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Cantharidin for the Treatment of Molluscum Contagiosum: A Prospective, Double-Blinded, Placebo-Controlled Trial

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Abstract

Background/Objective—To study the effects and safety of cantharidin in the treatment of molluscum contagiosum.

Methods—We conducted a prospective, double-blinded, placebo-controlled, randomized clinical trial to evaluate the safety and efficacy of topical cantharidin for treatment of pediatric molluscum contagiosum in an academic ambulatory care center. Twenty-nine children aged 5–10 with the diagnosis of molluscum contagiosum were enrolled to receive treatment with cantharidin or placebo. The main outcome measure was complete clearance of molluscum lesions.

Results—In contrast to previous retrospective observational studies, the performance of cantharidin treatment over 2 months was not substantially better than the performance of placebo.

Limitations—The scope of follow-up was limited to 5 visits over 2 months of treatment. In hindsight, we can hypothesize that a longer follow up period may have captured a greater effect of cantharidin.

Conclusion—We conclude that during a 2 month period, the magnitude of the cantharidin treatment effects in the target population are, at best, not large. This study provided objective unbiased estimates of the magnitude of cantharidin treatment effects and provided important prospective safety data. Our subjects experienced minimal side effects when treated with cantharidin.

Keywords

infections-viral; Lumps/bumps; Pharmacology; Therapy-topical

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Introduction

Molluscum contagiosum (MC) is a dermatologic disorder caused by the molluscum contagiosum virus (a poxvirus). MC commonly affects children of elementary school age. The virus is spread through close skin-to-skin contact, and patients can often auto-inoculate themselves, making MC a dynamic disease within individual patients. Infection can last from several months to four years.[1] Though self-limited, molluscum lesions can be symptomatic, unsightly, and embarrassing. Parents often seek treatment to decrease symptoms and improve the appearance. There are several treatment approaches: destructive, immunologic, antiviral, and active non-intervention. Destructive measures include curettage, cryotherapy, needle pricking, or topical vesicants such as cantharidin.[2,3] Other destructive approaches include retinoids, silver nitrate, potassium hydroxide, salicylic acid, and phenols.[4–14] Immunologic therapies include imiquimod, nitric oxide, and cimetidine, although the efficacy of these therapies remains controversial. Antiviral therapies are few, but cidofovir has been used in adult HIV patients with molluscum contagiosum.[15]

There is debate about the standard of care for molluscum contagiousm. Due to its self-limiting nature, treatment options attempt to minimize scarring and other side effects while speeding recovery time. Care must be taken to find non-traumatic modalities with minimal pain. Watchful waiting or “active non-intervention” is a practice commonly employed. However, parents may not be satisfied with waiting for an undetermined period of time that could last years. Additionally, there still exists the potential for spread to other children.

Cantharidin is a topical vesicant that has been used in the treatment of MC since at least the 1950s. It is an extraction from blister beetles, cantharis vesicatoris, and acts as a protein phosphatase inhibitor *in vitro*.[16] When applied to the skin, it produces a small intraepidermal blister that usually heals without scarring.

Recently there have been greater restrictions in the ability of dermatologists to access preparations of cantharidin. Ambiguity regarding its FDA status has made some academic institutions leery of condoning its use. However, cantharidin is often cited in dermatology and pediatric literature as a valuable treatment.[3,12,16,17] Unfortunately, there have been no randomized clinical trials of cantharidin. Our study is the first prospective, placebo-controlled, randomized trial evaluating the safety and efficacy of cantharidin for pediatric MC.

Materials and Methods

This prospective, double-blinded, placebo-controlled, randomized clinical trial was designed to evaluate the safety and efficacy of cantharidin for treatment of pediatric MC. This trial was registered with http://clinicaltrials.gov, under the identifier NCT00667225, and received approval from the Institutional Review Board of The University of North Carolina at Chapel Hill (UNC). Use of cantharidin also required an FDA Investigational New Drug application and number, obtained in 2007. Participating families received a $10 gas gift card at each visit.

Study Population

Patients were recruited from local pediatrician's offices, UNC Pediatrics Clinic, UNC Dermatology Clinic, and from mass emails to UNC students and staff during December 2007 to June 2009. Patients were included if 5–10 years of age and had a clinical diagnosis of molluscum contagiosum (confirmed by the principle investigators). There was no limit on duration of disease before enrollment. We excluded patients with immunosuppression such as HIV infection, organ transplantation, or use of immunosuppressive medications, including oral corticosteroids. Inhaled steroid use was not an exclusion criterion. Patients previously treated with cantharidin were excluded. Patients with only facial lesions were also excluded, as current convention discourages use of cantharidin on the face. Females that had reached menarche were excluded since the effects of cantharidin use in pregnancy have never been evaluated.

Study design

As approved by UNC's Internal Review Board (IRB) and the General Clinical Research Center (GCRC), the study protocol specified a target sample size of 30 children with complete data for 5 visits spanning 8 weeks. The intended 8-week length of the study was chosen based on anecdotal experience and logistical considerations; specifically, the study was designed to be conducted within a specific twelve month period in which funding and personnel were available. Primary considerations in choosing the target sample size, and the number of longitudinal evaluations (visits) included the availability of subjects, cost and time requirements, the anticipated precision of statistical estimators of interest, and reasonable conjectures about statistical power levels of a pair of hypothesis tests (interim and final) comparing rates of treatment success. The conjectures about statistical power were derived from rough estimates of efficacy based only on anecdotal experience, as there was no relevant data in the literature. The primary consideration in choosing the parallel-arm experimental design, rather than a crossover design, was immunologic: it is plausible that the irritation and blister caused by cantharidin (and not the vehicle) could attract inflammatory mediators and thereby have persisting systemic effects.

Randomization and Blinding

The eligible enrolled patients were assigned at random to cantharidin or placebo. With assistance from UNC's Investigational Drug Service, the patients, parents, and investigators were blind to treatment assignment. The randomization schedule was computed prior to first recruitment using the method permuted blocks of size two. The randomization was stratified on self-reported history of atopic dermatitis (AD) because AD was considered to be a known risk factor for molluscum contagiosum infection. Randomization was 1:1 within each of the two strata.

