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Feasibility study: Varespladib protects CD-1 mice from lethal doses of whole bee (*Apis mellifera*) venom

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ABSTRACT

Swarming Hymenoptera attacks can deliver high cumulative doses of venom resulting in death and life-threatening or chronically disabling injuries. Varespladib, a potent inhibitor of snake venom secretory PLA2 (sPLA2), is a relatively weak inhibitor of whole bee venom sPLA2 *in vitro* (pico-to low nanomolar for snake venom compared to μ M for *Apis millera*). Animal studies of varespladib against wasp (*Vespa mandarinia*) venom have shown promise against both nephropathy and coagulopathy, major markers of severe systemic toxicity distinct from hypersensitivity such as anaphylactoid and anaphylaxis reactions. We conducted a simple pilot study to evaluate if varespladib could feasibly decrease mortality against lethal doses of honeybee (*Apis mellifera*) venom in a murine model. When pre-mixed with a single dose of 10 mg/kg varespladib and administered intravenously (IV), varespladib prevented all mortality (0 of 10) in comparison to a cohort of mice administered lethal doses of whole bee venom alone (6 of 10) during a 24-h study period (N = 10 each group; log rank χ^2 = 8.29; $p < 0.005$), and it eliminated signs of toxicity within 2 h while control animals either died or continued to show signs of toxicity. Survival in these animals despite poor *in vitro* sPLA2 inhibition suggests that suppression of the host sPLA2 response itself might play a role in the treatment of venom toxicity using an enzyme inhibitor rather than antivenom antibodies. Varespladib could be a useful tool for dissecting fundamental interactions between exogenous toxins and their corresponding endogenous counterparts.

1. Introduction

Phospholipase A2 (PLA2) has recently become a focal point for toxicologists seeking to counteract the harmful effects of various medically significant animal venoms. Varespladib, a small-molecule PLA2 inhibitor, has previously demonstrated efficacy in neutralizing myriad snake venoms. Yet, the efficacy of varespladib against bee venom (*Apis mellifera*), also high in sPLA2, was found to be relatively limited in an *in vitro* study with an IC_{50} of 13.25 μM (Lewin et al., 2016).

While snakebites remain a global medical concern, massive sting attacks have become increasingly common due to the spread of invasive, more aggressive hymenopterans, such as Africanized bees, into warm climate areas (Pucca et al., 2019; Lin et al., 2018). Beyond the ecological concerns, the introduction of more aggressive stinging insects increases the incidence of medically significant mass sting attacks which lead to systemic toxicity in nonallergic patients. In Brazil, for instance, the importation of Africanized bees to bolster agricultural productivity has resulted in substantial increases in swarming attacks (Ferreira et al., 2012). As seen in snakebite epidemiology, there is an underwhelming amount of data available for Hymenoptera sting epidemiology; particularly so for cases of mass sting envenomings as opposed to hypersensitivity reactions.

Hymenoptera, the most diverse order of venomous animals, exhibit a wide variance in venom compositions across different families, genera, and species (Guido-Patiño and Plisson, 2022). Despite this diversity, certain toxins are found almost universally among stinging Hymenoptera. Among the most significant of the enzymes active in bee venom are secretory PLA2 enzymes (sPLA2), composing upwards of 15% of the dry weight of bee venom (Wehbe et al., 2019). These sPLA2 enzymes hydrolytically cleave phospholipid acyl bonds, leading to tissue destruction and coagulopathies, while simultaneously contributing to paralytic neurotoxicity via the inhibition of acetylcholine entry into the synaptic

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cleft (Vardjan et al., 2013). Consequently, the toxic manifestations of high-dose bee venom administration in CD-1 mice can be used as a model of an attack by a swarm of bees, distinct from the more familiar anaphylactoid and anaphylactic response elicited by even a single sting from a stinging bee or wasp.

The objective of this study was to assess the efficacy of varespladib in mitigating the lethality of bee venom when administered experimentally, at doses simulating the conditions of a massive sting attack.

