RISK OF INFECTION FROM APPLICATION OF TWO TYPES OF PHARMACEUTICAL CREAMS

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ABSTRACT

Introduction: Infection risk from the misuse of multi-dose medicinal products is a serious problem which affects final consumer health and may impact on the reputation of pharmaceutical companies adversely.

Objectives: The current study aimed to trace the most important contributing factors in the infection transfer through the application of two selected types of medicinal topical creams for the treatment of skin disease conditions.

Methods: One type of the product that was subjected to the present study is anti-psoriatic while the other is steroidal anti-inflammatory antimicrobial creams that were packed in Aluminum tubes with orifice diameter of 0.173 cm^2, approximately. The simulation study – conducted on these topical creams - integrated preservative efficacy test (PET) with dose-response model of infection to demonstrate the probability of infection that could occur due to unintentional transmission of pathogenic bacteria to damaged or injured skin of the patient.

Results: The studied model showed that although both products possessed antimicrobial power activity against standard strain microorganisms, yet the critical factor is the hygienic control of hands and fingers during application of the cream on the affected area.

Conclusion: The medicinal products itself were little affected by microbial contamination when they were enclosed in their primary packaging materials as was observed by the in-use study. However, the most important part was that portion of the product that was transferred to the patient skin. From the simulation study, it was expected that the situation could be aggravated if the hygienic practice was underestimated with hospital staffs.

UDC CODE & KEYWORDS

■ UDC: 613.6 ■ Multi-dose medicinal products ■ Topical creams ■ Simulation study ■ Preservative efficacy test ■ Dose-response model

INTRODUCTION

Healthy skin provides an effective hindrance against microbial invasion. However, for harmed skin the infection hazards are dramatically expanded. Multi-dose packaged products, especially those utilized by more than one individual, are liable to microbial intrusion, particularly in the healthcare centers, and there are reports of disease episodes from the use of such items. Pseudomonas aeruginosa is considered one of the most problematic nosocomial pathogen due to its ability to disseminate through medicinal products, even those with antimicrobial properties (Denyer and Baird, 2007).

Indeed, pharmacopeial guidelines are clear in stressing in microbiological testing of not only total aerobic microbial count (TAMC) and total yeast mold count (TYMC), but also both Staphylococcus aureus and P. aeruginosa should be strictly absent from the topical cream products. Topical creams possess high water activity (aw) of value about 0.97 which may encourage their spoilage if they were not well preserved (Clontz, 2009).

The current studied case aimed to examine the contributing factors in infection transfer through well-preserved two medicinal creams and to elucidate the value of reliance on cidal power of the product on the probability of infection using simulation of contamination approach. The imitation study would provide the evidence for the modifications and approaches required to optimize the antimicrobial study guidelines with the aim to provide safe administration and application of the pharmaceutical products during handling and use.

Material and Methods

Microbiological testing of the topical products:- Microbial limit test for the quality of two cream products was conducted as per compendial requirements (United States Pharmacopeia (USP) chapter<61>, 2015 and USP chapter<62>, 2015) and both were clean and showed absence of S. aureus and P. aeruginosa as objectionable microbes. One of the topical products was antimicrobial anti-inflammatory cream and the other for treatment of psoriasis. The following examination was preservative efficacy test (PET - USP chapter<51>, 2015) which demonstrated in Table 1. The standard strains that were detailed in Pharmacopeia were S. aureus (ATCC 6538), P. aeruginosa (ATCC 9027), Escherichia coli (ATCC 8739), Candida albicans (ATCC 10231), Aspergillusbrasiliensis (ATCC 16404) and Burkholderia cepacia (water-borne isolate that has been included in the test to verify the efficacy of the preservation system against this objectionable microbe). Burkholderia cepacia was identified using biochemical identification system. An investigation of the probability of infection using two indicators microbes was conducted using the results of antimicrobial efficacy test (AET). First of all, a simulated method of product application on a damaged skin was designed as the worst scenario of the product use. The detailed quantitative study of infection transfer was conducted as the following:

Integrating AET with infection risk from the applied medicinal products:- Dose-response models of infection were selected for selected indicator microbes (microbial reference per route of administration) which have the following parameters: S.

aureus followed exponential model with $k = 7.64 \times 10^{-08}$ for subcutaneous route of administration as demonstrated by Rose and Haas (1999). aeruginosa followed two types of models, exponential and Beta-Poisson. The first model is suited for bacterimia with $k = 1.05 \times 10^{-04}$ as shown by Hazlett et al. (1978).The second approach was adopted by Lawin-Brussel et al. (1993) with $\alpha = 0.19$, $N_{50} = 1.85 \times 10^{04}$.