Investigational drug

Cantharidin 0.7% was obtained from a local compounding pharmacy (Triangle Compounding Pharmacy, Cary, NC). It was compounded in a vehicle of acetone, hydroxypropylcellulose, and flexible colloidon. Serving as a placebo, the vehicle contained

the same formulation but did not include cantharidin. The vehicle was identical in both texture and smell. Testing of the vehicle did not produce blisters in investigators.

Study protocol

During visit 1, patients and their parents were consented and eligibility was established. Subjects and parents then provided information about demographic characteristics and potential risk factors, including history of dry skin, bathing with siblings/friends, pool use, and history of AD. The UNC Investigational Drug Service (IDS) then assigned the next unique subject identification number and dispensed the appropriate drug. Each child was assigned his or her own bottle (cantharidin or placebo), which was returned to IDS after each visit. All of the subject's topical treatments were taken from this bottle.

During each visit, Investigator #1 recorded the number and spatial distribution of all molluscum lesions (face, trunk, back, left or right arm, left or right leg, hands, feet, buttocks, groin). All subjects at all visits were examined by this particular investigator in order to avoid inter-examiner variation. Photographs of the lesions were taken if the patient consented to photography. Investigator #1 then left the room as Investigator #2 entered the room to apply the subject's assigned treatment (cantharidin or vehicle only). A small amount of medication was applied to the molluscum lesions via the stick end of a cotton-tipped applicator, with care not to apply to normal skin. Treatment was never applied to any lesions on the face. To allow the preparation to dry, the children were required to wait about 5 minutes before leaving with parents.

During visit 1, only one or two lesions were treated in order to screen for allergy or sensitivity to the preparation. In subsequent visits, up to 20 lesions were treated. Parents were instructed to wash the treated areas 4 hours after application.

Subjects and parents were asked to return for follow-up visits every 1–2 weeks for a maximum of 5 visits. During each visit, Investigator #2 asked if the child had developed any blisters, pain, or inflammation. This information was kept hidden from Investigator #1, whom performed the counting of lesions in subjects, as to not bias the lesion count. All molluscum lesions were counted, including new lesions.

Statistical Analysis Strategy

Evaluation of efficacy and safety comprised a final analysis using data from all subjects and an interim analysis based on the first ten patients completing the study.

For analysis of safety, simple tabular listings were used.

Efficacy was evaluated in terms of the total count of lesions observed longitudinally. The primary null hypothesis to be tested in the interim analysis ($\alpha = 0.001$) and the final analysis ($\alpha = 0.049$) was "cantharidin and placebo do not differ in regard to the incidence rate of complete clearance of MC lesions by visit 5." The two treatments were also compared in terms of the trajectory of longitudinal improvement in the lesion count. This analysis relied on statistical models supported by simple graphical figures.[a] In support of the primary

efficacy results, auxiliary analyses were performed to evaluate the robustness of those results to reasonable perturbations of the statistical methods and assumptions.[b]

Secondary aims of the study included exploration of patient characteristics as potential predictors of baseline $\log_{10}$ lesion count, or as predictors of the magnitude of cantharidin effects (if any). These exploratory analyses relied on linear statistical models and descriptive tabular and graphical statistical methods.

All statistical computations were performed using SAS System Software (version 9.2, SAS Institute, Cary, NC.)

Results

A total of 29 children were enrolled and randomized: 13 assigned to cantharidin, 16 assigned to placebo via block randomization. The 13:16 allocation imbalance (6:7 in the AD stratum, 7:9 in the non-AD stratum) was due to drop-out. Two of the patients randomized were subsequently excluded when it was discovered that they did not meet all eligibility criteria. As the reasons for exclusion were unrelated to treatment-response, the allocation imbalance did not bias the study.

Table 1 describes the distribution of patient-specific characteristics. These distributions were generally well-balanced between the two groups, with the exception of subjective history of “dry skin” being more common in the cantharidin group. Figure 1 illustrates the distribution of age (years) and self-reported duration of MC infection at visit 1 revealing some confounding of these two variables.

Median elapsed time between visits 1 and 5 (or final visit) was 8.0 weeks for cantharidin and 7.5 weeks for placebo. Most subjects (12 children in each group) were treated and followed for 7.0 – 9.0 weeks. (Figure 2)

All but two subjects completed five visits. Both children were female: one was assigned to placebo, had no lesions at visit 3 (at 8.0 weeks), and did not return for visits 4 and 5; the other subject was assigned to cantharidin and unaccountably did not return after visit 4 (at 7.7 weeks).

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[a]The primary model was a linear mixed-effects model[20] for the response, $\log_{10}(\text{count}+1)$. The regression equation expressed mean response as a treatment-specific linear function of *time* (represented by visit number 1,2,3,4,5). The model accounted for serial correlation by including a subject-specific random effect. Statistical estimates of the regression coefficients ($\beta 1$, $\beta 2$, $\beta 3$, $\beta 4$), the serial correlation coefficient (ρ), and the total variance (σ^2) were obtained by fitting the model to the final data. Those statistical estimates were used to compute treatment-specific estimates of the population mean response at each visit and the rate of improvement in mean response, along with corresponding estimates of group differences. All estimates were tabulated along with their 95% confidence intervals (CI).

[b]This sensitivity analysis included numerous variations on the linear mixed-effects model in regard to the following: variance-covariance assumptions, handling of missing values, choice of temporal index (visit number or elapsed time in weeks), choice of baseline covariates and interaction terms included, and choice of dependent variable. The sensitivity analyses also included approaches focusing on the counts at visit 5; e.g., a Wilcoxon two-sample test procedure. As appropriate for count data, various log-linear models fitted via GEE methods were also examined. The only role of these auxiliary analyses was to guide our level of confidence in the primary efficacy results by verifying that the primary efficacy results were not sensitive to the choice of methods and assumptions.