2. Methods

2.1. Experimental design and ethical considerations

Male CD-1 mice with body weights of 20.0–25.0 g were used for both experiments. Animals were housed five (5) per cage for the duration of the study. This study was performed by Pacific BioLabs, following their Animal Care and Use Protocol 17C-09 Toxicity Study in Mice, 9 CFR IA, developed in 2009. Animal treatment protocols were in compliance with the Final Rules of the Animal Welfare Act Regulations (9 CFR 1–3), the Public Health Service Policy on Humane Care and Use of Laboratory Animals (Office of Laboratory Animal Welfare, 2002), the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011), and the guidelines of the Pacific BioLabs Institutional Animal Care and Use Committee (IACUC). All animals received Certified Laboratory Rodent feed *ad libitum* and were acclimated to testing facility conditions for at least four (4) days prior to testing.

2.2. Preparation of dosing solutions

Dosing solutions were prepared from dry, powdered whole bee venom stored between −16 °C and −24 °C. The venom was diluted in 1× phosphate-buffered saline for administration. The varespladib dosing solution was diluted using 58% sodium bicarbonate for injection (8.4% w/v) and 42% dextrose.

2.3. Observation and mortality checks

Animals were monitored immediately post-administration and for up to 8 h, with two additional observations on Day 1 to identify any signs of toxicity, such as respiratory depression, ataxia, vasodilation, or mortality. Final mortality checks were conducted approximately 48 h post-administration for study 1 and 30 h post-administration for study 2. No necroscopies were performed.

2.3.1. Venom dose finding study - Acute toxicity of varespladib and whole bee venom following IV administration

Twenty-five (25) male CD-1 mice were allocated into five distinct groups of five individuals. Four groups were treated with various intravenous (IV) doses of whole bee venom at varying concentrations designed to assess a range of toxic responses. The group designations, treatments, dose concentrations and volumes are shown in supplemental data.

2.3.2. Acute toxicity of whole bee venom with and without varespladib

Twenty (20) male CD-1 mice were allocated into 2 treatment groups consisting of 10 individuals (Table 1). Each group was treated with a single intravenous (IV) dose of whole bee venom mixed with either varespladib or excipient (positive control group). Based on the venom dose finding, a dose of bee venom was administered (5.0 mg/kg) for both the excipient control and varespladib groups. The varespladib dose for the experimental group was 10 mg/kg based on previous studies using varespladib to protect or treat effects of experimental snakebite envenoming in a similar murine model (e.g. Gutiérrez et al., 2020; Lewin et al., 2022). Both groups received dose volumes of 10 mL/kg.

Table 1
Group designations and treatments.

Venom Dose Level (mg/kg)	Treatment	Number of Animals in Group	Varespladib dose level (mg/kg)	Dose volume (mL/kg)
5.0	Whole bee venom + excipient	10	0	10
5.0	Whole bee venom + varespladib	10	10	10

2.4. Statistical methods

T-test comparison was used to verify the mean weights of pseudo-randomized CD-1 mice did not vary significantly between venom-only (positive) control and experimental groups.

The Cox proportional hazards model was used to verify that body weight did not have a significant effect on likelihood of survival.

The statistical comparison of the survival curves for the two cohorts (N = 10 for both groups) was performed using a log-rank test, a commonly-employed non-parametric test for survival comparison. This test is appropriate for this study as our data are censored and left-skewed (skewness coefficient −0.77).

Statistical tests (log-rank, skewness) were performed using pandas version 2.1.4 (https://pandas.pydata.org).

Kaplan-Meier plots and Cox proportional hazards were generated with lifelines version 0.29.0 (Cameron David-Pilon).

