



REVIEW

Evidence of incompatibility for topical anionic agents used in conjunction with chlorhexidine gluconate: A systematic review

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Abstract: Chlorhexidine gluconate (CHG) is a widely used antiseptic agent for skin and wound disinfection. The cationic properties of CHG may allow its inactivation and precipitation by anionic agents in commonly used topical agents. We conducted a systematic review by searching through PubMed, Cochrane Library, and Web of Science databases and selected original research articles reporting on CHG incompatibility, defined as inactivation or precipitation. The search yielded 22 publications that demonstrated CHG incompatibility via: (1) reduced antibacterial activity (carbomer, acrylates/C10-C30 alkyl acrylate crosspolymer, dentin, bovine serum albumin, copolymer M239144, sodium lauryl sulfate, heat-killed microbes, triethanolamine, and bark cork); and (2) visible precipitate formation (sodium hypochlorite, EDTA, saline, ethanol, and nystatin). Only three publications reported on CHG incompatibility in dermatology, specifically for carbomer, triethanolamine, and acrylates/C10-C30 alkyl acrylate crosspolymer. Although limited evidence linking CHG incompatibility and anionic agents exists, clinicians should carefully consider the nature of topical agents used if CHG is concurrently applied. Increased awareness of CHG incompatibility may result in better antibacterial activity thus ensuring optimal patient management.

Keywords: chlorhexidine; incompatibility; inactivation; skin; reduced antibacterial activity; precipitation; systematic review

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Introduction

Chlorhexidine gluconate (CHG) is a widely used, broad-spectrum antiseptic agent for skin and wound disinfection^[1]. The cationic bisbiguanide moiety is a characteristic feature of CHG that allows its binding to keratinocytes. This produces bacteriostatic and bactericidal effects from the interactions with

anionic bacterial cell walls^[2,3]. CHG has been shown to have cumulative antibacterial persistence on the skin^[4]. Despite all these positive attributes, its cationic properties may allow inactivation or precipitation by anionic agents found in products commonly applied as emollients immediately after CHG application. We conducted a systematic review to evaluate the evidence of CHG incompatibility in a dermatological clinical setting.

Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, where applicable (the PRISMA checklist can be found in *Appendix 1*)^[5]. We searched PubMed, Cochrane Library, and Web of Science databases from their inception up to October 2015 using the following key words: “chlorhexidine AND inactivation”, “chlorhexidine AND incompatibility”, “chlorhexidine AND precipitate”, and “chlorhexidine AND anionic”. Results were filtered for English language and human studies, if possible, within the databases. Original research articles were deemed eligible if there are reported chlorhexidine incompatibilities (i.e., reduced antibacterial activity by inactivation or by visible physical precipitation). Two independent reviewers (Tran G and Huynh TN) selected, screened, and reviewed the search results. Variance was reconciled by consensus or, if necessary, through a third reviewer (West DP). Data collection included the type of study (*in vivo* or *ex vivo*), incompatible agents, and significance of incompatibility reported as *p* values (**Table 1**).

Results

The search yielded 414 articles: 78 from PubMed, 15 from Cochrane Library, and 321 from Web of Science. 231 articles were found evaluable after removal of duplicates. After screening the titles and/or abstracts, we excluded 209 articles and hence 22 eligible articles remained. After the final screening, only three articles addressed the dermatologic usage of topical CHG and its incompatibility, specifically addressing the following compounds: carbomer^[6], triethanolamine^[7,8], and acrylates/C10-C30 alkyl acrylate crosspolymer^[6,7]. **Figure 1** showed a flow diagram outlining the selection of articles. Of the 22 eligible articles, 10 articles reported reduced antibacterial activity from the following compounds: carbomer^[6], acrylates/C10-C30 alkyl acrylate crosspolymer^[6,7], dentin^[9-12], bovine serum albumin^[11], copolymer M239144^[13], sodium lauryl sulfate^[14], heat-killed microbes^[9,12], triethanolamine^[7,8], and bark cork^[15]. The 12 remaining articles reported precipitation related to the following compounds: sodium hypochlorite^[16-25], EDTA^[16-18,26], saline^[16], ethanol^[16], and nystatin^[27]. The most commonly reported incompatibility was sodium hypochlorite (bleach, *N* = 10, 45%) and the most commonly reported indication for CHG and its incompatibility was oral mucosal applications (*N* = 19, 86%).

