

Evaluation of Dermal Irritation and Skin Sensitization by Curaderm

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Abstract

Purpose: To establish whether Curaderm, a topical pharmacotherapy for skin cancer, irritates or sensitizes normal skin. **Methods:** The dermal irritation and skin sensitization toxicity of Curaderm were investigated in rabbits and guinea pigs in compliance with the Organization for Economic Cooperation and Development guideline. To assess dermal irritation, rabbits were dermally exposed to Curaderm for varying periods of time. To assess hypersensitivity, the guinea-pig maximisation test was applied. **Results:** Curaderm was only negligibly irritating using the criteria of erythema and oedema. Curaderm did not produce any sensitization toxicity of the skin. **Conclusion:** These studies confirm the non-toxic observations on normal skin experienced in the clinical setting when treating skin cancer and reinforce the specificity of Curaderm towards cancer cells.

Keywords

Curaderm, BEC, Solamargine, Skin Cancer, Dermal Irritation, Skin Sensitization, Psoriasis

1. Introduction

In 1987, it was reported that plant-derived glycoalkaloids—BEC [1] induced anticancer effects in cell culture [2] [3] [4], animals [5], and humans [6] [7].

BEC, the initials of the inventor of this technology, is composed mainly of solamargine and solasonine [1]. The anticancer effect of solamargine is 9 times more potent than solasonine [8].

Since then, a plethora of further investigations has taken place resulting in the placement of BEC as a very promising antineoplastic agent with vast potential to serve as a targeted anticancer agent [9]-[23].

Anticancer efficacy studies have determined that BEC specifically targets a

wide variety of cancer cells [24], but has no deleterious effects on normal cells [25]. Toxicity studies of BEC have been well documented [8].

Consequently, cream formulations for the treatment of skin cancer in humans were investigated. Ultimately, an effective topical cream formulation, Curaderm, was devised [6] [25]-[30]. Very low concentrations of BEC are present in Curaderm, corresponding to similar concentrations of BEC used in cell culture and animal anticancer studies.

Moreover, the amount of BEC in one tube (20 mL) of Curaderm is 1 mg BEC and is equivalent to the content of BEC in 10 grams of eggplant fruit [25] [31].

In addition, toxicological studies have shown that at this concentration of BEC, it is completely harmless [5].

However, in order for Curaderm to be effective, at very low concentrations of BEC, for treating skin cancers, keratolytic agents were necessary to enhance the bioavailability of BEC with the skin cancer cells [18] [32].

The concentrations of the keratolytic agents in Curaderm are within the concentration range that is found in many skin care products. Notwithstanding the apparent safety profile of the separate ingredients in Curaderm, it was considered appropriate to conduct biocompatibility studies with Curaderm that entailed all ingredients in Curaderm representing the end product that is used by patients. The reason for this approach is to ensure that the individual components in Curaderm do not interact with one another to exert properties of unknown and/or unwanted sequelae. For example, in a positive manner, it was recently reported that BEC shows a synergistic anti-cancer effect with cisplatin [24].

Similarly, BEC when added to an anti-psoriasis cream formulation vastly improves its therapeutic effect [33].

The significance of having available an effective, safe and simple treatment for skin cancer and psoriasis is of paramount importance. For example,

- The incidence of skin cancer is higher than all other cancers combined.
- The incidence of skin cancer is rapidly increasing worldwide.
- Skin cancers are major causes of morbidity and mortality.
- The cost of skin cancer in the USA alone is US\$1.5 billion yearly and rapidly increasing. This is of concern to the Health Care System and public [34].

Similarly, psoriasis is a chronic autoimmune disease that affects 1% to 3% of the general population and involves an estimated 4.5 to 7.5 million Americans. The effects of the disease on the quality of life or physical and emotional well-being are well known. The heavy economic burden of psoriasis has been estimated to exceed US\$3 billion to the Health-Care Industry annually [35].