Interim Analysis of Relative Efficacy and Safety

An interim analysis of the first 10 subjects (5 per group) did not unblind the identities of the two treatment arms and did not unblind patient assignments. Average age was 7.3 years, average duration of disease at visit 1 was 8.8 months, and 7 of the 10 children were females. At visit 1 the number of lesions per patient ranged from 3 to 204 with a median of 17.5.

Efficacy—In terms of the primary endpoint, the performances of the two treatment regimens were identical as none of the 10 children experienced complete clearance by visit 5. By visit 5, the median lesion count (and CI) for the cantharidin group was 8 [1, 106], representing an improvement of 41% [−56%, 100%], while the median count (and CI) for the placebo group was 18 [5, 111], representing an 8% [−66%, 90%] improvement. The difference of the two medians was 10 [−84, 81]. The extremely wide confidence intervals around the 41% and 8% indicate that the numerical difference between 41% and 8% is not meaningful.

Safety—The first 10 subjects experienced no adverse events associated with treatments.

Final Analysis of Relative Efficacy and Safety

Efficacy—The longitudinal counts per child (Figure 2) decreased for 85% of those given cantharidin and 75% of those given placebo. Complete clearance of lesions by visit 5 was experienced by few: 15% (2/13) with CI [0%, 35%] for cantharidin, 6% (1/16) with CI [0%, 18%] for placebo. The difference between the two rates of complete clearance was 9% with CI [−16%, 36%] and two-sided p-value = 0.99. The one-sided 95% upper confidence limit was 30%. The two groups were similar in the number of subjects who had 0 or 1 lesions on their final visit: 23% (3/13) with CI [5%, 54%] for cantharidin, 19% (3/16) with CI [4%, 46%] for placebo, and difference 4% with 95% CI [−23%, 34%]. The longitudinal trajectory of MC toward eventual clearance is characterized by Figure 3 and Table 2 in terms of mean response on the $\log_{10}$ count scale and in terms of median count. The entries in Table 2 were obtained by fitting a linear mixed-effects model for $\log_{10}$ count. This model provided estimates and inferences about the visit-to-visit rate of change: for cantharidin the rate of −0.17 logs per visit corresponds to a median count decrease of about 32% per visit, while for placebo the rate estimate of −0.10 corresponds to median decrease of about 21% per visit. The difference between the two rates was −0.07 with CI [−0.19, 0.05] (p-value = 0.24). If the intended primary null hypothesis had been “cantharidin and placebo are not different with respect to rate of change in mean response”, the test of that hypothesis would not be statistically significant.

Auxiliary analyses demonstrated that these efficacy results were not sensitive to the choice of statistical methods and assumptions used.

Safety—Pain was reported by 23% (3/13) of cantharidin-treated children and by 6% (1/16) of placebo-treated children. The difference was 17% with CI [−10%, 44%]. Blistering (Table 3) was reported by 92% (12/13) CI [67%, 99%] of cantharidin-treated children, and by 50% (8/16) CI [28%, 72%] of placebo-treated children. The difference between these two

incidence rates was 42% with CI [9%, 65%] and p-value = 0.02. Six patients reported hypo- or hyperpigmentation after treatment, all of which were in the cantharidin group.

Exploratory Analyses—Patient characteristics recorded at baseline are listed in Table 1. It is plausible that some of these nine variables may be predictive of baseline lesion count; however, such predictive value was not detected. It is also plausible that some of the nine variables may be predictive of the rate of clearance of lesions. In exploratory analyses, such predictive value was detected only for age (years). Figure 4 illustrates the apparent relationship between age and rate of change in the $\log_{10}$ count per week. This result suggests the hypothesis that cantharidin may have efficacy that depends on the age of the child; i.e., efficacy increasing with age, or with increasing age and duration which are partially confounded together (Figure 1).

Discussion

Previous literature has noted the commonplace use of cantharidin in pediatric dermatology practice.[18] Parents[19] and practitioners[3] have reported satisfaction with results achieved with cantharidin. In a previous retrospective review of a similar patient population, the average time to molluscum clearance was 2.3 months using monthly follow-up visits.[19] Our 2-month study aimed to quantify cantharidin's efficacy compared to vehicle. To our knowledge, there have been no other vehicle controlled randomized trials evaluating cantharidin's efficacy.

In this randomized, 2-month, placebo-controlled clinical trial, the performance of cantharidin was observed to be similar to that of placebo. In terms of the temporal rate of improvement in median lesion count, the estimated rate for cantharidin was 32% fewer lesions per visit, while the estimated rate for placebo was 21% fewer lesions per visit. The primary hypothesis test of efficacy was inconclusive (i.e., not statistically significant.) This test procedure does not, and cannot, establish that cantharidin has zero efficacy. Although the hypothesis test was inconclusive, the point estimates and confidence intervals do provide information about the plausible range of the magnitude of efficacy. In terms of complete clearance of lesions by visit 5, the observed treatment success rate was 15% (2/13) for cantharidin patients and 6% (1/16) for placebo, yielding an observed difference being 9% with CI [−16%, 36%]. The confidence interval suggests that it is plausible that the true magnitude of difference is in the range of −16% to 36%. It also suggests that it is unlikely that the true difference is as large as anecdotal and retrospective reports have suggested.

Cathcart et al[19] noted that 54% (29/54) of cantharidin-treated patients reported subjective complete clearance when treated for about 2 months. Silverberg et al[13] reported that 95% of parents of cantharidin-treated patients stated that they would proceed with cantharidin treatment again. A possible explanation for the contrast between our study and these retrospective studies is the preciseness and strictness of our definition of clearance. Additionally, parents may look back favorably on their treatment with cantharidin even without complete resolution of all lesions. If this is the case, then there may be some recall bias and over-estimation of clearance. Additionally, there may be some pressure to please investigators in a telephone survey and potential for inflation of satisfaction.