3. Results

3.1. Venom dose finding study: Acute toxicity of whole bee venom following IV administration

Animals administered whole bee venom in the venom dose finding groups at 16 mg/kg and 8 mg/kg died on average at 4 (SD = 1.1) and 42 (SD = 14.9) minutes post-administration, respectively. Signs began with loss of motor control then progressed to unresponsiveness, vasodilation, and slowed respiration. Severe convulsions, with vocalizations, occurred in the 8 mg/kg group prior to death as well. Two of five animals in the 4 mg/kg died on average at 1510 min (SD = 278), with signs prior to death including lethargy, vasodilation, and difficult respiration. The remaining animals exhibited similar toxic symptoms but recovered by 7 h after dose administration. Animals in the 2 mg/kg exhibited slight lethargy and vasodilation post dosing through 1 h, then presented no toxic symptoms for the remainder of observation.

The first-dosed animal of the varespladib group died 4 min post-dosing. For the remaining animals, the rate of injection was slowed. The remaining animals began recovering from symptoms 2 min post dosing, with all toxic symptoms resolved by 1 h and for the remainder of observation.

3.2. Acute toxicity of whole bee venom in the presence or absence of varespladib

Six (6) of ten (10) animals administered whole bee venom mixed with excipient control died within 25 h of dose administration, with an average time to death of 1048 min (SD = 537) (Fig. 1). All animals exhibited prone posture, tremors, vocalizations, vasodilation, and ataxia in the first 8 h post dose administration. The four surviving animals recovered from symptoms by the first observation on Day 1.

All animals administered whole bee venom in conjunction with varespladib survived throughout the duration of the study (i.e., >30 h). All animals exhibited slight ataxia, piloerection, and slight lethargy 1–2 h post dose administration; however, no additional toxic symptoms were observed through the remainder of the study.

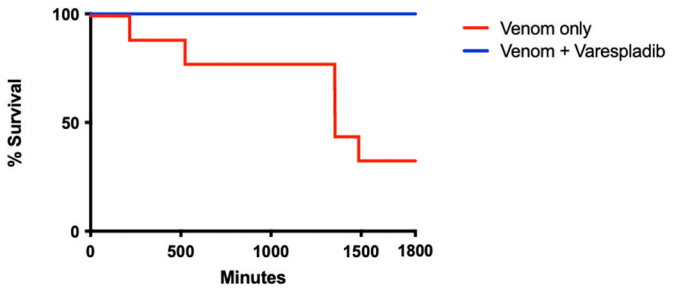

Fig. 1. Percent survival for whole bee venom in presence or absence of varespladib; intravenous (IV). n = 10 for each group. Bee venom administered at 5 mg/kg, varespladib 10 mg/kg.

Varespladib significantly prevented mortality in the experimental group, with 100% survival (10/10) in the experimental group compared to 40% survival (4/10) in the positive control group, log rank $\chi^2 = 8.29$; $p < 0.005$.

Mean body weights between the venom-only (positive) control and experimental animals did not vary significantly and were 21.77 and 21.38 g, respectively ($p = 0.35$). A Cox proportional hazards model indicated that, while heavier animals in the control group were slightly less likely to die (hazard coefficient −1.53), body weight was not a significant factor in death risk ($p = 0.24$).

4. Discussion

This pilot study examined direct toxicity of whole bee venom and a potentially protective effect of varespladib *in vivo*. This work begins to expand on the exploration of varespladib's potential in the treatment of various venomous bites and stings. Varespladib has previously been investigated as an inhibitor of wasp venom PLA2 in a murine model of acute kidney injury (Wang et al., 2022). However, considering varespladib's IC_{50} for snake venoms was in the nano- and sub-nanomolar range, compared to 1000× higher for bee venom (Lewin et al., 2016), the potential clinical value of its inhibitory effects against systemic toxicity from swarming hymenopteran stings *in vivo* is unexpected. As such, performing the most advantageous experiment (pretreatment) successfully suggests advancement to more challenging studies in animals could be ethically acceptable.

