

Treatment outcome of *Paederus dermatitis* due to rove beetles (Coleoptera: Staphylinidae) on guinea pigs

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Abstract. Linear dermatitis (or dermatitis linearis, DL) is a skin blistering inflammatory lesion caused by exposure to the pederin toxin from rove beetles. Although it is prevalent in many countries of the Middle East region, this is not a notifiable disease. In recent years, a number of clinical symptoms outbreaks of DL has been reported from a few neighboring countries of Iran, but no report of experimental treatment among small laboratory rodents is known. This is a prerequisite to ascertain the nature of the best treatment strategy in cases of infestation with these beetles, as it occurs among local settlers during hot seasons in certain parts of the southern Iranian province of Fars. Live *Paederus* beetles were collected, identified to species level, sexed apart and partly processed to obtain their hemolymph toxin pederin in ethanol for dermal application on guinea pigs. Two *Paederus* species were found. *Paederus ilsae* (Bernhauer) (Coleoptera: Staphylinidae) was more abundant than *P. iliensis* (Coiffait). Recovery from DL due to live *P. ilsae* beetles was quicker and less complex than that of pederin in ethanol on guinea pigs. The application of potassium permanganate with calamine to heal DL was also more effective than fluocinolone treatment. This topical corticosteroid is thus considered less able to avert the cytotoxic action of pederin on the skin of guinea pigs than the antipruritic and cleansing agents. It seems likely that fluocinolone has certain effects which delays the recovery period for the treated skin.

INTRODUCTION

Linear dermatitis (or dermatitis linearis, DL) is a widely neglected insect-induced skin lesion especially in the tropics. It has been reported from many countries in the world including those in the Middle East and Far East; Iraq (Davidson *et al.*, 2009), Iran (Zargari *et al.*, 2003), Turkey (Sendur *et al.*, 1999), Afghanistan (Chambers, 2003), Pakistan (Kakakhel, 2000) and South Korea (Kim *et al.*, 2007). It appears as a superficial linear lesion caused by various

species of rove beetles in the genus *Paederus*. DL is a seasonal self-healing form of acute irritant erythematous lesion characterized by vesiculopustules on intensely inflamed skin (Brazzelli *et al.*, 2002). It is due to contact with the extremely vesicating polyketide cytotoxin pederin exuded from rove beetles, when they are accidentally rubbed onto the skin (Frank & Kanamitsu, 1987; Frank, 2008). Pederin is synthesized by bacterial endosymbionts and protects chemically against predators (Kellner & Dettner, 1996;

Kellner, 2002; Haine, 2008). A pederin-like cytotoxin has also been isolated from a marine sponge (Ueoka *et al.*, 2009).

No immediate histopathological effect is evident, so only a small number of patients who seek medical care are properly diagnosed. Subsequently, the haemolymph toxin pederin penetrates the intact human skin which turns red with a burning sensation and the first clinical signs appear only about 24-72 h later. This period of unresponsiveness from the time of pederin dermal application to the time of first erythematic appearance is called the latent period (McCrae & Visser, 1975). After a few days, vesicles form which typically fuse into bullae enduring 7-15 days and finally crust over, dry and get detached leaving transient red hyperpigmentation spots for months. An average dose of about 1 µg per every *Paederus* induces an inflammatory reaction with blisters and subsequent necrosis (Borroni *et al.*, 1991). The LD₅₀ (the lethal dose to kill 50% of animals) of pederin for domestic mouse, rat and guinea pig is about 2 µg/100g of their body weight (Brega *et al.*, 1968). All lesions, however, typically disappear within two to three weeks (Zargari *et al.*, 2003).

DL is widespread in the northern and southern provinces of Iran. In southern Iran, *Paederus ilsae* (Bernhauer) and *Paederus iliensis* (Coiffait) (Coleoptera: Staphylinidae) are active from late April to early September. In addition, *P. ilsae* produces more severe and long-lasting ulceration than *P. iliensis* (Nikbakhtzadeh & Sadeghiani, 1999). These beetles are locally known as “Balaloos” or “Onion fly” in this region for decades, and referred to as “Dracula” in the north of Iran. The rove beetles pose a considerable public health threat since they are small (size ≤1 cm), able to run or fly, nocturnally active, positively phototactic, and associated with high humidity along ditches and cultivated croplands to defer becoming dehydrated during dispersal flights, since their wings (elytra) are vestigial only partially covering their first abdominal segments (Veraldi & Suss, 1994).