In secondary analyses we explored self-reported patient characteristics as potential risk factors for poor outcomes and as predictors of lesion count at baseline. The exploratory results suggested a new hypothesis: the biological effects and relative efficacy of cantharidin may depend on the age of the child; specifically, increasing efficacy with increasing age.

Self-reported patient characteristics of interest included previously inflamed lesions. Molluscum lesions that exhibit irritation or inflammation are classically thought to be nearing spontaneous resolution. It has been hypothesized that a “switch” occurs when the immune system starts to recognize an individual focus of molluscum virus, gathers inflammatory cells and mediators in the area, and soon thereafter clears the virus with subsequent disappearance of the lesion. We did not detect any association between lesion clearance and prior history of irritated, inflamed, or previously resolved lesions.

For the immunologic reasons cited above, we did not choose to use a crossover study design. The irritation and blister caused by cantharidin (and not with the vehicle) could theoretically attract inflammatory mediators and possibly speed the resolution of untreated or vehicle-treated lesions, via the hypothesis outlined above.

Blistering was self-reported and not observed by the physician, as blistering typically occurred at home after the patient encounter. As expected, almost all (92%) cantharidin-treated subjects reported blistering. The substantial number of placebo-treated subjects that reported blistering (50%) was surprising. However, this blistering was not confirmed by the investigators – it is our sense that patients may have interpreted the colloidon membrane from the vehicle as a blsiter. There may be some recall bias in patients’ self reporting as well. Finally, the sometimes surprisingly-strong placebo effect should not be discounted.. None of the ingredients in the vehicle preparation are known to have blister-inducing properties.

No patients dropped out due to side effects. The most common side effects were local irritation and blistering with cantharidin. Six cantharidin and no vehicle patients reported pigmentary change. We suspect this is due to post-inflammatory pigment alteration that is comparable to other destructive techniques, however subjects were not followed for longer than 8 weeks to assess duration of the pigmentary change.

Pain was reported by 6% of placebo-treated patients, and 23% (3/13) of cantharidin-treated subjects; e.g., one experienced pain when scrubbing off the medication. The 23% rate is much lower than would be seen with other destructive techniques, and the discomfort is delayed until after the patient leaves the office. This allows for non-traumatic treatment of molluscum and preservation of the relationship and trust between the dermatologist and child. Our results demonstrate that when used correctly, cantharidin can be used with minimal side effects.

This study characterized longitudinal improvement in total lesion counts during 8 weeks of treatment. Anecdotal experience and previously published retrospective reviews suggested an expectation that roughly half of cantharidin-treated subjects would experience complete clearance of lesions. This study was not designed to address the longitudinal course of MC

beyond the first 8 weeks of treatment, which could potentially capture a greater efficacy of cantharidin – further studies would be needed to investigate this theory.

The target sample size, 30, was chosen based on considerations of the availability of subjects, cost and time requirements, the anticipated precision of statistical estimators of interest, and reasonable conjectures about statistical power levels of a pair of hypothesis tests (interim and final) comparing rates of treatment success. The conjectures about statistical power were derived from rough estimates of efficacy based only on anecdotal experience, as there was no relevant data in the literature.

Enrollment of 30 subjects was surprisingly difficult. Families were reluctant to enroll their child in a study that had a 50% risk of being assigned to placebo when they could decline participation and receive verified cantharidin in the regular clinic.

An important aspect of our study design was the stratification of atopic dermatitis patients. Future studies involving patients with molluscum contagiosum should control for atopic status because other studies have demonstrated that they tend to have a more prolonged and severe course.

It is possible that the two treatment groups were not balanced with respect to other important factors in spite of randomization. For example, we do not know how many subjects in each group were patients on the verge of spontaneous remission; consequently, it might be conjectured that there were more “spontaneous resolvers” in the placebo arm of the study. However, clearance was infrequent in both arms: neither arm of the study experienced the higher rates of complete clearance that had been expected based on anecdotal experience and previous retrospective observational reports.

We do know that the subjects assigned to placebo had had their MC lesions for 8.5 months, on average, while the average duration for cantharidin-treated subjects only 6 months. The longer the lesions are present the better the chance for spontaneous remission. However, clearance was infrequent even in the placebo arm. Furthermore, the primary efficacy results were invariant to whether or not duration of MC was taken into account as a covariate.

The interim analysis demonstrated, as did the final analysis, that (1) the “complete clearance” endpoint is a poor summary variable in this context, (2) characterization of the longitudinal trajectory of lesion counts is more informative, and (3) that the counts follow distributions that are approximately log-normal. In contrast to the “complete clearance” endpoint, endpoints defined in terms of interval-scale measures of the decrease in lesion count offer more powerful tests of efficacy hypotheses.

This study serves as a platform for future studies investigating tools for the treatment of molluscum contagiosum. It has provided objective unbiased estimates of the magnitude of cantharidin treatment effects and of variance and correlation, has contributed important prospective safety data, and it has generated a new hypothesis about age-dependent efficacy. If the relative efficacy of cantharidin is small compared to placebo, than in future studies a larger sample size may be warranted.

The value of our study is it can help future studies better assess the efficacy of cantharidin in molluscum contagiosum. In addition, the clinician is informed that almost weekly application of cantharidin to molluscum lesions over a span of 8 weeks does not have statistically improved benefit over placebo. Our institution has patients willing to come on a weekly basis to clear the virus from their homes; we can confidently inform them that weekly visits are not necessary. Based on our anecdotal experience, we still believe cantharidin is useful and safe in the treatment of childhood molluscum contagiosum and are in favor of further studies with a larger sample size and longer duration.

We conclude that in our study the magnitude of the cantharidin treatment effect in the target population was, at best, not large during the 2 month study period: the temporal rate of clearance of lesions and the incidence of complete clearance of all lesions were not dramatically different from that achieved with placebo. We also conclude that cantharidin can be used with minimal side effects and is safe in children when used properly.