The use of varespladib to inhibit snake venom sPLA2 is well-established in mechanistic studies, *in vitro* inhibition assays, and *in vivo* murine models of snakebite neurotoxicity, and viperid envenoming, among others (Salvador et al., 2019; Lewin et al., 2016 & 2022, Gutiérrez et al., 2020; Zinenko et al., 2020). These studies point to the broad-spectrum activity of varespladib against sPLA2 across myriad snake species, justifying the basis of an experiment extending the scope to Hymenoptera venom. Previous demonstration of varespladib's protective effects against AKI from wasp venom *in vivo* has shown that its nonspecific inhibitory potential expands beyond snake venoms, meriting investigation into its efficacy against systemic toxicity from swarming Hymenoptera attacks.

Following venom dose selection, this study evaluated the protective effect of varespladib against bee venom toxicity *in vivo*. While 60% of mice in the control group died, all mice injected with the combination of varespladib and bee venom survived without any signs of toxicity 2 h post-administration. This outcome was unexpected, especially considering the findings of Lewin et al. (2016), which found varespladib's *in vitro* IC_{50} against bee venom to be more than three orders of magnitude higher than any of the snake venoms tested. These results hint at complex interactions between varespladib and innate host responses to Hymenoptera venom.

The differences between the *in vitro* and *in vivo* model of varespladib's ability to inhibit bee venom may arise from innate host responses to envenoming. It has been shown in *Echis* sp. viper venom that NETosis plays a major role in the sequestering of venom in the bite site, with modified chromatin entrapping various venom toxins including PLA2 (Katkar et al., 2016). While this partially inhibits the systemic circulation of venom, local damage can be exacerbated following both the concentration of local venom as well as the collateral damage induced by NETosis mechanisms. Varespladib's interaction with PLA2 family enzymes could be mediated by such intrinsic factors, as it has been shown to have varying neutralization potential between *in vivo* and *in vitro* models.

In contrast to the results found in this study, varespladib was shown to neutralize the cytotoxic PLA2 enzyme MjTX-II more effectively *in vitro* than *in vivo* (Salvador et al., 2019). Moreover, host-mediated inflammation pathways involving arachidonic acid may play a large role in varespladib's ability to decrease the toxic effects of bee venom. Melittin, a small peptide comprising about 50% of the dry weight of bee venom (Habermann, 1972) causes cytotoxicity associated with local inflammation in bee stings. Melittin is also known to induce endogenous PLA2 activity, leading to arachidonic acid activation and amylase secretion in pancreatic acini. A previous study found that the PLA2 inhibitors mepacrine and aristolochic acid are able to completely inhibit melittin's ability to stimulate amylase secretion in the pancreas, linking PLA2 inhibitors to pathways beyond exogenous venom PLA2 (Hou et al., 1997). The 2022 study by Wang et al. demonstrated varespladib's efficacy against acute kidney injury in rats injected with wasp (*V. mandarinia*) venom, further outlining its potential role across a broad spectrum of envenoming treatments. Considering wasp venom is rich in PLA_1, as opposed to the PLA_2 found in bee venom (Perez-Riverol et al., 2019), the role of PLA_2 inhibitors in envenoming pathologies that involve pathways such as endogenous PLA_2 activity or arachidonic acid could be manifold. Consequently, future mechanistic studies into the role of host responses to Hymenoptera envenoming are required in order to elucidate how PLA_2 inhibition by varespladib results in massively decreased mortality despite having relatively low inhibition *in vitro*.

This study tested only one dose of varespladib, however, demonstrating effectiveness against systemic toxicity albeit without providing dose information for minimum efficacy. Dosing at different levels, routes and with different time delays should provide greater understanding of the potential efficacy of varespladib against envenoming by swarming Hymenoptera. The exclusive use of intravascular delivery limits the scope of the study as this route of venom delivery is rare in snakebite and would not meaningfully occur with honey bee stinging apparatus even in a mass envenoming. Moreover, the methodology of pre-mixing varespladib with bee venom limits the scope of this study; a future study using delayed-administration varespladib to rescue mice envenomed with high dose hymenopteran venom is needed to further determine the practicality of varespladib as a definitive treatment in swarming hymenopteran attacks.