The strengths and limitations of currently used treatments for skin cancer and psoriasis have been documented. There is no doubt, a great need for simple, safe and effective treatments for these diseases are required. The safety studies reported in this communication contribute partly to the establishment of such a requirement.

2. Materials and Methods

The biocompatibility procedures were followed by the recommended ISO 10993-10:2010-current edition procedure. The animal welfare requirements were according to ISO 10993-2:2006-Part 2: Animal welfare requirements.

Curaderm cream in a 20 mL tube. Batch number 014672 was obtained from Curaderm Global Limited. Curaderm was composed of 5 mg% BEC, 10% salicylic acid and 5% urea in a stabilized cetomacrogol cream base.

Rabbits

Three male White New Zealand rabbits weighing 3675 - 3690 grams were used.

Before commencement of this study, the rabbits were kept in quarantine and were acclimatized for one week. They were observed daily during this period. At the end of the quarantine week, the rabbits were carefully examined to evaluate their suitability for the study. Animals were then randomly selected from the suitable assessed group.

Each rabbit was housed in NORYL cages with the dimensions of 70 cm × 70 cm × 47 cm height, the cages were identified by a label. The animal facility was maintained as recommended by ISO 10993-2:2006-Part 2: Animal welfare requirements, and a 12 h light/dark cycle with fluorescent lamps throughout the experiments. The room temperature and humidity were regulated by an air conditioning unit and were continuously monitored.

The cages and the housing room were cleaned before accommodation of the rabbits and subsequent cleaning and disinfecting were periodically performed. The rabbits were fed with a standard pellet complete diet (LAP KLIBA). Filtered tap water was supplied ad libitum. The animals were identified by number tagging through the edge of the right ear.

Treatment region

The right caudal region and left cranial region of each animal were treated with 0.5 mL Curaderm cream per each region. As control, an established non-irritant gauze (25 mm × 25 mm) humidified with physiological solution was applied to the right cranial region and the left caudal region.

Skin preparation

Approximately 24 hours before commencement of the test, the fur was removed from an area of approximately 240 cm² wide by clipping and shaving the dorsal and flank zones of the animals. An area of the back of approximately 6 cm² was used for the application of 0.5 mL test samples directly to the skin and covered with a non-occlusive dressing, thus protecting the trunk of each rabbit. The patches were removed 4 hours after application.

General conditions of the animals were verified daily. Reactions were evaluated following the removal of the patches and were evaluated again at 24, 48 and 72 hours after exposure. Skin irritation was scored and recorded to the scores reported in **Table 1**.

Acute dermal irritation

Table 1. Scoring of skin irritation.

GRADING VALUES	
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness with slight eschar formation; injuries in depth)	4
Oedema formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

The acute dermal irritation study was performed in accordance with the ISO 10993-10:2010-current edition guidelines. Dermal responses were determined in accordance with OECD guidelines. Erythema and Oedema were scored on a scale of 0 - 4, with 0 showing no effect and 4 representing severe symptoms reported in **Table 1**.

Interpretation of the observations

For the acute exposure, the Primary Irritation Index (PII) is determined as follows.

For each animal, the PII scores of erythema and Oedema for Curaderm were added at each specified time point. These values were then divided by the total number of observations (two tests/observation sites) with the three time points.

The PII of the controls were similarly calculated and these values were then deducted from the scores of the Curaderm treatment.

This resulted in the PII score of Curaderm at the observation times 24, 48 and 72 hours. The scores for each animal were added and then divided by the total number of animals yielding the value of PII for Curaderm.

Table 2 shows the criteria used for the evaluation of Curaderm's Primary Irritation Index.

Guinea Pigs

Eighteen guinea pigs weighing 300 - 500 grams were used in the Delayed Hypersensitivity Test, also known as the Guinea Pig Maximisation Test (GPMT).

A group of 10 animals was treated with Curaderm, a group of 5 animals served as controls and another group of 3 animals were used for preliminary testing. The GPMT consisted of a preliminary test, an induction phase and a challenge phase.