Few attempts have been made in the past to report the treatment of DL using topical or systemic corticosteroids, cleansing and antipruritic agents. Topical corticosteroids are used for the treatment of dermal inflammations and localized lesions. The comparative efficacy of fluocinolone cream, triclocarbon soap and betamethasone lotion in the treatment of DL was recently investigated on 77 patients in the north of Iran (Davoudi *et al.*, 2006). The main aim of the present study was to determine the effects of fluocinolone cream compared to potassium permanganate solution with calamine in the treatment of DL on guinea pigs by the cytotoxin pederin from *Paederus* rove beetles. There appear to have been no previous reports on the experimental treatment of DL among laboratory animals.

MATERIALS AND METHODS

Sample site collection

Beetles were collected using aspirators from the beginning of May to end of October. Sampling was performed at night twice weekly. Their flight activity reached a peak following the rainy season. Night catches were performed from one hour after sunset to midnight near fluorescent lamps which mostly attracted adult beetles and stood at fixed vertical stations 150 cm above ground. An aggregation focus of *Paederus* beetles was also found in the key electrical and motor installations room of Kavar School of Sciences and Technology (52°43'41"E, 29°11'32"N at an altitude of about 1386 m above sea level) about 45 km to the south east of Shiraz, Fars province, Iran. The high humidity and temperature at this place provided the necessary conditions for beetles seeking shelter, although other factors such as aggregation pheromones could be equally important. Beetles were forced out of crevices and cracks in the building wall by pouring warm water. They quickly crept out of their shelters and wandered around (hence called rove beetles) curling the tip of their abdomen up like scorpions. Using forceps

or aspirators, they were caught and mostly transferred to screw capped vials containing about 10 ml of 70% ethanol (50 beetles per vial).

Sample identification and toxin extraction

Beetles were taxonomically identified on the basis of their morphological features using valid keys (Coiffait, 1982). The predominant species which could be responsible for most clinical symptoms in this region was selected out. Species of beetles were sexed apart. Only female insects were used to extract their coelomic fluid, since they mostly carry the symbiotic bacteria responsible for pederin biosynthesis as a defense against potential predators and produce eggs which have the bacteria in their outer shell walls. More than two and a half dozens of them were kept alive for direct rubbing onto the skin of guinea pigs. The procedures were approved by the institutional ethics committee on laboratory animal research. Overall, 200 *P. ilsae* were ground by pestle in a mortar to get aliquots of their haemolymph with pederin. The mixture was transferred to 40 ml of absolute (100%) ethanol and shaken vigorously 2-3 times daily for the next three days. It was then filtered through Whatman filter paper into a conical flask to get a stock concentrated solution.

Rodent treatment

Only 30 adult male guinea pigs (white Abyssinian homogeneous stock) were used to test the therapeutic efficacy of various chemicals, since females were usually obese and subject to enormous hormonal fluctuations that could influence the experimental outcomes. They were allocated to six cages, animals in each cage subjected to a different treatment. Animals in two cages (10 guinea pigs) were used for the treatment with live *Paederus* and pederin in ethanol, both without medication (control). Fluocinolone (0.025%) cream and potassium permanganate with calamine solution were

medicated for the second and third pair of caged guinea pigs following live beetles or pederin toxin in alcohol administration. Each male guinea pig was shaved on part (4x5 cm) of its posterior dorsal surface (dorsum) to make its skin exposed to treatment. Equal volumes of toxin (0.5 ml, representing 2.5 *Paederus* beetles) were gradually dripped onto their skin and subsequently rubbed for 2 min to get maximal absorption. Alternatively, two live *Paederus* beetles were crushed on the dorsum of each guinea pig. Temperature and humidity values were simultaneously recorded. After two days, on the appearance of first dermal manifestations, 10 ml potassium permanganate was used to wash the dorsum and then 5 ml calamine lotion was applied after one hour. Alternatively, about one centimeter of fluocinolone cream was rubbed onto the dorsum after two days. These medications were done twice daily (every 12 h) and the signs were accordingly recorded.

Data analysis

Data on each treatment and its corresponding medication were processed by Kruskal-Wallis 1-way Anova and confirmed by the median test using SPSS software version 16. Results with $p < 0.05$ were considered to be statistically significant.