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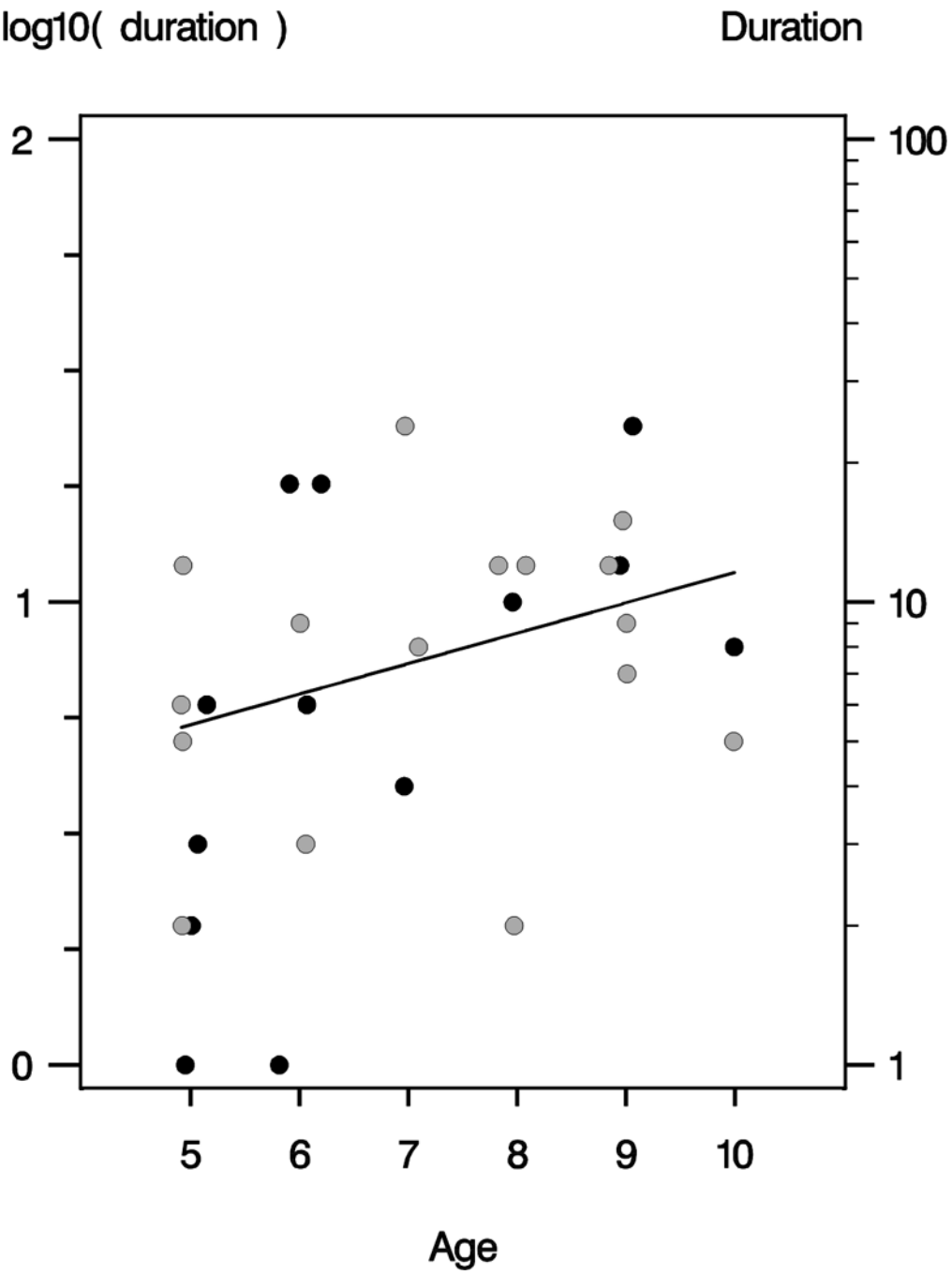

Figure 1.

At visit 1, duration of MC infection (weeks) was moderately confounded with age (years). The coefficient of correlation between age and $\log_{10}$(duration) was r = 0.42 with 95% CI [0.06, 0.68]. Values plotted are for subjects assigned to cantharidin (solid dots) and for subjects assigned to placebo (open circles).