Method of application and transfer of the specific pathogen or microbe of interest could be quantified and calculated by the following equation:

$$D = T.W + S.\ (K + (I/R)) \qquad (1)$$

D = Dose of specific microorganism received by patient as colony forming unit (CFU)

T and W = Density of objectionable microbe (T) (CFU/g) per certain weight (W) (g) of the applied product for the affected individual.

S = Density of the pathogenic microbe in certain area of the skin of the applicator (CFU/cm^2).

K = Area of the hand used in the application of the cream on the affect skin of the patient (cm^2).

I = Internal surface area of the orifice of the aluminum tube for the cream (cm^2).

R = Reduction factor of the microbial population within specific dosing interval time.

Aluminum tube orifice diameter about 4.70 mm, surface area = 0.173 cm^2. Measurement of the area of one finger used partially in spreading the cream was about 10 cm2. All measurements were made by electronic caliber. Range of skin flora count = 100 - 1000 CFU/cm^2, of which S. aureus contributes to about 25% of the total bioburden as demonstrated by Kowalski (2012) and Todar (2017). On the other hand, P. aeruginosa has minimum infective dermal dose of 1000 CFU (Leggett, 2012).

Reduction factor for topical corticosteroid antimicrobial (Rc) and antiposriatic (Ra) creams were >1.35 and >1.54, each per successive application intervals respectively. In the absence of any microbial recovery from both products R_c and R_a was considered as a cut-off threshold values for further calculations. The product innate contamination was excluded because it was previously tested for the absence of both microorganisms. This will reduce equation (1) into equation (2). When assuming fixed orifice area for both tubes of the cream products and the part of the hand (or finger) that is used for application of the product, then equation (3) is obtained:

$$D = S.\ (K + (I/R)) \qquad (2)$$

$$D = S.\ (10 + (0.173/R)) \qquad (3)$$

When applying the equation (3) for both types of cream products equations (4) and (5) developed for topical corticosteroid antimicrobial (D_c) and anti-posriatic creams, respectively (D_a). Equations (4) and (5) showed in the present case that the dermal hygiene of the applicator of the topical medicine plays major role in the transmission of the infectious microbes to the patient's skin. Thus, both equations could be regarded equivalent to each other.

$$D_c = 10.13.S_c \qquad (4)$$

$$D_a = 10.11.S_a \qquad (5)$$

The assumed continuous contamination model delivers constant amount of contamination with each use. This is because with each handling of the mender for the tube through the opening, the dermal flora of the finger will contaminate the surface of the cream in the tube orifice (not mixed with the remaining amount with the whole tube, in contrast of the liquid products). This microbial bioburden in the cream surface will be delivered in the next application of the dose.

Results and Discussion

Results of PET are shown in Table 1 and demonstrated the efficacy of the preservation system. Both products met and exceeded the acceptance criteria (i.e. showed antimicrobial activity) stated by the pharmacopeial (United States Pharmacopeia, 2015a, 2015b, 2015c) guideline. The selected models used indicator microorganisms at worst scenario to account for maximum risk i.e. assume damaged skin with possible thinning of the dermis layer, exposed subcutaneous tissues or bleeding injured skin area. A control group was introduced concurrently with the test group but the cream products were replaced with saline. The microbial count of the control group was within the normal counting variability as indicated by Clontz (2009) i.e. there was no significant reduction and hence any decrease in bioburden of the inoculated products can be attributed to the pharmaceutical formulae alone. Table 2 showed the results of interpretation for the simulated scenario of the assumed method of cream application.

The present case study showed that P. aeruginosa possesses significant health risk hazard over S. aureus about 520 times (exponential) and over 990 times (Beta-Poisson). The hand hygiene is crucial in infection transfer rather than the product as could be deduced from the current investigation. The criticality of using contaminated hands in the healthcare settlings have been demonstrated by researchers in the medical field such as Kampf and Kramer (2004). The application of quantitative measurement of the probability of infection provided a mean for evaluation of the process and practice of medicinal products use and handling. Moreover, it provides scientific approach in decision making and risk assessment (Eissa, 2016). In addition, it revealed the limitations of the guidelines of evaluation of microbiological safety of multi-dose products with significant a_w.

