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Efficacy of an alcohol-based healthcare hand rub containing synergistic combination of farnesol and benzethonium chloride

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Abstract

Healthcare workers are required to disinfect the hands several times a day using hand disinfectants, which leads to chronic hand exposure to high levels of antimicrobials contained in the disinfectants, which could compromise the skin integrity. This problem may be addressed by developing hand disinfectants containing synergistic combinations of small amounts of antimicrobials and other agents. The synergistic effect of farnesol and essential oils with several antimicrobials was studied in vitro to select an effective antimicrobial system in preservative concentration for use in healthcare hand rub. Farnesol and lemon oil showed synergistic activity against *S. aureus*, in combination with benzalkonium chloride and benzethonium chloride, but not with other antimicrobials studied. All essential oils studied showed synergy with benzethonium chloride against *Staphylococcus aureus* and *Escherichia coli*. An alcohol-based healthcare hand rub (ZBF hand rub) containing this unique synergistic combination of farnesol and benzethonium chloride was then developed and its efficacy as a healthcare hand rub was evaluated in human volunteers according to the US FDA-TFM protocol using *Serratia marcescens* as a marker organism. The ZBF hand rub showed a 3.22 $\log_{10}$ reduction in the microbial count after the first application and a 5.49 $\log_{10}$ reduction after the tenth application in vivo and exceeds the US FDA-TFM criteria for healthcare hand rub. The ZBF hand rub did not irritate the hands when tested on human volunteers when applied 10 times everyday for five consecutive days. The ZBF hand rub exhibits more than 5.5 $\log_{10}$ reduction in the microbial count within 15 s and more than 2.8 $\log_{10}$ reduction in the two types of viruses tested within 30 s in vitro. When evaluated in an in vitro pig skin model, the ZBF hand rub shows better prolonged activity (20–35 min post-application) against transient bacteria (*S. aureus* and *E. coli*) compared to other alcohol-based hand rubs. These findings suggest that the use of the ZBF hand rub amongst health care workers may lower the risk of chronic hand exposure to high levels of antimicrobials without compromising the efficacy.

Keywords: Healthcare hand rub; Hand hygiene; Pigskin model; Transient bacteria

Introduction

The Centres for Disease Control (CDC) has issued guidelines recommending the use of alcohol-based products for hand disinfection (Boyce and Pittet, 2002). Several in vitro and in vivo studies have indicated

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considerably better antimicrobial killing with the use of alcohol-based hand rubs than with hand washing (Girou et al., 2002; Hilburn et al., 2003; Trampuz and Widmer, 2004). A decrease in nosocomial infection rates has also been noted with the use of alcohol hand rubs (Hammond et al., 2000; Larson, 1999; Pittet et al., 2000). Alcohol hand disinfectants can eliminate transient microbial skin flora and reduce resident microbial skin flora rapidly. However, formulations containing only alcohol do not show prolonged activity since the alcohol evaporates off fast. A product which continues to show activity after product application can help in eliminating the transient organisms which may come in contact with the hand in between the product applications. Prolonged activity in health care hand rub is also important since healthcare workers may not comply with the CDC guidelines of applying the hand rubs between each patient care. Health care hand rubs containing 61% w/w ethanol and 1% chlorhexidine gluconate (CHG) (Avagard™), and 61% w/w ethanol and 0.25% zinc pyrithione as a preservative (Triseptin®) are being used in hospitals in USA and have been shown to have immediate and prolonged reduction in the hand flora (Guthery et al., 2005; Hobson et al., 1998; Mulberrry et al., 2001). Although the use of alcohol-based hand rubs are on the rise, there are some reports which show skin sensitization resulting from the use of some of these products, either due to the alcohol, the antimicrobials or other ingredients used in these products (Cimiotti et al., 2003; Dyer et al., 1998; Rilliet et al., 1980). Since healthcare workers are required to apply the product several times a day, the use of a hand rub containing high levels of antimicrobials may lead to chronic exposure of the hands to these chemicals.

We have reported earlier that quaternary ammonium compounds (QAC) such as benzalkonium chloride (BZK) and benzethonium chloride (BZT) exhibits synergistic activity with ethylhexylglycerin (Gaonkar et al., 2005) or farnesol (Shintre et al., 2006). An alcohol-based surgical hand rub containing a synergistic combination of farnesol and a preservative level of BZT (Shintre et al., 2006) have been shown to provide rapid and persistent activity against resident flora, comparable with that of hand rubs containing high concentration of antimicrobials such as Avagard™ and Triseptin® (Guthery et al., 2005; Hobson et al., 1998; Mulberrry et al., 2001). Similarly, alcohol-based healthcare handrubs containing synergistic combinations of ethylhexylglycerin and a small concentration of BZK (Gaonkar et al., 2005) was shown to have rapid and prolonged activity against transient bacteria. It appears that alcohol-based hand disinfectants with rapid and prolonged activity can be developed by using synergistic combinations of small amounts of antimicrobials and other ingredients, thus reducing the incidence of skin sensitization.

In this study, we further evaluated the synergistic effect of farnesol and essential oils with various antimicrobials to select the most effective synergistic combination of antimicrobials in preservative levels for use in an alcohol-based healthcare hand rub. This study also describes the effect of using the superior synergistic preservative combination (farnesol and BZT) in an alcohol-based healthcare hand rub along with a zinc gel (ZBF hand rub) on the in vitro and in vivo efficacy and skin sensitization. The zinc gel (a mixture of soluble zinc salts, panthenol, and a gelling agent) has been shown to impart anti-irritant activity when used in a topical cream (Modak et al., 2005). The ZBF hand rub was evaluated for its antimicrobial efficacy in human volunteers by the US FDA-TFM protocol (Anonymous, 1994) for use as a healthcare hand rub. Since farnesol has been reported to have some skin-sensitization effects (Goossens and Merckx, 1997; Hemmer et al., 2000; Schnuch et al., 2004), we tested the ZBF hand rub for its possible skin-irritation effects in human volunteers. The test for rapid antimicrobial efficacy of ZBF hand rub against several microorganisms and two types of viruses was carried out in vitro. The prolonged efficacy of the ZBF hand rub against transient bacteria (*Staphyloccus aureus* and *Escherichia coli*) was evaluated and compared to that of the commercially available alcohol-based hand rubs Avagard™, Prevacare™ and Triseptin®, using an in vitro pig skin model developed in our laboratory earlier (Gaonkar et al., 2005). Results of these studies are presented in this report.

Materials and methods

Antimicrobials

BZT was obtained from Lonza Inc., Fairlawn, NJ. BZK and CHG were obtained from Stepan Company, Northfield, IL. PHMB (Cosmocil CQ) was obtained from Avecia, Wilmington, DE. Cetylpyridinium chloride (CPC) was obtained from Aldrich Chemical Company, Inc., Milwaukee, WI. Cetrimonium chloride (CTAC) and stearalkonium chloride (STAC) were obtained from Croda Inc., Edison, NJ. Triclosan (TC) was from Ciba Specialty Chemicals Corporation, High Point, NC. Zinc pyrithione (ZP) was from Arch Chemicals Inc., Norwalk, CT.

Essential oils and ingredients

Farnesol was obtained from Symrise, Totowa, NJ. All the essential oils were purchased from Herbal Remedies, Casper, WY.