Evaluation of a Waterless, Scrubless Chlorhexidine Gluconate/Ethanol Surgical Scrub for Antimicrobial Efficacy

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Abstract

A new waterless surgical hand scrub product containing 1% chlorhexidine gluconate (CHG) and 61% ethyl alcohol in an emollient-rich lotion base (CHG/ethanol-emollient hand preparation) was evaluated. Clinical studies were based on the Tentative Final Monograph for Health Care Antiseptic Drug Products (TFM)[1]; Proposed Rule and ASTM E1115-91[2], Standard Test Method for Evaluation of Surgical Hand Scrub Formulations.

Two randomized, blinded well-controlled clinical studies involving over 100 healthy subjects evaluated the antimicrobial effectiveness of CHG/ethanol-emollient hand preparation in producing an immediate and persistent reduction in the normal bacterial flora of the hands. CHG/ethanol-emollient hand preparation was applied without scrubbing or the use of water, while a 4% CHG reference product was applied using scrub brushes in two traditional 3-minute surgical scrubs.

Over a 5-day period, each subject performed a series of 11 surgical scrubs using one of the products. After the first treatment on Days 1, 2 and 5, surgical gloves were worn for 3 and/or 6 hours. Bacterial samples were taken using the glove juice technique at 1 minute, 3 hours and/or 6 hours after treatment. The immediate bactericidal effect of CHG/ethanol-emollient hand preparation after a single application resulted in a 2.5 log reduction in normal flora. This bactericidal effect persisted throughout the study, and eventually increased to a 3.5 log reduction after the eleventh scrub on Day 5. The log reductions of CHG/ethanol-emollient hand preparation proved to be significantly better ($p<0.05$) than that of the 4% CHG product at each sampling interval on Days 1 and 2, and at the 6 hour sampling on Day 5, exceeding the TFM requirements. Use of this new waterless product as a surgical hand scrub lowers bacterial flora on the hands.

Introduction

This white paper describes the results of two clinical studies designed to determine the antimicrobial effectiveness of CHG/ethanol-emollient hand preparation using the log reduction criteria for bacterial counts on the hands defined by the Food & Drug Administration's (FDA) Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM). In these trials, CHG/ethanol-emollient hand preparation is compared with Hibiclens® (Stuart Pharmaceuticals, Wilmington, DE), a currently marketed presurgical antimicrobial hand-wash product containing 4% CHG in a detergent base. Changes in baseline skin condition were also measured based on results of subject self-assessment questionnaires.

Objectives

- To evaluate the effectiveness of the CHG/ethanol-emollient hand preparation formulation as a surgical hand scrub in meeting the TFM criteria for immediate and persistent reductions in the number of bacteria on the hands.
- To assess bacterial reductions achieved within 1 minute and at 3 and 6 hours post-treatment, comparing the CHG/ethanol-emollient hand preparation product versus Hibiclens.
- To compare the skin condition of the hands as assessed by subjects receiving the CHG/ethanol-emollient hand preparation product to that of subjects receiving Hibiclens.

Methods

Study design

Two prospective, randomized, partially-blinded, parallel-group trials (the design was identical for Studies A and B):

- 14-day pretreatment washout period for stabilization of hand bacterial flora, during which subjects refrained from using any topical antimicrobials, systemic antibiotics, or medicated soaps, lotions, shampoos, etc.
- 5 to 7 days of baseline bacterial evaluations where three baseline samples of hand bacterial flora were taken.

Subjects with baseline bacterial populations ≥ 1.0 x 105 colony forming units (CFU) per hand at the first and second baseline samplings were eligible to be enrolled in the treatment period.

- 5-day treatment period during which subjects performed a series of 11 simulated surgical hand scrubs using one of the test products:
  - once daily on Treatment Days 1 and 5, and
  - three times daily on Treatment Days 2, 3, and 4.

Treatments

Subjects were randomized to receive one of the following two* treatments during each hand wash procedure:

- CHG/ethanol-emollient hand preparation (6 mL, 3 x 2 mL), or
- Hibiclens (10 mL, 2 x 5 mL).

* Note: In one of the two studies, some subjects were also randomized to receive a vehicle control formulation. Those data are not presented here.

Bacterial samples

- Samples were collected following scrubs on Treatment Days 1, 2 and 5.
- Hands were randomized to bacterial sampling times. The first hand was sampled at 1 minute or 3 hours after scrubbing. The second hand of each subject was then sampled at either 3 or 6 hours after scrubbing.
- Sampling technique:
  - Loosely fitting sterile surgical gloves were placed over the hands to be sampled, then 75 mL of sampling solutions was aseptically added to the gloves.
  - Gloves were occluded above the wrist and the gloved hand was uniformly massaged for 1 minute.

- After massaging, an aliquot of the fluid in the glove was aseptically transferred to a serial dilution tube containing suitable antimicrobial neutralizers to achieve a 1:10 dilution.
- Solutions were plated using Trypticase Soy Agar and incubated for 48 to 72 hours at 30°C ± 2°C. Colonies were counted and viable cells in the undiluted sample were calculated by standard methods.