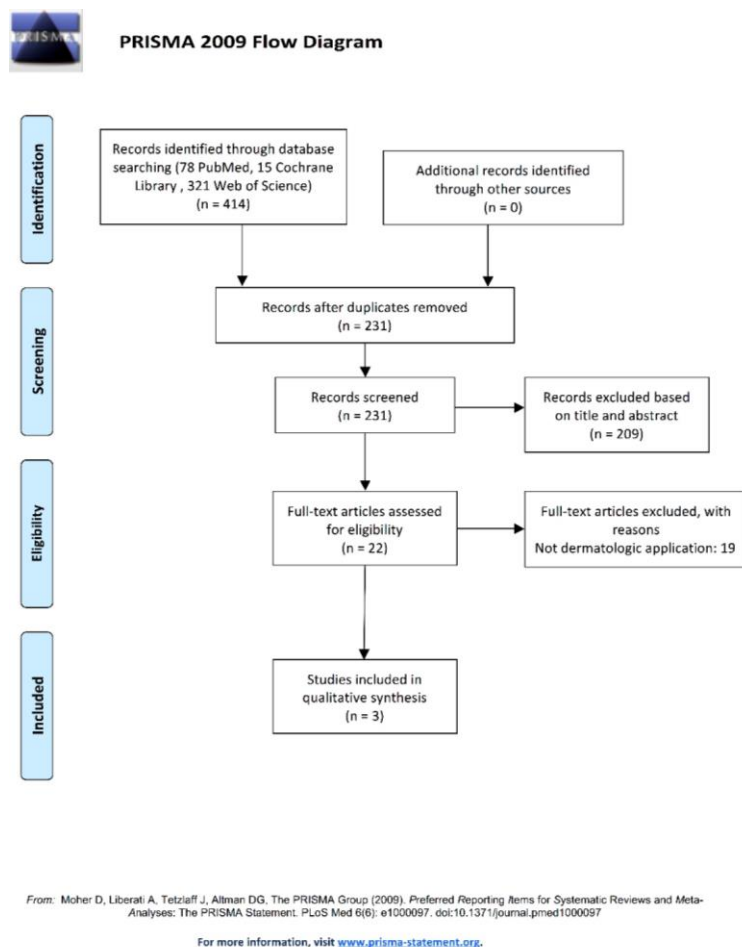


Figure 1. The PRISMA flow diagram for study selection

Discussion

A clinically advantageous feature of CHG compared to other antibacterial agents is its affinity to keratinocytes and persistence within skin tissue. To maintain this clinical feature, it is important to be aware that some concurrently applied topical products may have the potential to disrupt the persistent antibacterial activity. This systematic review identified three publications reporting CHG inactivation after concurrent application of topical agents^[6-8]. Emulsifiers and thickeners found in these topical agents contributed to CHG inactivation. As revealed by our systematic review, there was a distinct lack of literature addressing topical CHG incompatibility. In an *ex vivo* study by Benson *et al.*, anionic surfactant systems almost completely eliminated prolonged residual antibacterial effect of CHG, whereas minimal effect occurred with nonionic products over the same prolonged residual period^[7].

Table 1. Summary of articles exploring dermatologic chlorhexidine incompatibility

Study	Type of study	Bacteria	Inactivating agent	p value
Kaiser et al. (2009) ^[6]	<i>in vivo</i> + <i>ex vivo</i>	<i>Serratia marcescens</i> , <i>in vivo</i> <i>Staphylococcus aureus</i> , <i>ex vivo</i>	Carbomer, C10-C30 alkyl acrylate crosspolymer	<0.0001
Benson et al. (1990) ^[7]	<i>ex vivo</i>	<i>Serratia marcescens</i>	Triethanolamine, C10-C30 alkyl acrylate cross-polymer (Vaseline® Intensive Care)	<0.01
Walsh et al. (1987) ^[8]	<i>in vivo</i>	<i>Escherichia coli</i>	Triethanolamine	<0.001