The housing and conditions of keeping the animals were as described for the

Table 2. Characterization of the primary irritation index.

Response category	Mean score
Negligible	0 to 0.5
Slight	>0.5 to 2
Moderate	>2 to 5
Severe	>5 to 8

rabbits, with the exceptions that all animals were non-pregnant females and they were caged in groups of five in NORYL cage with the dimensions of 74.3 cm × 54.3 cm × 25 cm. The animals were fed with a standard complete diet (KLIBA).

The preliminary test was used to determine the appropriate concentration of Curaderm cream for use in the sensitization test. Neat (100%), 90%, 80%, and 70% of the Curaderm formulation was tested.

When appropriate, Curaderm was diluted with sterile physiological Sodium Chloride solution. No erythema was observed with the diluted or neat Curaderm.

Consequently, undiluted, neat Curaderm was used for the topical application for the induction and challenge phases.

For the suitability of the injection at the induction phase, Curaderm was diluted 1:1 (mL/mL) with intradermal stabilized emulsion injections containing Freund's complete adjuvant and sodium chloride.

The skin sensitization test was conducted according to the OECD guideline.

One day before the first induction, fifteen healthy guinea pigs were assigned to two groups: a placebo group (n = 5), and a transdermal patch Curaderm—treated group (n = 10). Approximately 50 cm² wide area on the back of each guinea pig was clipped for experimental use. Transdermal patch was applied to the shaved area of each animal at the induction phase.

On day zero, 0.1 mL was injected intradermally in the interscapular region of each animal on each side of the midline. Six days after the induction, topical application occurred by gentle massage. Seven days after the intradermal injections, 0.5 mL of the test sample or placebo was applied to the corresponding animal and held in place with an occlusive patch. The dressing was left in place for 48 hours.

The challenge phase occurred 14 days after the topical induction phase. An occlusive patch with 0.5 mL of the Curaderm sample was applied to the right flank of all 15 guinea pigs, whereas sodium chloride solution was applied to the left flank. The dressing was left in place for 24 hours. 24 and 48 hours after removal of the patches all treated and control animals were evaluated for possible skin reactions. The intensity of erythema and/or oedema was evaluated according to the scale in **Table 3**.

Positive controls

Reliability of the experimental procedures was validated every six months using positive controls with Mercaptobenzothiazole according to OECD 406 and ISO 10993-10.

Table 3. Grading of the intensity of erythema and/or oedema.

Patch test reaction	Grading scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

3. Results

Skin irritation test in rabbits

A slight erythema was detected in all treated sites of three animals at 60 minutes and 24 hours after removal of the dressing. A slight erythema was observed in all treated sites of one animal (number 1200), 48 hours after removal of the dressing. No changes were detected at all sites of all three animals 72 hours after removal of the dressing. Similarly, no changes were detected at all control sites throughout the experimental period (**Table 4**).

With this assessment, it was concluded that the Primary Skin Irritation index (Treated minus Control) is 0.44 and is considered NEGLIGIBLY IRRITANT to the skin.

Delayed hypersensitivity test in guinea pigs

No sensitization was noted among the guinea pigs that were challenged with Curaderm patch or with the placebo patch. Similarly, no erythema or oedema was observed after the challenge with Curaderm or placebo. None of the ten Curaderm treated rabbits produced skin reactions at 24 hours and 48 hours after the patches were removed. This was also the case with the five control animals.

Positive controls

The sensitivity and reliability of the experimental procedure are assessed every 6 months following the conditions of OECD 406 and ISO 10993-10 by the centre carrying out this study. During the current study period a reliability study was performed utilizing 2% Mercaptobenzothiazole in cottonseed for the intradermic injection at the induction phase, 45% Mercaptobenzothiazole in cottonseed for the topical application of the induction phase and 30% Mercaptobenzothiazole in cottonseed oil for the challenge phase. Fifty percent of the treated animals showed a positive skin reaction, whereas, the control placebo animals showed no skin reactions.