RESULTS

A total sample of 458 beetles was collected in the district of Kavar. Two species of beetles, namely *P. ilsae* (92%) and *P. iliensis* (8%), were identified. The former species was clearly predominant over the latter. They were mostly associated with leaf litter among hay grass, *Medicago sativa*. The sex ratio of *P. ilsae* was about 1:1 (55.1% females *v.* 44.9% males). There was a latent period of approximately two days for all treated and untreated (control) guinea pig groups. No evidence of dorsal dermal reaction was apparent up to the first 48 h post-exposure to *Paederus* or pederin

in alcohol. Treatment with live *Paederus* produced a similar but quicker and simpler response than pederin in alcohol (Table 1).

At the end of the latent period, all three groups (control, fluocinolone and potassium permanganate with calamine) exhibited inflammation with maculae. Drug treatments were thus initiated in the last two groups. On the third and fourth day post-exposure, erythema was progressing in the control groups, while it was diminishing in the drug-treated groups. From this stage onward, a series of pathological reactions from dermal desquamation to necrosis exacerbated the skin disorder in the control groups. One of the cavies in the control group died on the 10th day post-exposure due to the destruction of the dermal layer, intensive bleeding and septicemia emanating most likely from secondary bacterial infections. Following the use of living *P. ilsaе* beetles (Figure 1a), the corresponding pathological reactions were quickly resolved and milder than when the pederin toxin in alcohol was applied (Figure 1b). The adverse reactions were prevented from developing by the administration of drugs in the fluocinolone-treated or potassium permanganate with calamine-treated groups.

On analyzing the outcome of various treatments on guinea pigs, it was generally found that the potassium permanganate with calamine group produced the highest (78.89%) average signs interval reduction

for each guinea pig treated with pederin in alcohol (Table 2). The lowest (62.70%) average signs interval reduction for each guinea pig treated with live beetles was the group administered with fluocinolone cream. The difference between these percentages was significant ($p < 0.05$) indicating the therapeutic effect of these cleansing and antipruritic agents in averting the toxic properties of pederin on skin. The topical corticosteroid, fluocinolone cream, was similarly effective though to a lesser extent (70.56%).

DISCUSSION

Linear dermatitis (DL) is a skin blistering inflammatory lesion caused by exposure

Table 1. Chronological manifestation of lesion characters among control groups of guinea pigs

Lesion Characters	Post-exposure time interval (day)	
	Clb*	Cpa*
Erythema and Maculae	2.0	2.1
Complete Erythema	4.3	3.5
Desquamation	7.6	7.4
Haemorrhage	–	8.1
Extensive External Bleeding	–	10.4
Dermal Necrosis	–	11.3
Coagulation	–	12.2
Regeneration and Resolution	8.7	15.8
Complete Cure	12.6	18.0

*Clb, control with live beetles, Cpa, Control with pederin in alcohol

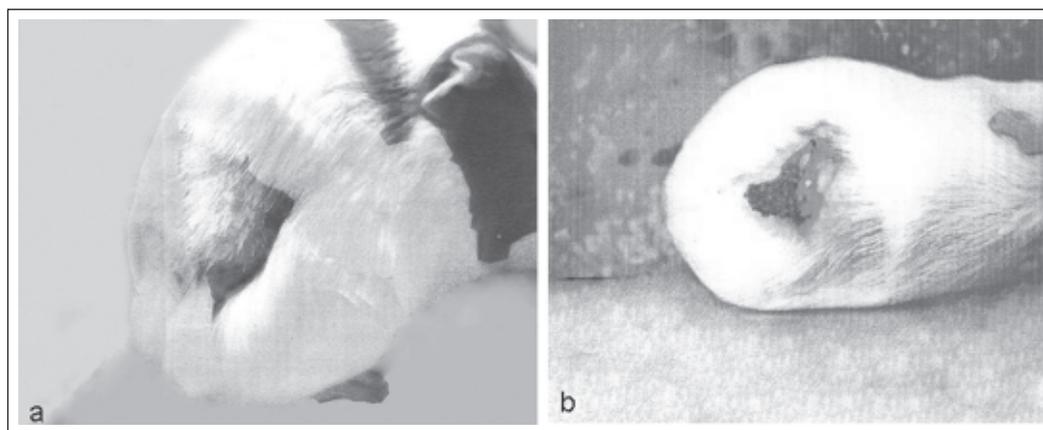


Figure 1. Control guinea pig with erythematous lesion on dorsum using (a) live *Paederus* and (b) pederin in alcohol without medication