• Log reductions in bacterial counts were measured after 1 minute, 3 hours, and at 6 hours on Days 1, 2, and 5.

• Reductions in bacterial counts achieved with CHG/ethanol-emollient hand preparation were compared with those of a reference control treatment (Hibiclens).

Subjects

Healthy, male or female volunteer subjects, ages 18 to 65 years old, inclusive, with 1st and 2nd baseline counts ≥ 1.0 x 105 CFU per hand.

Demographic and baseline characteristics of the study population were similar across test groups. (Table 1)

Table 1. Demographic characteristics

Parameter	Study A (HTR)		Study B (VML)	
	CHG/ethanol-emollient hand preparation (N=27)	Hibiclens (N=25)	CHG/ethanol-emollient hand preparation (N=33)	Hibiclens (N=20)
Age years				
Mean (SD)	51.3 (10.3)	54.8 (7.8)	30.1 (7.3)	27.9 (7.5)
Gender N (%)				
Male	4 (15)	7 (28)	11 (32)	7 (35)
Female	23 (85)	18 (72)	23 (68)	13 (65)
Race N (%)				
White	27 (100)	22 (88)	31 (91)	20 (100)
Black	-	3 (12)	-	-
Hispanic	-	-	3 (9)	

Evaluation criteria

Efficacy:

Efficacy evaluations were based on the immediate and persistent activity of CHG/ethanol-emollient hand preparation as measured by the log reductions from baseline counts per hand at the following post-scrub sampling time points:

• Treatment Day 1 at 1 minute, 3 hours, and 6 hours.

• Treatment Day 2 (after the 1st scrub) at 1 minute, 3 hours, and 6 hours.

• Treatment Day 5 at 1 minute, 3 hours, and 6 hours.

Skin condition:

Based on subject self-assessment questionnaires, change from baseline skin condition at Day 4 was calculated for several skin characteristics (appearance, intactness, moisture content, and sensation), based on a seven-point scale (1=abnormal, red, dry itchy, etc., to 7=normal).

Safety:

Assessments based on observed and reported adverse events.

Statistical Methods

Efficacy:

• Raw data on microbial counts from each baseline determination on each hand (CFU/hand) were converted to base 10 logarithms, then were averaged to determine each hand's baseline count.

• Log reductions were calculated by subtracting the post-treatment log count from the average baseline log count on the same hand.

• The differences between groups in log reductions at each time period were analyzed using a t-test, with significance at p≤ 0.05 (2-tailed).

Skin condition:

• Change from baseline at Day 4 was calculated for each item on the subject self-assessment questionnaire.

• A one-way analysis of variance (ANOVA) on the rank-transformed change scores was used to test the effect of the formulation on each aspect of skin condition.

Results

Disposition of subjects is displayed in Table 2.

Table 2. Disposition of subjects

Category	Study A		Study B	
	CHG/ethanol-emollient hand preparation	Hibiclens	CHG/ethanol-emollient hand preparation	Hibiclens
Enrolled	27	25	34	20
Completed study	24	24	31	19
Reasons for discontinuation*				
Adverse event	2	0	1	0
Personal reasons	2	1	-	-
Lack of compliance	-	-	2	1
Lost to follow-up	1	0	-	-

*More than one reason for discontinuing could be provided.

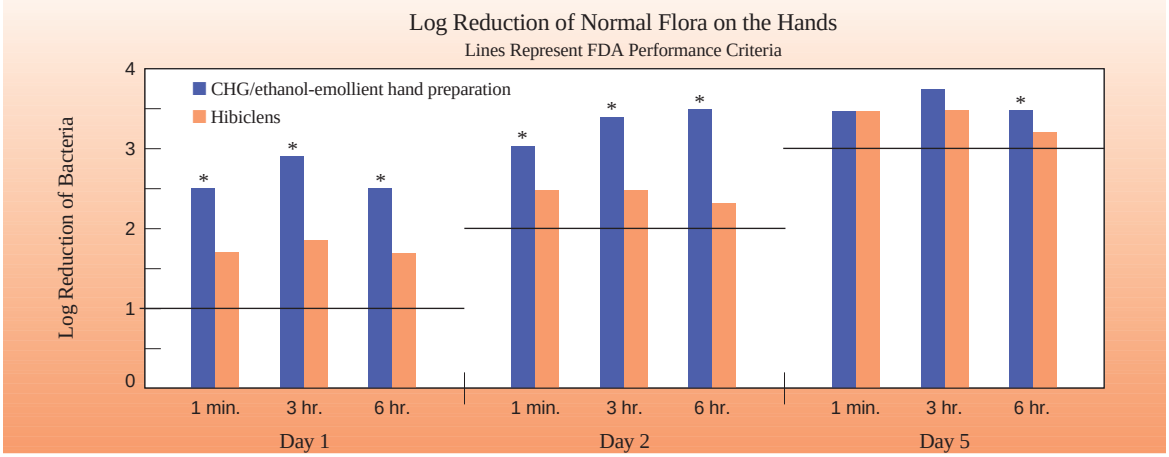
In Study A, both the CHG/ethanol-emollient hand preparation and Hibiclens groups showed statistically significant reductions from baseline bacterial counts at all time points. The log reductions from baseline bacterial counts on Days 1, 2, and 5 exceeded the TFM criteria at the specified time points for both groups (Table 3). In comparing CHG/ethanol-emollient hand preparation and Hibiclens, CHG/ethanol-emollient hand preparation had significantly greater log reduction at 1 minute and 3 hours on Day 1 and 6 hours on Day 2. In Study B, the log reductions from baseline bacterial counts were statistically significant and exceeded the TFM criteria at the specified time points for both CHG/ethanol-emollient hand preparation and Hibiclens. In comparing CHG/ethanol-emollient hand preparation and Hibiclens, CHG/ethanol-emollient hand preparation had statistically significantly greater log reductions in bacteria at 3 and 6 hours on Day 1 and at all time points on Day 2 (Table 3).