During the experimental period, the general wellbeing of all animals was monitored and was not affected.

4. Discussion

It is usual practice to evaluate “new” substances that are to be introduced into the marketplace for possible risks that may affect the end user.

The toxicity of BEC has been evaluated with cell culture studies, animal studies and human studies resulting in high safety outcomes at therapeutic concentrations.

Table 4. Evaluation of skin irritation of Curaderm and placebo controls over 72 hours observation in rabbits.

Time After Removal of Patch	REACTION	RABBIT N.											
		1200				1206				1213			
		TREATED		CONTROL		TREATED		CONTROL		TREATED		CONTROL	
		CA	CR	CA	CR	CA	CR	CA	CR	CA	CR	CA	CR
		dx	sx	sx	dx	dx	sx	sx	dx	dx	sx	sx	dx
60 minutes	Erythema	1	1	0	0	1	1	0	0	1	1	0	0
	Oedema	0	0	0	0	0	0	0	0	0	0	0	0
24 hours	Erythema	1	1	0	0	1	1	0	0	1	1	0	0
	Oedema	0	0	0	0	0	0	0	0	0	0	0	0
48 hours	Erythema	1	1	0	0	0	0	0	0	0	0	0	0
	Oedema	0	0	0	0	0	0	0	0	0	0	0	0
72 hours	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
	Oedema	0	0	0	0	0	0	0	0	0	0	0	0

CA = Caudal, CR = Cranial, dx = Right, sx = Left.

The approval of a drug to enter the market place is achieved after passing Phases I, II and III of clinical trials. The success of a drug depends on the outcome of Phase IV clinical trial observations showing that the new drug has been proven to be safe for its use by the general public. An example has occurred recently whereby a drug for the treatment of keratosis had to be withdrawn from the marketplace because of unacceptable side effects observed during Phase IV observations. In order to minimize such occurrences, tests such as irritation tests and sensitivity tests of the new drug are carried out. Although help-full, these tests do not guarantee full safety.

The new active ingredient of a formulation may be biocompatible with the skin, but it is the full formulation that the public will use that has to be safe.

In the current study, irritation of Curaderm to the skin has been investigated by assessing its erythema and oedema effects on the skin. Erythema is redness of the skin caused by hyperaemia of superficial capillaries. Oedema is the swelling caused by fluid in the body's tissue.

Under the conditions studied, Curaderm was negligibly irritant to the skin. This is not surprising, since 10% salicylic acid and 5% urea were added to the formulation to obtain improved bioavailability of BEC with the skin cancer cells [32], without harming normal skin. The limitation of the current investigation is that not all parameters that may indicate irritation or sensitivity were studied.

It is interesting that in the clinical setting when treating skin cancers with Curaderm, no adverse reactions are observed when Curaderm is applied to normal skin surrounding the skin cancer lesion. However, the reported reactions of transient erythema, pruritis, swelling, postulation and ulceration of Curaderm therapy with actual skin cancers appear to be related to BEC in Curaderm specifically interacting and disposing of the cancer cells.

These results also explain why the observed side effects are minimal when Curaderm is used by the public to treat skin cancers [36].

The results in this communication show that Curaderm is negligibly irritating to the skin of rabbits and that there is no sensitization of Curaderm to guinea pigs, supporting the clinical observations in humans who are treated with Curaderm for skin cancer.

5. Conclusions

Treatment of skin cancers with Curaderm has reportedly resulted in impressive efficacious and cosmetic outcomes. To have a treatment available that specifically seeks out and destroys cancer cells by stimulating apoptosis and yet does not affect normal cells is a rare phenomenon. BEC in Curaderm is a targeted therapy for treating skin cancers. This is unlike other skin cancer treatments, including surgery.

The results in this communication enforce the clinical observations that pharmacotherapy of skin cancers with Curaderm results in the removal of cancer cells without affecting normal cells resulting in the impressive cosmetic outcomes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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