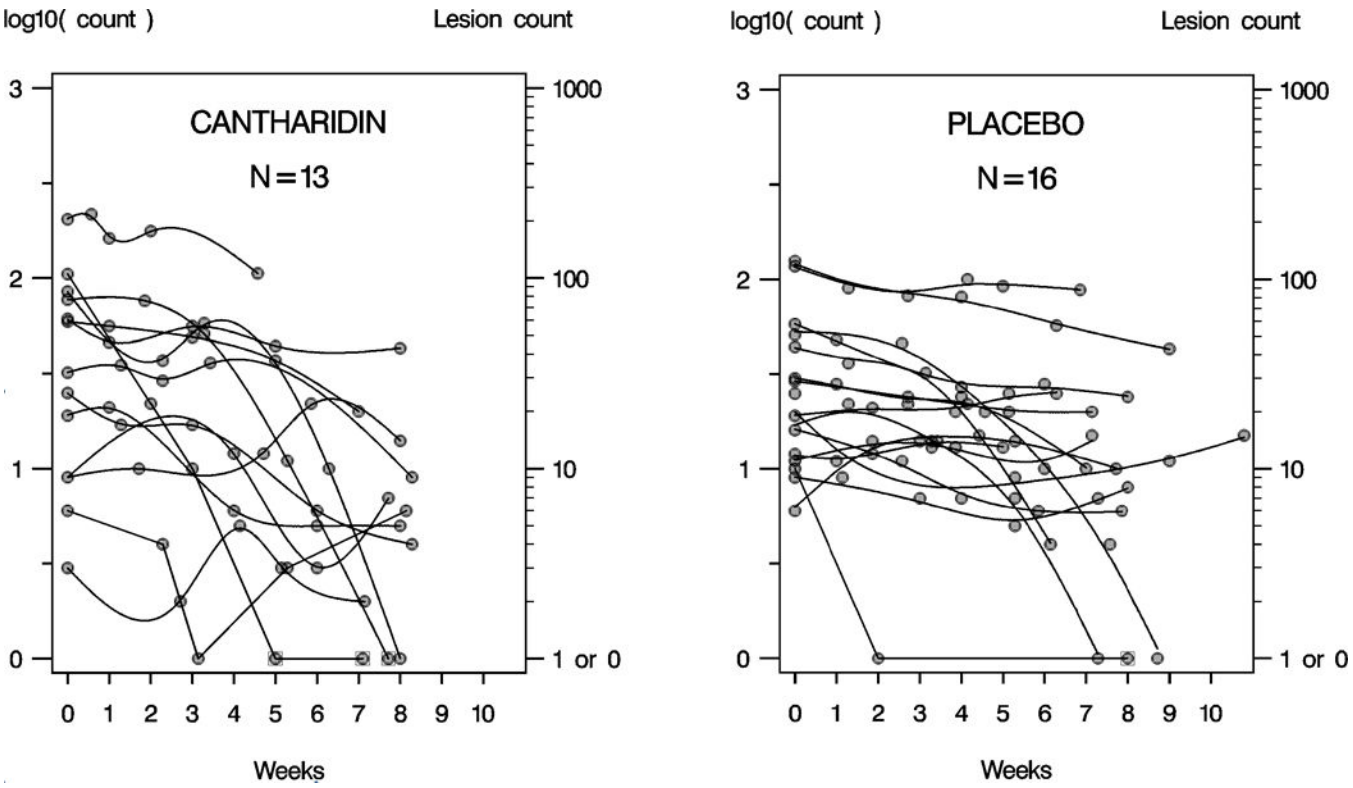

Figure 2.

The individual-specific lesion counts in $\log_{10}$ scale for each treatment group. As a visual aid, each nonparametric smooth curve descibes the trajectory for an individual child. The temporal index is *Weeks*. Only 3 subjects experienced complete clearance (squared symbol plotted at "1 or 0"). Two other subjects (placebo) has 1 lesion at visit 5. Another subject (cantharidin, age 5) had only 1 lesion at visit 3, but 6 lesions at visit 5.

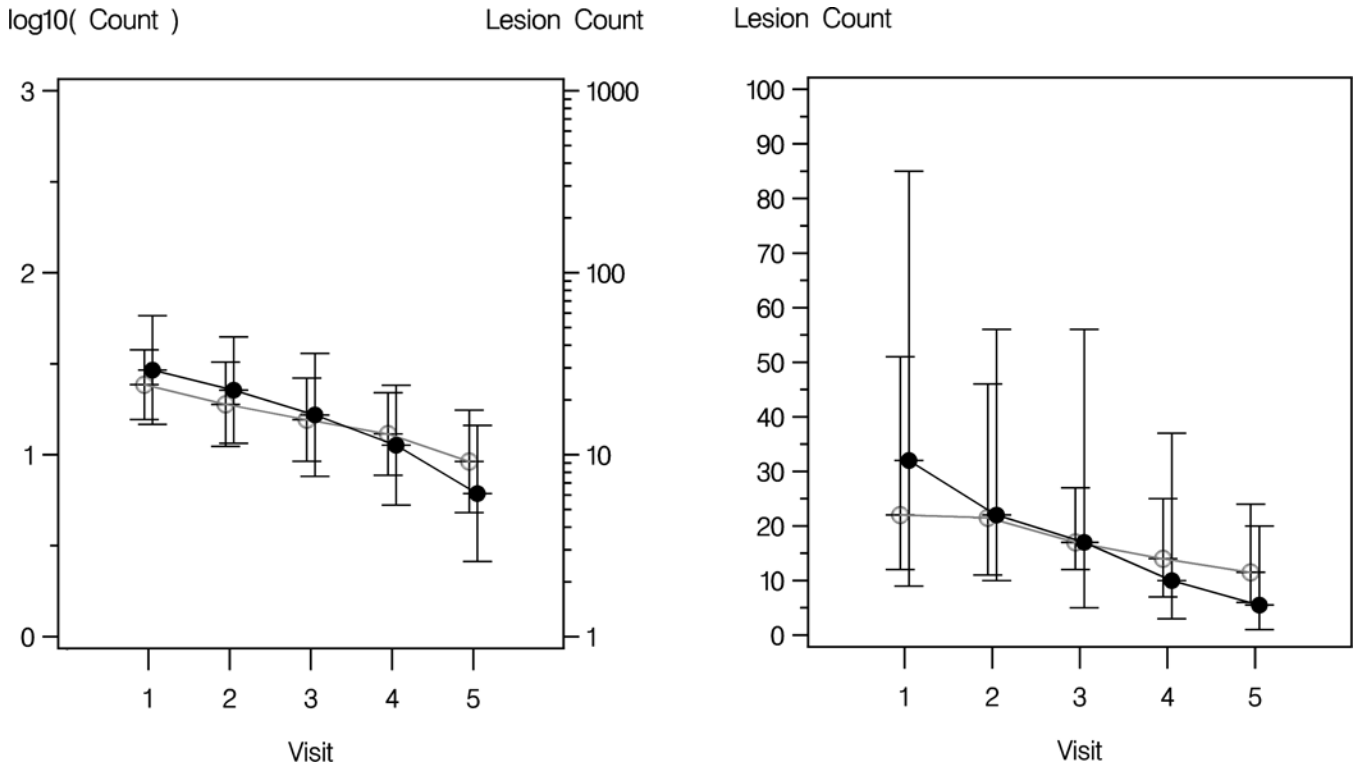

Figure 3.

For cantharidin (●) and for placebo (⊕), visit-specific sample means (left) and sample medians (right) are shown with their corresponding 95% confidence intervals.