Triethanolamine and C10-C30 alkyl acrylate cross-polymer were the implicated inactivating agents in the anionic surfactant system. Another *ex vivo* study also demonstrated statistically significant decreases in log₁₀ reductions in alcohol hand sanitizing gels^[6]. Of note, emulsifying and thickening agents, carbomer, and C10-C30 alkyl acrylate crosspolymer were associated with CHG inactivation rather than the alcohol itself. Moreover, these results paralleled *in vivo* testing involving 11 human subjects. Hand creams containing triethanolamine, an emulsifier and thickener, yielded similar *in vivo* CHG inactivation^[8]. Based on the Cosmetic Ingredient Review (CIR) Expert Panel, triethanolamine, carbomer, and C10-C30 alkyl acrylate crosspolymer were found in 3756, 1610 and 1696 cosmetic formulations, respectively^[28-30]. This demonstrated the prevalence of these compounds as well as the potential for inactivation if concurrently applied.

CHG is widely known for its antibacterial superiority over many antiseptics and its substantial residual activity on skin^[31-34]. CHG typically has a very rapid action onset with high bacterial kill rate efficacy and additionally has been shown to reduce bacterial counts of drug-resistant *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* strains by 99.9% within three minutes^[35,36]. After several decades of clinical use with no clinically significant events reported concerning the interaction and/or inhibition of antibacterial effect with concurrent application of other topical products, the immediate kill by CHG might be its most important clinical property. One study suggested that the residual kill of CHG may be an artifact of testing protocols and was dependent on the skin being wet^[37]. Generally, if avoidance of an incompatible agent is not possible, and because of the rapid and relatively complete kill rate by CHG, topical anionic agents may likely be applicable after a short period, with a low likelihood of impaired CHG efficacy. Despite this, clinicians should weigh the risks and benefits in deciding the appropriate amount of elapsed time subsequent to CHG application to ensure adequate efficacy.

A limitation of this study was that chemistry (non-biomedical) databases were not included – such databases may yield additional supporting evidence in re-

gards to the incompatibility of anionic agents that may be utilized in biomedical products applied to skin or mucous membranes concurrent to CHG use. Despite the fact that we only reported three agents for CHG inactivation with concurrent application, there are other agents not yet investigated and reported for this potential interaction. Moreover, there is a clear gap in clinician knowledge of CHG incompatibility. According to a survey in Washington State, a cohort of only 48% health personnel was aware of CHG inactivation by some topical anionic moisturizers^[38]. This survey illustrated a need for further education and research on CHG incompatibility with selected concurrently used topical agents. Future exploration of this issue should perhaps focus on health outcomes to delineate the clinical significance of CHG incompatibility.

Conclusion

Despite widespread use of anionic agents in topically applied products, this systematic review of CHG incompatibility, as measured by reduced antibacterial activity or physical precipitation, yielded very limited evidence of incompatibility and only with very few anionic agents. Given the several decades of clinical use without reports of reduced efficacy due to topical incompatibility, CHG's relatively immediate killing property may be its predominant function and therefore the potential for reduction in antibacterial efficacy may be minimal due to this ability. However, in light of the very limited but relatively high level of evidence for *ex vivo* incompatibility, clinicians should carefully consider the possibility of CHG incompatibility with concurrent use of topical anionic agents. Clinicians should be aware of the ingredients in topical emollient/skin regimens for patients who concurrently use CHG. Although further investigation to determine the ionic nature of topical agents may be somewhat tedious, this information affords the opportunity for optimizing antibacterial activity and, ultimately, health outcomes.

Author contributions

The study was conceived and designed by Ahmad N, Budris WA, Posligua A, Hammel JA, Nardone B, and

West DP, Tran G, Huynh TN, and West DP reviewed the articles. The manuscript was prepared by Tran G, Huynh TN, and Bruins FM with revisions by Tran G, Huynh TN, Bruins FM, Ahmad N, Budris WA, Posligua A, Hammel JA, Nardone B, and West DP.

Conflict of interest

West DP is a consultant for Sage Products LLC but he did not receive any financial support to conduct the work reflected in this research. All the other authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Supplementary information

Appendix 1: The PRISMA checklist of items to include when reporting a systematic review or meta-analysis. The supplementary information is available free of charge on JSD's website at doi: 10.18282/jsd.v1.i2.21.

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