Antimicrobial activity of a novel adhesive containing chlorhexidine gluconate (CHG) against the resident microflora in human volunteers

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Objectives: To evaluate the antimicrobial activity of a new, transparent composite film dressing, whose adhesive contains chlorhexidine gluconate (CHG), against the native microflora present on human skin.

Methods: CHG-containing adhesive film dressings and non-antimicrobial control film dressings were applied to the skin on the backs of healthy human volunteers without antiseptic preparation. Dressings were removed 1, 4 or 7 days after application. The bacterial populations underneath were measured by quantitative cultures (cylinder-scrub technique) and compared with one another as a function of time.

Results: The mean baseline microflora recovery was 3.24 log_{10} cfu/cm². The mean log reductions from baseline measured from underneath the CHG-containing dressings were 0.87, 0.78 and 1.30 log_{10} cfu/cm² on days 1, 4 and 7, respectively, compared with log reductions of 0.67, –0.87 and –1.29 log_{10} cfu/cm² from underneath the control film dressings. There was no significant difference between the log reductions of the two treatments on day 1, but on days 4 and 7 the log reduction associated with the CHG adhesive was significantly higher than that associated with the control adhesive.

Conclusions: The adhesive containing CHG was associated with a sustained antimicrobial effect that was not present in the control. Incorporating the antimicrobial into the adhesive layer confers upon it bactericidal properties in marked contrast to the non-antimicrobial adhesive, which contributed to bacterial proliferation when the wear time was ≥4 days.

Keywords: catheter-related infections, antisepsis, infection control, vascular access, dressing, IV securement, cutaneous flora

Introduction

Human skin plays host to a population of resident microbes that under ordinary circumstances pose no significant health risks.1 But this normally benign microflora can also be pathogenic, given the opportunity. For example, the skin-resident Staphylococcus epidermidis is the most commonly implicated culprit in bloodstream infections associated with the placement of short-term vascular access catheters.2–6 Catheter-related bloodstream infections (CR-BSIs) in general are one of the most significant categories of healthcare-acquired infections. Because vascular access is fundamental to patient care, heavy utilization of these devices translates to an estimated 250,000–500,000 attributable bloodstream infections in the USA each year.5 Each CR-BSI carries a heavy burden, both in terms of morbidity and economics, increasing the length of the patient’s hospital stay and substantially increasing the cost of care.7–13

Because an intact skin barrier is the body’s most effective defence against microbial invasion, breaching it via a vascular access procedure creates an opportunity for infection. The migration of resident skin flora through the catheter tunnel (i.e. into the insertion wound) has been identified as a primary route for catheter-related infection,2,4,5,14 with one animal study even suggesting that capillary action plays a role in accelerating the transit of microbes deep into the skin tissue.15 Dressing the insertion site after using an antiseptic to suppress the native microflora is the recommended practice to mitigate the risk of extraluminal infection.1 One limitation of this protocol is that antisepsis takes place at a single point in time. Without a source of sustained antimicrobial activity, the skin flora will eventually regenerate

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on its own, and furthermore the site is vulnerable to re-colonization in the event of dressing disruption.

It stands to reason that a continuously available supply of an antimicrobial agent held in place on the skin’s surface should favour reduced colonization and possibly lead to a reduced risk of CR-BSI. To this end, a foam disc (BioPatch®; Johnson & Johnson Corporation, New Brunswick, NJ, USA) and a gel pad (Tegaderm® CHG IV Securement Dressing; 3M Company, St Paul, MN, USA) containing chlorhexidine gluconate (CHG) are commercially available for use as vascular access site dressings, both designed to stay in contact with the insertion site throughout the duration of wear. Clinical evidence exists supporting each product’s efficacy with respect to CR-BSI, but each has its own limitations: e.g. the BioPatch® prevents visualization of the insertion site and the Tegaderm® CHG can be difficult to remove.

In addition, they can be relatively expensive compared with non-antimicrobial film dressings and this tends to restrict their use to central venous catheter placement sites. One strategy to overcome these limitations has been to incorporate antimicrobial agents directly into a film dressing’s adhesive layer; chlorhexidine acetate, iodine, and silver have all been formulated in this way, but clinical evaluations of the latter two products revealed limited antimicrobial efficacy and the former product containing chlorhexidine acetate is no longer marketed.

