cohol, was formulated for topical application in an aqueous cream (Abreva) and compared with a novel topical control compound, polyethylene glycol (PEG), unrelated to the n-docosanol vehicle. The authors report that n-docosanol shortened the time to lesion healing and cessation of pain in comparison with the control. These studies were the basis for a New Drug Application, which was rejected by the US Food and Drug Administration (FDA) in 1999, who cited the need for additional trials. However, the company appealed this decision and eventually won approval for topical n-docosanol as an over-the-counter product.[2] There are several features of these studies that deserve comment.

The use of a substance other than the drug vehicle as a control represents a major departure from accepted practice and introduces doubt concerning the stated outcome of the study. The usual comparison in topical drug studies, drug versus drug vehicle, ensures that any effect of the vehicle on the disease will occur equally in the treatment groups and that any differences between the treatment groups can be attributed to the test drug. The use of the same vehicle as a control is also important if the study is to be double-blinded (neither the investigator nor the patient knows which treatment is being given).

PEG is a common component of many topical products, such as cosmetics, and is the vehicle for Zovirax ointment. We use Zovirax ointment and the PEG vehicle regularly in our guinea pig model of cutaneous herpes simplex virus infection.[3] PEG is nonirritating and does not affect the short-term course (4 days) of the experimental infection.[4] We are not aware of any studies of the effects of PEG on the full course of experimental herpes simplex virus infections, specifically lesion healing, or on the course of human wounds or skin infections.

There are at least 2 theoretical ways that the use of PEG as a control could influence the relative rates of wound healing and create an appearance of efficacy, erroneously, in the n-docosanol treatment arm. PEG is hygroscopic (absorbs water) and may dehydrate the skin.[5] The state of hydration of the skin is well known to influence the rate of wound healing.[6,7] Second, because the protocol called for continuous use of the study medication until lesion healing, it is possible that the n-docosanol aqueous cream vehicle had a greater ability than PEG to dissolve or loosen the lesion crust, a healing end point, resulting in the appearance of accelerated healing for the n-docosanol treatment arm. These questions could be answered by study of the vehicles in an animal model, such as the pig wound healing model of Eaglstein and Mertz.[6,8] Indeed, these investigators have already demonstrated that several so-called inert vehicles were capable of ei-

N-docosanol (Abreva) for herpes labialis: Problems and questions

To the Editor: I read with interest the recent article in the Journal concerning a clinical trial of topical docosanol 10% cream for the treatment of herpes labialis.[1] N-docosanol, a 22-carbon, straight-chain saturated al-

ther accelerating or retarding the rate of wound healing in their model.[9] The magnitude of effects they observed was similar to the differences between treatment arms in the n-docosanol trial.

The mechanism of action of n-docosanol against herpes labialis is unclear. The authors state that the compound is an antiviral agent that acts predominantly by blocking the process of viral fusion with the host cell.[10] The compound is insoluble in water (it is tested as a suspension); it is not a microbicide (does not inactivate virus directly); it is not cytotoxic; and it must be added before infection for optimal activity.[10,11] Although these in vitro observations are not disputed, proof that a compound has clinically relevant antiviral activity commonly involves one or more of the following: generation and characterization of a drug-resistant mutant virus, correlation of antiviral activity and clinical activity in one or more animal models, and correlation of antiviral activity and clinical activity in humans with the disease. None of these have been demonstrated for n-docosanol. To the contrary, in the dorsal cutaneous guinea pig model of herpes simplex virus type 1 infection, we found no clinical or antiviral activity associated with topical n-docosanol cream in comparison with either vehicle-treated or untreated control sites.[3] In the n-docosanol clinical trial,[1] no virologic studies were performed.

To complicate the issue, there is evidence that n-docosanol is an antiinflammatory agent. Based on observations in murine models of arthritis and the antiinflammatory activity of a related compound, triacontanol, the manufacturers studied the effect of n-docosanol and stearic acid for the treatment of phenol burn wounds in mice.[12] N-docosanol and stearic acid reduced mean lesion severity scores 76% and 57%, respectively. Recently, studies in an animal model[13] and a clinical trial[14] have shown that topical corticosteroids may be a potent therapy for herpes labialis. Indeed, the pattern of clinical findings in our corticosteroid study and the n-docosanol trial have similarities: the effect on lesion healing time was greatest when normal skin (absence of inflammatory signs such as erythema and swelling) was the healing criterion rather than loss of crust (wound healing). If the results of the n-docosanol trial are to be believed, an antiinflammatory activity has more supporting evidence as a mechanism of action than the claim of antiviral activity.

In summary, the use of the drug vehicle as a control in clinical trials of topical medication should be maintained as the "gold standard," the n-docosanol trial and the apparent approval of the trial by the FDA notwithstanding. Before clinical trials of treatments for herpes simplex virus infections are performed, the mechanism of drug action and drug efficacy should be clearly spelled out by appropriate tissue culture and animal model experimentation, establishing biologic plausibility. Positive clinical trial results may then be greeted with a measure of comfort, even anticipation, while the odds that they have occurred by chance or artifact are considerably reduced.

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