Table 3: Log reductions in bacterial counts (CFU/Hand) **from baseline**

	Study A		Study B	
	CHG/ethanol-emollient hand preparation	Hibiclens	CHG/ethanol-emollient hand preparation	Hibiclens
Baseline Period Mean	6.3	6.4	6.1	6.0
Day 1 Log Reduction				
1 Minute	2.5*	1.8	2.5	1.6
3 Hours	2.6*	1.8	3.1*	1.8
6 Hours	2.2	1.9	2.8*	1.4
Day 2 Log Reduction				
1 Minute	3.0	2.6	3.2*	2.4
3 Hours	3.1	2.7	3.7*	2.3
6 Hours	3.3*	2.3	3.6*	2.3
Day 5 Log Reduction				
1 Minute	3.7	3.7	3.5	3.6
3 Hours	3.6	3.7	3.9	3.6
6 Hours	3.8	3.5	3.5	3.0

*Statistically significantly higher for CHG/ethanol-emollient hand preparation than for Hibiclens.

Figure 1. Combined Analysis



*Statistically significant difference.

When data from the two studies were combined, CHG/ethanol-emollient hand preparation had statistically significantly greater log reductions in bacteria at all time points on Days 1 and 2 and at the 6-hour sampling on Day 5 compared to Hibiclens (Figure 1).

Skin assessments

In Study A, at the end of Day 4, CHG/ethanol-emollient hand preparation was statistically significantly superior to Hibiclens with respect to change from baseline moisture content ($p=0.0091$), although no statistically significant differences were found for appearance, intactness, or sensation.

In Study B, a statistically significant treatment effect was demonstrated for all skin assessments, indicating that CHG/ethanol-emollient hand preparation was associated with better skin condition than Hibiclens. Pairwise comparisons of CHG/ethanol-emollient hand preparation and Hibiclens yielded statistically significant results for all skin condition assessments (appearance, intactness, moisture content, and sensation) in favor of CHG/ethanol-emollient hand preparation.

Safety

No serious or severe adverse events occurred during either study.

Two subjects reported three adverse events in the CHG/ethanol-emollient hand preparation groups, which were "probably related" to the study formulation:

- One subject reported a maculopapular rash on the dorsal surface of both wrists where the gloves had been secured.
- One subject experienced two adverse events—conjunctivitis and abnormal vision—after rubbing his eyes after application.

Four other reported adverse events which were "probably not related" to study formulation included: a viral infection, menorrhagia, an upper respiratory infection, and an inflicted injury of cuts to the knuckles of one hand.

Two adverse events were reported with the use of Hibiclens:

- One subject experienced an allergic reaction considered "possibly related" to use of the product.
- One subject experienced an erythematous rash considered "probably not related" to use of the product.

Conclusions

- CHG/ethanol-emollient hand preparation met or exceeded TFM criteria for antimicrobial effectiveness.
- CHG/ethanol-emollient hand preparation was equal or superior to Hibiclens in antimicrobial effectiveness, as assessed by log reductions in counts of hand bacteria.
- CHG/ethanol-emollient hand preparation was associated with less drying of the skin than Hibiclens, as assessed by subject evaluations of Moisture Content at the end of Day 4 in Study A, and with statistically significantly better skin condition scores for appearance, intactness, moisture content, and sensation scores than Hibiclens in Study B.
- CHG/ethanol-emollient hand preparation was well tolerated in both studies.

References

1. Federal Register Part III, Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule. Vol. 59, No 116 (Friday, June 17, 1994). Code of Federal Regulations, Title 21 CFR Parts 333 and 369.

2. ASTM Standard 1115-91. Standard Test Method for Evaluation of Surgical Hand Scrub Formulations. Annual Book of ASTM Standards, Vol. 11.05., p. 447-450, 1996.

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