The purpose of this study was to evaluate the antimicrobial activity of a new transparent film dressing that uses an adhesive containing CHG. Similar to an ordinary film dressing, this product is thin, breathable, conformable, easy to apply and allows visualization of the insertion site. But unlike an ordinary dressing, the skin-contacting adhesive layer contains a well-known broad-spectrum antimicrobial agent commonly used in antiseptic skin preparations and valued for its superior efficacy. Incorporating CHG in this way was expected to yield a bactericidal effect against the native skin flora. To test this expectation, a comparison was made between the CHG film dressing and a control by quantitatively culturing the skin flora underneath dressings worn by healthy human volunteers for up to 7 days.

Methods

Test materials

The test product, ‘CHG adhesive’, was the BeneHold® CHG Transparent Film Dressing, a 75×60 mm dressing featuring a novel acrylic adhesive containing 4% CHG by weight. A standard film dressing, Tegaderm® 1624W (3M Company), ‘control adhesive’, was chosen as the control on the basis that it is similar in size (70×60 mm) and its adhesive is also in the acrylic family but does not contain an antimicrobial agent. Both dressings are indicated for use to cover and protect peripheral intravenous catheter insertion sites.

Study population

Research using human subjects was conducted in accordance with current FDA and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines for good clinical practice and in a manner consistent with the principles of the Declaration of Helsinki. The study protocol was approved by the Gallatin Institutional Review Board (Bozeman, MT, USA) and participating subjects provided written informed consent. Subjects were all ≥18 years of age and competent to provide consent.

These results represent a subset of a larger investigation involving a total of six different treatment configurations, two of which are relevant here. In total, 66 subjects were enrolled to accommodate the sample size requirements for the entire study. To be included in the study, subjects were required to be in generally good health and free of any skin disorders on or around the test sites. Pregnant and nursing women and individuals with known allergies to CHG or any of the other materials used in the test were excluded from the study, as were individuals using topical or systemic antibiotics. There were no selection criteria for age, sex or race, other than the minimum age requirement of 18 years.

Enrolled subjects underwent a 7 day pre-test wash-out period in which they agreed not to use any personal hygiene products containing antimicrobial ingredients and to avoid exposure to biocidal influences such as treated swimming pools or UV tanning beds. Personal hygiene kits containing non-antimicrobial soap, shampoo and lotion were provided for use during the pre-test period. The same restrictions also applied throughout the 7 day test period itself, but subjects further agreed not to allow the test sites to get wet throughout the entire test period and for 3 days prior to its commencement. When necessary, the hair was clipped from the test sites within 3 days prior to test product application; subjects were instructed not to shave the treatment sites within 5 days prior to the start of the test.

Treatment

Each subject was randomly allocated four treatments selected from six possibilities. Only two of those treatments are of interest for this analysis (CHG adhesive or control adhesive). First, a sterile surgical marker was used to demarcate four zones on each subject’s upper back and a baseline quantitative bacterial sample was taken from the centre of each zone. Within each zone, the skin was further demarcated into four subsections. A computer-generated randomization schedule was then used to assign one treatment to each zone and to select three subsections from each zone to receive that type of treatment (one for each timepoint of interest). A border of Mastisol® skin adhesive (Ferndale IP, Inc., Ferndale, MI, USA) 20 mm wide was applied around the edge of each application site and allowed to dry for 30 s before applying dressings to the assigned sites. The arrangement of test sites in zones and subsections is illustrated in Figure 1.

Subjects returned to the laboratory at three points in time: 24 ± 1, 96 ± 2 and 168 ± 4 h after the dressings were applied. During each return visit, one dressing was removed from each zone using a computer-generated randomization schedule to determine which subsection to

Figure 1. Diagram illustrating the demarcation of the back into four zones, each made up of four subsections, labelled A, B, C and D. The locations where baseline counts were taken, at the centres of each zone, are denoted BL.
address at each timepoint. A quantitative bacterial sample was taken from the centre of the application site immediately after the dressing was removed. Samples were not taken from subsections where the dressing had lost contact with the skin to such a degree that there was a clear pathway for potential contamination of the site from external sources or the surrounding, untreated skin.