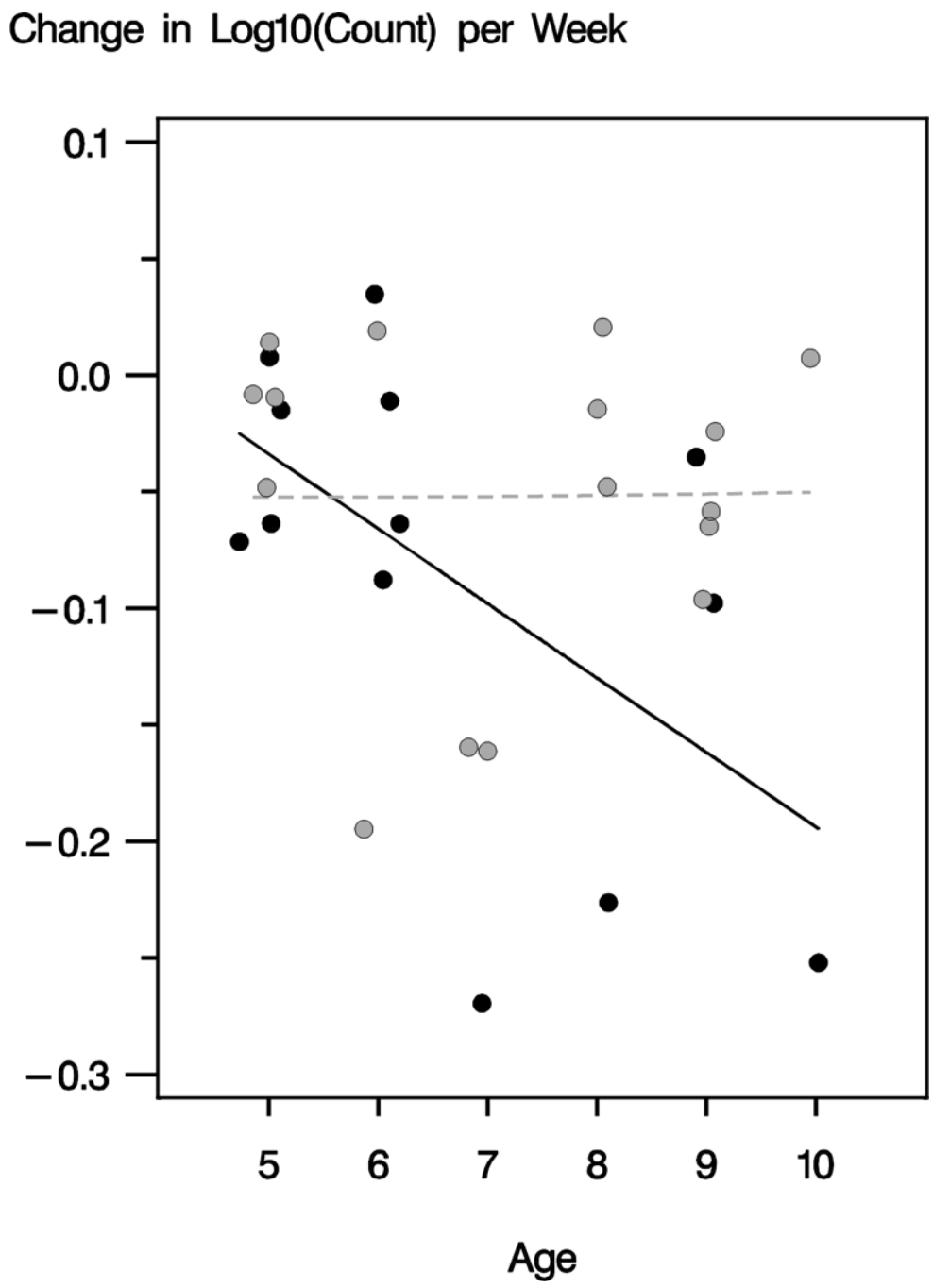

Figure 4.

Rate of change in $\log_{10}$(count) per *week* was computed for each child by linear regression. Rate = 0 indicates the count did not change, while Rate = −0.5 indicates a rapid decrease in lesion count. For cantharidin (solid dots), the coefficient of correlation between *Age* (yrs) and *Rate of change* (per week) was r = −0.57 with 95% CI [−0.85, −0.03]. For placebo r = 0.01 with 95% CI [−0.49, 0.50].

