a topical ointment vehicle base that is cosmetically elegant, creamy, suitable for use as a vehicle for pharmaceutical agents and effective as a water-barrier for use on the skin. No signs of hypersensitivity reactions have been observed with this formulation.¹³

In the present comparison of BCT-O and BCT-S, the significant difference between the two study drugs is the formulation of the vehicle base and not

the active ingredients. The vehicle base in BCT-S is suitable for an aerosol liquid spray. The vehicle base in BCT-O is a patented (U.S. Patent Number 6,479,060) low-temperature preparation utilizing hydrogenated castor oil to form the vehicle base. The formulation of a topical agent for use on the skin can have a powerful effect on the drug action when applied. Tsai et al,¹⁴ for example, found that the distribution of salicylic acid in human stratum corneum varied among different formulations studied.

Johnson et al¹⁰ have demonstrated that BCT-S was more toxic to fibroblasts in culture than Hibiclens (Astra Zeneca, Wilmington, Del.), Betadine (Purdue Frederick, Norwalk, Conn.), or Carrington Dermal Wound Gel (Carrington Laboratories, Inc., Irving, Tex.) in a test system of explants of newborn foreskins. Toxicity was quantified as the amount of radioactive chromium released from labeled fibroblasts after exposure to the test agents. Control cells released 3% to 5% of the total ⁵¹Cr during 30-minute incubation. Cells treated with betadine, BCT-S, or Hibiclens released 55% to 62% of the total ⁵¹Cr label, with BCT-S releasing the greatest amount.

The FDA/Center for Drug Evaluation and Research Orange Book¹⁵ defines pharmaceutical equivalents as drug products that contain the same active ingredients, are of the same dosage form, route of administration, and are identical in strength or concentration. Furthermore, to be therapeutically equivalent, drug products must be pharmaceutically equivalent. The standard tests for equivalence are designed primarily for drugs that are absorbed into the body (pharmacokinetic and pharmacodynamic studies). Topical drug products often must be tested by clinical endpoints, where plasma drug concentrations are not useful to determine delivery of the drug substance to the site of activity. Consequently, in the words of the Orange Book, "Even though different

**TABLE 3
ADVERSE EVENTS**

Adverse Event/Subject	Comparison	Observation	Relationship
BCT-S/006	BCT-O/BCT-S	Wound not sufficiently healed at Day 7	Probable
BCT-S/015	BCT-O/BCT-S	Wound dry and sticking to bandage, causing bleeding on removal of bandage at Day 7	Definite
BCT-S/025	BCT-S/Saline	Severe erythema at wound site at Day 7, mild edema, and little re-epithelialization	Probable
BCT-S/027	BCT-O/BCT-S	Erythema at wound site at Day 7, slight edema, and incomplete re-epithelialization	Probable
BCT-S/034	BCT-O/BCT-S	Wound dry and sticking to bandage, causing bleeding on removal of bandage at Day 7	Definite
Saline/040	BCT-O/Saline	Wound not sufficiently healed at Day 3	Probable

*BCT-O = Balsam of Peru, castor oil, and trypsin ointment
BCT-S = balsam of Peru, castor oil, and trypsin spray*

topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered therapeutically equivalent. Therefore, they are not considered therapeutically equivalent."¹⁵ The Orange Book makes it clear that "products may differ in other characteristics" even when they have been judged to be therapeutically equivalent and that it is the responsibility of the physician and pharmacist to make appropriate decisions regarding the use of apparently similar products.

Consistent with the FDA and Orange Book wording, the conclusion from the present study is that BCT-O and BCT-S are not pharmaceutical equivalents and should not be substituted for each other in the treatment of wounds. While the results of this study pertain to acute wounds, it is assumed that they apply to chronic wound and skin conditions.

The protocol deviation described for BCT-S could have potentially influenced these results. Adhesive bandages are semi-occlusive; whereas, gauze provides no occlusion, which could have biased the results in favor of BCT-O and saline. The effects of different dressings on wounds treated with BCT-O and BCT-S on wound healing are under investigation.

Conclusion

The effectiveness of BCT-O in promoting cutaneous wound healing is attributed to two properties of the ointment. First, the topical circulatory stimulant in the BCT-O formulation effectively increases epidermal microcirculation at the site of application. Balsam of Peru, castor oil, and trypsin ointment has been demonstrated to increase local blood flow by 45%.¹³ Although BCT-O and BCT-S contain the same active ingredients, these data show that BCT-O did not result in increased inflammation as measured by its lower scores of erythema and edema. Second, the patented base provides a water-barrier function, protecting the wound site from fecal or urinary incontinence. In addition, the present study has demonstrated that the formulation of the vehicle base also plays a vital role in the total performance of the formulation. Additional clinical studies are underway to further investigate BCT-O's efficacy in promoting wound healing and its barrier properties. - OWM

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