**Bacterial enumeration**

Quantitative bacterial cultures were obtained from the skin using a previously described cylinder sampling technique. A sterile metal cylinder with a 2.54 cm inner diameter was pressed against the skin and charged with 3.0 mL of scrub solution containing antimicrobial neutralizers. After massaging the surface of the skin inside the cylinder with a sterile rubber policeman for 1 min, the solution was removed by pipette and the process was repeated with a fresh 3.0 mL aliquot of scrub solution. The two aliquots were pooled at the end. Duplicate cultures were prepared from each recovered scrub solution by spiral-plating 50 μL of undiluted solution onto tryptic soy agar containing neutralizers and incubating at 30 ± 2 °C for 3 days. The number of cfu on each plate was then quantified using the computerized QCount system (Spiral Biotech, Inc., Norwood, MA, USA) and the results from duplicate plates were averaged and converted into the number of cfu/cm² of scrubbed skin. When the average count from the duplicate plates was zero, the value was set to 1 cfu/cm² so that a zero value would result after log transformation.

**CHG neutralization**

A neutralization study was performed to ensure that the neutralizers used in the recovery medium (scrub solution) effectively quenched the antimicrobial activity of the treatment products and were not toxic to the challenge species. Study procedures were based on ASTM E1054-08(2013) (Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents). Staphylococcus epidermidis (ATCC 51625) was used as the challenge species in the neutralization study.

**Statistical analysis**

First, a log transformation was performed on the microbial counts. Then, any zone that yielded a baseline count of <2.5 log₁₀ cfu/cm² was excluded from data analysis, which is a standard practice intended to reduce variability in the microbial recovery data. Log reductions in microbial recoveries were calculated by subtracting each data point from the corresponding baseline measurement made in the same zone. Using these data, a blocked two-factor analysis of variance (ANOVA) was performed on the log reductions. It had the form:

\[ \hat{y} = Blocks + A_i + B_j + AB_{ij} + e \]

where \( \hat{y} \) is the log reduction in microbial recovery, Blocks represents subjects (levels: one per subject), A represents treatment (levels: CHG adhesive or control adhesive), B represents day (levels: day 1, 4 or 7), \( AB_{ij} \) is an interaction term and e is an error term.

The ‘subjects’ factor was modelled as random, while the ‘treatment’ and ‘day’ factors were modelled as fixed. Factors were deemed significant if the resulting P values were <0.05.

When the ANOVA indicated significant differences between factors, a detailed understanding of the relationship between different factor/level combinations was achieved by constructing 95% CIs around the mean log reductions for each group. The CIs were computed using the formula:

\[ \mu = \bar{x} \pm z_{0.975} \frac{s}{\sqrt{n}} \]

where \( \mu \) is the 95% confidence limit, \( \bar{x} \) is the mean log reduction for a specific factor/level combination, \( s^2 \) is the individual variance of data from the group, \( n \) is the sample size of the group and \( z_{0.975} = 1.96 \), the value from the standard normal distribution at the 95% CI (i.e. \( z_{\alpha/2} \) with \( \alpha = 0.05 \)).

If two group’s 95% CIs did not overlap, their means were judged to be significantly different from one another.

**Results**

**Sample size and demographics**

Fifty individuals completed the study in its entirety. Fifteen were dismissed on day 4, when baseline count data became available showing that all four zones failed to meet the threshold of 2.5 log₁₀ cfu/cm², and one subject voluntarily discontinued the study. The group that completed the study consisted of 26 men and 24 women, aged 19–78 years.

There were no adverse events reported during the study. Both treatments were well tolerated and no significant skin irritation was observed. Using the Berger–Bowman scale for quantifying skin irritation, neither treatment was associated with any score greater than ‘minimal erythema, barely perceptible’ at any point during the study.

**Baseline cultures**

Forty-two subjects had at least one zone assigned to the CHG adhesive or control adhesive test configuration, resulting in an initial set of baseline cultures taken from 69 unique zones. An additional 11 subjects were excluded from this analysis after the minimum requirement of baseline recovery >2.5 log₁₀ cfu/cm² was applied. Of the final, relevant population of 31 subjects, 12 had one zone assigned to the CHG adhesive and one assigned to the control adhesive. Eight subjects had only one zone assigned to the CHG adhesive (and no control adhesive zones) and 10 had only one zone assigned to the control adhesive (and no CHG adhesive zones). Due to a deviation from protocol, one additional subject had two zones assigned to the CHG adhesive. In total, there were 44 zones meeting all of the criteria to be included in this analysis, which were divided equally between the two treatments (22 zones treated with CHG adhesive and 22 zones treated with control adhesive).

The mean baseline density of microflora was 3.24 log₁₀ cfu/cm² and the standard deviation was 0.58 log₁₀ cfu/cm². The minimum was 2.54 log₁₀ cfu/cm², the maximum was 4.80 log₁₀ cfu/cm² and 73% (32/44) were <3.5 log₁₀ cfu/cm².