Table 2. Treatment group distribution of cases with live beetles (lb) or pederin in alcohol (pa)

Groups	Average (%) signs interval per cavy per total period (days)	Average (%) signs interval reduction per cavy per total period (days)
Control (lb)	12.6 (100.00)	— (—)
Ppc*-treated	3.3 (26.19)	9.3 (73.81)
Fln*-treated	4.7 (37.30)	7.9 (62.70)
Control (pa)	18.0 (100.00)	— (—)
Ppc-treated	3.8 (21.11)	14.2 (78.89)
Fln-treated	5.3 (29.44)	12.7 (70.56)

*Ppc, potassium permanganate with calamine, Fln, fluocinolone cream

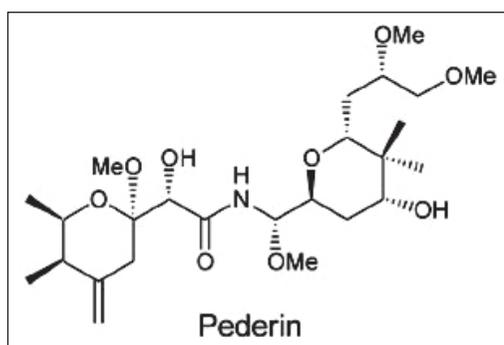


Figure 2. Chemical structure of the toxin pederin

to the toxin pederin from rove beetles. Pederin is an amide bearing two tetrahydropyran rings (Figure 2) (Frank, 2008). The pederin toxin is soluble in ethanol with an aggravated dermal pathology. The pederin producer is not the rove beetle itself, but Gram-negative symbiotic bacteria most likely related to the genus *Pseudomonas* (Kellner, 2002; Piel *et al.*, 2004). The rove beetles are not directly responsible for DL, since the harm is inadvertently self-inflicted by humans smearing the rove beetle and hence its pederin toxin often linearly across their own skin.

In the district of Kavar, where every year notorious outbreaks of DL arise among the local settlers towards the end of spring season, seeking medical care and treatment becomes their primary goal. To date, no report of experimental treatment of DL among small laboratory rodents is known.

This is a prerequisite to ascertain the nature of the best treatment strategy. The rove beetles are highly speciose containing 47744 described species (Herman, 2001), and the genus *Paederus* comprising more than 623 members (Frank, 2008), only nine species of which are medically important in Iran (Nikbakhtzadeh & Tirgary, 2008). Two species are mainly prevalent in southern Iran (Zargari *et al.*, 2003). The underlying causes for the preponderance of *Paederus ilsae* over another *P. iliensis* in this region remain unresolved. The reverse of this situation was reported to be true in southern Iraq (Davidson *et al.*, 2009).

Although some essential medicines diminish the length of DL affliction period, none of the tested drugs to date have had an absolute therapeutic effect. It appears that the problem of treatment needs to be investigated at the cellular and systemic levels. This problem lies partly in the fact that treatment applied against the pederin toxin could only be administered after the latent period when lesions are well in progress (McCrae & Visser, 1975). Treatments after the latent period of DL are mostly palliative in effect.

The corresponding pathological reactions were quickly resolved and milder after the use of live *P. ilsae* beetles than when the pederin toxin in alcohol was applied. This could partly be explained by the fact that rove beetles like other insects have a rigid nitrogenous polysaccharide moiety called chitin in their outer cuticle which serves to protect them against harsh environmental conditions. Chitin is also known to have many other useful properties one of which is its anticoagulant and wound healing character (Gullan & Cranston, 2005). Chitin may thus be effective reducing the recovery period and malignant character of lesions in the skin of guinea pigs. A more cogent concept, however, could also be that the pederin in alcohol penetrates easier through the skin, or it could also be due to the fact that the cuticle of a beetle is so strong that it is difficult to break it properly and release all the haemolymph.

It was found in this study that antipruritic and cleansing agents were more effective than the topical corticosteroids in averting the cytotoxic action of pederin on the skin of guinea pigs. It seems that fluocinolone cream has some side effects which delays the recovery period in the treated skin. It is in no sense curative but palliative.

DL is not just deleterious for its severe skin rash, but also fever, neuralgia, arthralgia and vomiting may develop in some cases (Frank, 2008). The best strategy to curtail the symptoms is public awareness and health education among local and immigrant people. Washing the afflicted site promptly after exposure with clean water will remove much of the toxin before it has time to do any harm.

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