After the second application of the products no increase of microbial count would be expected theoretically provided that the microbial flora of the therapist hand did change significantly. This could be attributed to the limited contamination sourced from the product in addition to the continuous wash off the microbes from the surface of the cream and addition

of new contaminant with each use. However, the problem will be intensified when considering creams prepared in wide-bore jars where it is common to penetrate the product with bare fingers and hence spoilage of the topical product may also happen. If medical staff overlooked the simple but essential hand sanitization, the risk of cross contamination between products and patients may exacerbate infection problems. The previous analysis showed that the transfer medium (hand or finger) may play major rule in infection dissemination. Cream is usually absorbed fast and with comparison with contact time in AET it may not have enough time to suppress extraneous bioburden on patients. On the other hand, It should be noted that in-use simulation study of these creams did show any significant contamination of the enclosed intact packaged-products.

Literally, the conducted PET test showed that both creams not only met the acceptance criteria but also possessed cidal activity against microbes. But, the actual imitation of the product usage showed that short interval of extensive use of the medicine is more important rather than the too long test interval because if the “washout” effect of the medication not enough, then the built-up of contamination will overcome the killing rate of the formulation. Eventually, the patient may be infected when sufficient dose (CFU) of the microbe is reached. The lengthy study is more suited for product hold on the shelf or long storage after opening of the package with few uses of the product and leaving the remainder for long time before conducting another application. The new approach of studying infection risk through drug use can provide a milestone for investigation other types of formulations, dosage forms with different antimicrobial activity, different microbes and various disease conditions. In the same line, Elder and Crowley (2012) demonstrated similar prospective view that should involve broader insight for AET rather than relaying on routine pharmacopieal test only.

Table 1: Preservative efficacy test results of selected creams based on USP chapter<51>(2015).

Dosage Form	Microorganisms	Logarithmic Reduction in Testing Days		Antimicrobial Components of Product	Dosage and Frequency
		14	28		
Topical antimicrobial anti-inflammatory cream	S. aureus*	>5.48	>5.48	Neomycin, Gramicidin, Nystatin, Methyl- and Propyl Paraben	5g x 3 times/Day x 15 gm tube
	E. coli*	>5.48	>5.48		
	P. aeruginosa*	>5.48	>5.48		
	B. cepacia*,†	>5.48	>5.48		
	C. albicans*	>5.23	>5.23		
	A. brasiliensis*	>5.30	>5.30		
Anti-psoriatic cream	S. aureus*	>5.38	>5.38	Benzalkonium Chloride and EDTA	7g x 2 times/Day x 20 gm tube
	E. coli*	>5.00	>5.00		
	P. aeruginosa*	>5.18	>5.18		
	C. albicans*	>5.18	>5.18		
	A. brasiliensis	4.44	>5.04		

* = Microorganisms that have not been recovered at any stage of the test from the recovery medium.
† = Non-pharmacopeial, water-borne isolate was included in the study of the products from facilities from which this microorganism was found and identified using BBL™ Crystal™ Enteric/Non-fermenter ID Kit as described by Ashour et al., 2011.

Source: Author

Table 2: Dose-Response models of infection applied on two types of topical cream.

Model	Product	Probability of Infections from Doses		
		1st Application	2nd Application	3rd Application
S. aureus (Exponential)	Antimicrobial Anti-inflammatory	<0.000191	<0.000194	<0.000194
	Antipsoriatic	<0.000191	<0.000193	<0.000193
P. aeruginosa (Exponential)	Antimicrobial Anti-inflammatory	<0.099675	<0.100904	<0.100904
	Antipsoriatic	<0.099675	<0.100715	<0.100715
P. aeruginosa (Beta-Poisson)	Antimicrobial Anti-inflammatory	<0.189507	<0.190839	<0.190839
	Antipsoriatic	<0.189507	<0.190635	<0.190635

Source: Author

CONCLUSION

The current case highlighted that the method of handling and the degree of sanitary behavior of the medicinal product applicator has the greatest influence to the patient health especially if the skin is damaged. It is recommended to include shorter intervals for PET test and study all other factors that may contribute to the possible product infectivity - including container geometry (either tube, wide-bore jar or any other type of reservoir) - to the patient rather than reliance on the killing ability of the medicinal product to judge its safety to the consumer administration.

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