**Recovery of bacteria from underneath dressings**

The mean bacterial recoveries from underneath CHG adhesive specimens were, expressed as mean (SD), 2.41 (1.20), 2.51 (1.62) and 1.92 (1.49) log₁₀ cfu/cm² on days 1, 4 and 7, respectively. In comparison, the mean recoveries from underneath control adhesive specimens were 2.52 (1.32), 4.06 (1.59) and 4.49 (1.54) log₁₀ cfu/cm² on days 1, 4 and 7, respectively. Two of the CHG adhesive dressings and one control adhesive dressing intended for analysis on day 7 were lost because they detached from the skin, slightly reducing the day 7 sample sizes to n=20 and n=21, respectively.
The mean log reduction values for the CHG adhesive were 0.87, 0.78 and 1.30 log10 cfu/cm² on days 1, 4 and 7, respectively. For the control adhesive, the mean log reduction values were 0.67, 0.87 and 2.1.29 log10 cfu/cm² on days 1, 4 and 7, respectively, indicating an increase above the baseline value at days 4 and 7. These results are shown in detail in Table 1. The blocked, two-factor ANOVA showed that each factor was significant and pairwise comparisons within factors revealed a significant difference between CHG adhesive versus control adhesive and between the day 1 timepoint versus days 4 and 7 (Table 2).

A graphical illustration of the relationship between the mean log reductions from each of the two treatments at each point in time was generated by plotting the values together with their 95% CIs (Figure 2). This shows there was no significant difference between the reductions in bacterial populations attributable to the CHG adhesive and control adhesive on day 1, but on days 4 and 7 the log reduction associated with the CHG adhesive was significantly higher than that associated with the control adhesive. Looking within treatment groups, log reductions measured from underneath the CHG adhesive were equivalent at all three timepoints, but in the control adhesive days 4 and 7 were not equivalent to day 1.

**Discussion**

The experimental design was essentially a time–kill study demonstrating the bactericidal effect of the CHG adhesive against the native microflora present on human skin. The mean baseline microbial density of 3.24 log10 cfu/cm² on the subjects' back sites was consistent with prior literature reporting native aerobic microflora densities between 3.1 and 3.3 log10 cfu/cm² on the upper back using similar quantification techniques.19,37 While the bioburdens beneath both the CHG adhesive and the control adhesive were below baseline at the 24 h timepoint, only the CHG adhesive had a sustained antiseptic effect, as demonstrated by the continuous maintenance of an ≏ 1 log10 cfu/cm² decrease in bacterial load over the entire 7 day test period. In contrast, the control adhesive was associated with a proliferation of microflora when the residence time was ≥ 4 days, resulting in a 1.3 log10 cfu/cm² increase by the end of the 7 day test. The effect

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**Table 1.** Mean log reductions measured for each treatment group at each timepoint

| Timepoint | Treatment      | n   | Mean log reduction (log10 cfu/cm²) | Standard deviation (log10 cfu/cm²) | Minimum (log10 cfu/cm²) | Maximum (log10 cfu/cm²) |
|-----------|----------------|-----|----------------------------------|-----------------------------------|------------------------|------------------------|
| Day 1     | CHG adhesive   | 22  | 0.87                             | 0.98                              | −0.52                  | 3.31                   |
| Day 4     | CHG adhesive   | 22  | 0.78                             | 1.44                              | −1.55                  | 2.90                   |
| Day 7     | CHG adhesive   | 20  | 1.30                             | 1.42                              | −1.47                  | 3.33                   |
| Day 1     | control adhesive | 22  | 0.67                             | 1.21                              | −2.70                  | 3.07                   |
| Day 4     | control adhesive | 22  | −0.87                            | 1.65                              | −3.00                  | 3.24                   |
| Day 7     | control adhesive | 21  | −1.29                            | 1.51                              | −3.12                  | 1.77                   |

**Table 2.** Results from the blocked two-factor ANOVA on the log reduction data

| Source                   | Degrees of freedom | Sequential sum of squares | Adjusted sum of squares | Adjusted mean square | F      | P      | Significance |
|--------------------------|--------------------|--------------------------|-------------------------|----------------------|--------|--------|--------------|
| Subject                  | 30                 | 113.761                  | 97.020                  | 3.234                | 2.17   | 0.003  | significant  |
| Treatment                | 1                  | 50.188                   | 50.793                  | 50.793               | 34.07  | 0.000  | significant  |
| Day                      | 2                  | 19.297                   | 18.916                  | 9.458                | 6.34   | 0.003  | significant  |
| Treatment × day          | 2                  | 32.166                   | 16.083                  | 10.79                | 0.000  | significant  |
| Error                    | 93                 | 138.666                  | 138.666                 | 1.491                |        |        |              |
| Total                    | 128                | 354.078                  |                         |                      |        |        |              |

*a*Adjusted mean square value of the source divided by the adjusted mean square value of the error.