Exploration of treatments for systemic toxicity from massive sting envenomings with novel pharmacological treatments could address an epidemiological gap. This is particularly relevant for populations vulnerable to both Hymenoptera attacks and snakebites, which share certain epidemiological characteristics such as long delays in receiving medical care and a disproportionate effect on rural populations (Xie et al., 2013; Arif and Williams, 2023). Previously, medical research into sting-related mortality had predominantly focused on treatment or prevention of anaphylactic reactions. Yet, the rising prevalence of mass sting attacks warrants exploration into accessible antitoxic treatment for nonallergic patients. For instance, among patients who presented to hospital with mass sting attacks in China, the major contributing factors to mortality were systemic toxic effects such as mass hemolysis, coagulopathy, hypovolemia, and acute kidney injury. Only six of fifty-four (11%) deaths were attributed to anaphylaxis (Xie et al., 2013). Furthermore, a case series from Vietnam wherein patients stung by swarming *V. affinis* presented to hospital with systemic toxicity found that high sting counts were associated with increased incidence of renal failure, rhabdomyolysis, and delayed hypotension (Xuan et al., 2010).

Based on our findings, further investigation into appropriate leveraging of wide-spectrum PLA_2 inhibitors such as varespladib could hold potential in alleviating the burden of the growing affliction that is mass sting attacks by swarming Hymenoptera.

Exploration of antibody-based treatments for Africanized bee venom has been conducted with promising protective effects (Teixeira-Cruz et al., 2021). This antiserum was shown to be effective at inhibiting not only phospholipase, but also hyaluronidase enzymatic activity *in vitro*, in addition to effectively neutralizing many of the systemic toxic effects of mass bee envenoming *in vivo*, including hemoconcentration and lethality. The challenges of traditional antisera in terms of broad access at the time of a mass stinging event would likely to be similar to those encountered with other neglected envenoming syndromes however (World Health Organization, 2023), and could be similarly mitigated by recent approaches to novel field treatment strategies using small molecule inhibitors (Bulfone et al., 2018; Arias et al., 2017).

Varespladib's inhibition of PLA2 in snake venoms is well documented, but this research suggests a logical extension to explore its potential role in the treatment of swarming Hymenoptera envenomings.

Considering the similarity between patient outcomes from massive sting attacks and snakebite envenoming, wherein the majority of fatalities occur before reaching the hospital, effective prehospital treatment is paramount to decreasing their medical burden. This pilot study suggests the feasibility of this pursuit for untangling the roles of endogenous and exogenous active sPLA2 species and for potentially useful treatments in appropriate preclinical models (Knudsen et al., 2020; Gutiérrez et al., 2024).

CRediT authorship contribution statement

James Hearth: Writing – original draft, Formal analysis. **Kaitlin Linne:** Writing – review & editing, Visualization. **Jerry Harrison:** Resources, Funding acquisition. **Hossein Zolfaghari:** Writing – review & editing. **Matthew R. Lewin:** Writing – review & editing, Project administration, Conceptualization.

Statement on animal subject ethics

All studies were performed by qualified personnel at an AAALAC-certified testing facility. All study protocols were approved by Pacific Biolabs Institutional Animal Care and Use Committee (IACUC): Animal treatment protocols were in compliance with the Final Rules of the Animal Welfare Act Regulations (9 CFR 1–3), the Public Health Service Policy on Humane Care and Use of Laboratory Animals, the Guide for the Care and Use of Laboratory Animals.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthew R. Lewin reports financial support was provided by Ophirex, Inc. Matthew R. Lewin reports a relationship with Ophirex, Inc. that includes: employment and equity or stocks. Jerry Harrison reports a relationship with Ophirex, Inc. that includes: equity or stocks. Matthew R. Lewin has patent #11000506 issued to Ophirex, Inc. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.toxcx.2025.100214.

Data availability

Data will be made available on request.

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