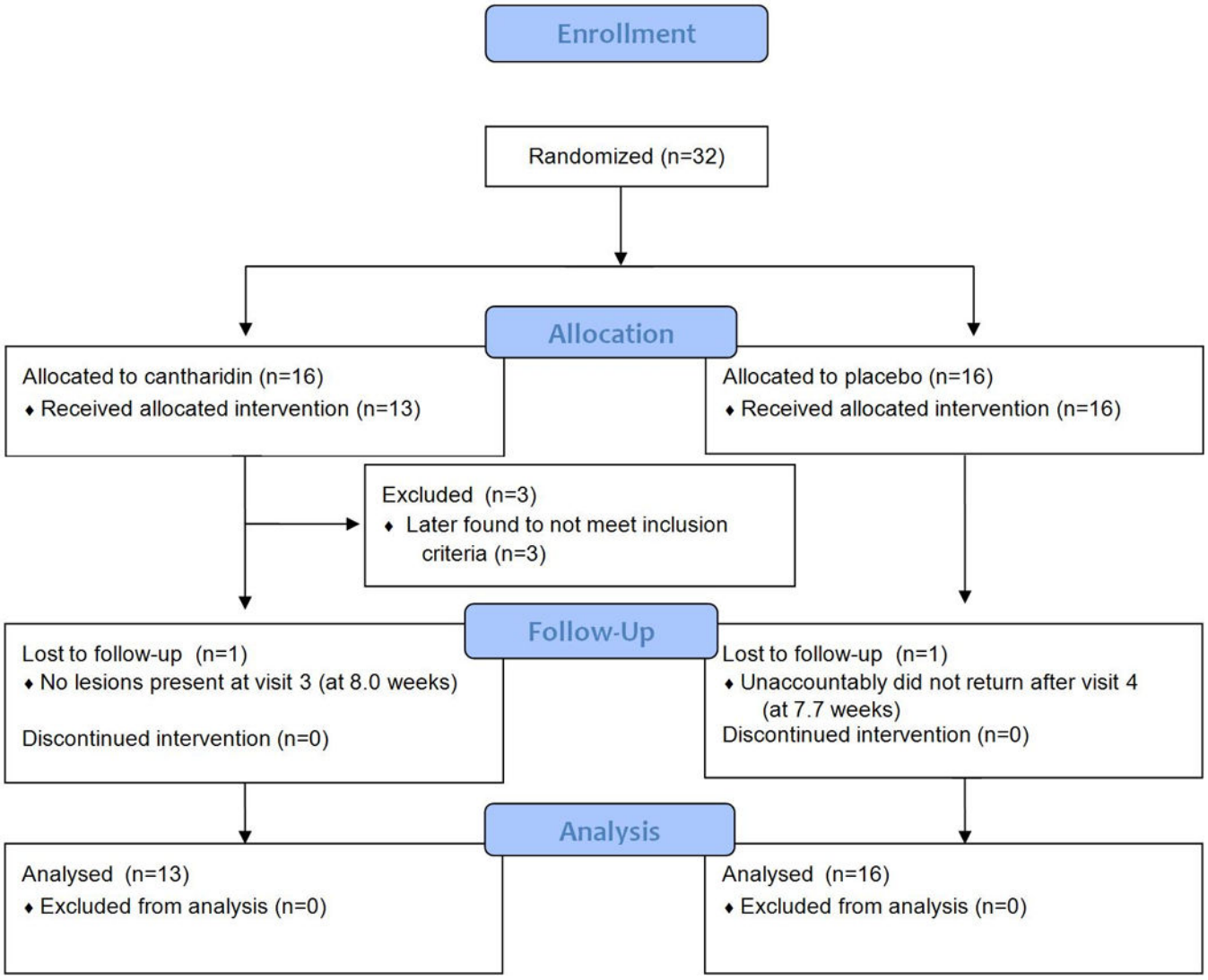

Figure 5.
Flow diagram of participant progress throughout the trial.

Table 1
Distribution of Patient Characteristics of Interests

	Cantharidin	Placebo
	N=13	N=16
% Female	62% (8/13)	63% (10/16)
% Self-Reported Dry Skin	67% (8/12)*	38% (6/16)
% Self-Reported Atopic Dermatitis History	46% (6/13)	44% (7/16)
% Reported History of Inflamed Lesions	25% (3/12)*	19% (3/16)
% Reported Resolution of some Lesions Prior to Study	42% (5/12)*	44% (7/16)
% Reported Bathing with Siblings	45% (6/13)	38% (6/16)
% Reported Frequent Swimming Pool Use	77% (10/13)	81% (13/16)
Age in Years at Visit 1: mean (standard deviation)	6.7 (1.8)	7.3 (1.7)
Duration of MC in Months at Visit 1: median (range)	6.0 (0–24)	8.5 (2–24)
Weeks of treatment and follow-up: median (range)	8.0 (4.6–8.3)	7.5 (5.0–11.0)

*The missing data all come from the same subject.

Table 2

Response by Treatment and Visit

characterizes the longitudinal trajectory of MC toward eventual clearance. The statistical estimates of means and medians are shown along with their corresponding 95% confidence intervals (CI). From visit to visit, these estimates of mean response decreased by 0.17 log units for cantharidin, and by 0.10 log units for placebo ("slope"). Similarly, from visit to visit the median estimates decrease by about 32% for cantharidin and by about 21% for placebo. The estimates of means and medians were obtained by fitting a linear mixed-effects model for $\log_{10}$(count). The estimates of the differences between medians were computed using the nonparametric method of Hodges and Lehmann[22].

		Treatment					
		Cantharadin		Placebo		Treatment Difference	
		Mean	95% C.I.	Mean	95% C.I.	Difference	95% C.I.
Log_{10}(Count)	VISIT						
	1	1.5	[1.2, 1.8]	1.4	[1.1, 1.6]	0.1	[−0.2, 0.5]
	2	1.3	[1.1, 1.6]	1.3	[1.0, 1.5]	0.0	[−0.3, 0.4]
	3	1.2	[0.9, 1.5]	1.2	[0.9, 1.5]	0.0	[−0.4, 0.4]
	4	1.0	[0.6, 1.4]	1.1	[0.8, 1.4]	−0.1	[−0.6, 0.4]
	5	0.8	[0.4, 1.3]	1.0	[0.6, 1.4]	−0.2	[−0.7, 0.4]
	Slope	−0.17	[−0.25, −0.08]	−0.10	[−0.18, −0.02]	−0.07*	[−0.19, 0.05]
		Median	95% C.I.	Median	95% C.I.	Median Difference	95% C.I.
Lesion Count	VISIT						
	1	32	[17, 61]	24	[14, 43]	10.0	[−12, 47]
	2	22	[12, 42]	19	[11, 35]	3.0	[−12, 24]
	3	15	[7, 30]	15	[8, 29]	1.0	[−11, 29]
	4	10	[4, 23]	12	[6, 26]	−2.5	[−11, 12]
	5	7	[3, 18]	10	[4, 23]	−4.0	[−13, 5]

*p-value = 0.24 for a two-sided test of the null hypothesis that "difference is slopes is zero".

Table 3

Percent of Subjects with Self-Reported Blisters

For each visit and across visits 2–5, the entry shown is the percent of children who reported blisters. Almost all subjects treated with cantharidin reported blistering.

	Visit 2	Visit 3	Visit 4	Visit 5	During Study
Cantharidin (N = 13)	31%	77%	54%	46%	92%*
Placebo (N = 16)	25%	31%	20%	25%	50%*

* For the test of "the proportion of children experiencing blisters is the same for cantharidin and placebo" using Fisher's exact procedure, p-value = 0.02.