*b*The *P* value is $P(F ≥ x^*|H_0$ true), where *x* is the calculated *F* value.

*b*Significant/not significant at $\alpha = 0.05$. If the *P* value is ≤ 0.05, the test is significant. If the *P* value is >0.5, it is not significant.

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**Figure 2.** Mean log reductions measured from back sites treated with either the CHG adhesive (filled circles) or the control adhesive (open circles) at each timepoint. The error bars indicate the 95% CI of the mean.
of incorporating CHG into the adhesive translated to a 2.6 log reduction difference in the bacterial population after 7 days versus the non-antimicrobial adhesive.

The CHG adhesive’s antimicrobial activity is a unique feature in comparison with standard film dressings. In vascular access applications, these dressings are typically applied to antisepsically prepared skin, where they form a waterproof barrier to protect against gross bacterial contamination, and while a non-antimicrobial film dressing may initially help to maintain low levels of colonization, it cannot eliminate the natural skin flora’s eventual regrowth in subsequent days. Studies in healthy humans have reported either full\textsuperscript{16,17} or partial\textsuperscript{18,19} regrowth of the microflora within 3–4 days after applying film dressings to antisepsically prepared skin. These results have been corroborated by larger, in-hospital clinical studies\textsuperscript{20–23} some of which have also established skin colonization under the dressing as a significant risk factor for catheter-related infection.\textsuperscript{20,21} The control adhesive data are consistent with the established literature on the dynamics of bacterial populations underneath semi-occlusive film dressings, but, in marked contrast, the CHG adhesive clearly demonstrates an ability to reduce the skin’s bioburden on its own, even when antiseptic preparations such as povidone–iodine, isopropyl alcohol or CHG solutions are not used.

Certainly, antiseptic preparation of the insertion site represents the standard of care, but there may, nevertheless, be advantages to the added protection offered by an adhesive dressing with sustained antimicrobial activity of its own. First, depending on the preparatory technique, some of the skin underneath the dressing may go unprepared if the antiseptic solution is applied to an area smaller than the dressing itself. This may set the stage for a zone of bacterial proliferation adjacent to the insertion site whose migration will be unpredictable. Second, there are known circumstances in which less than ideal preparations are made before catheter insertion, especially in the trauma setting.

CR-BSIs.\textsuperscript{25,26} A clinical study using the CHG gel also showed it to be effective at reducing CR-BSIs.\textsuperscript{27} Studies in healthy humans have shown that both of these products maintain the skin microflora near post-antisepsis levels underneath film dressings applied to prepared skin,\textsuperscript{19} and both have an antiseptic effect on native skin flora.\textsuperscript{28} Comparison with other published data offers some insight into how the CHG adhesive performs relative to the established products.

This investigation followed a protocol similar to the time–kill study of Maki et al.\textsuperscript{37} against resident flora \textit{in vivo}, including virtually identically techniques used for quantitative cultures and similar sample sizes. Interestingly, direct comparison with those data reveals that the CHG adhesive’s antimicrobial activity was very similar to CHG foam’s antimicrobial activity on days 1, 4 and 7, and also to CHG gel’s antimicrobial activity on days 1 and 7. In contrast, recoveries from underneath the control adhesive were markedly higher than those from under any of the three CHG-containing products on days 4 and 7. The favourable comparison between CHG adhesive, CHG foam and CHG gel suggests the possibility that the CHG adhesive may provide significant clinical benefit by combining antisepsis with the useful properties of film dressings (e.g. transparency for ease of site visualization, thinness and conformability), but further clinical studies will be needed to establish whether or not there is a protective effect against catheter-related infections.

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Transparency declarations

Vancive Medical Technologies\textsuperscript{TM} is an Avery Dennison business. N. C., A. W., C. W. and P. J. are employees and stockholders of Avery Dennison, which, as the manufacturer of the BeneHold CHG Transparent Film Dressing has a financial interest in the study’s test product. D. S. P.: none to declare.

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