

A Topically Applied Quaternary Ammonium Compound Exhibits Analgesic Effects for Orthopedic Pain

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Abstract

OBJECTIVE: To investigate the effectiveness of a topically applied emulsion of an analgesic ammonium solution for the temporary treatment of pain associated with arthritis, tendinitis, and bursitis. **DESIGN:** 100 subjects in a single center, presenting with chronic pain associated with arthritis, tendinitis, or bursitis trialed against placebo in a double-blind cross-over protocol. **MAIN OUTCOME MEASURES:** Measures of treatment success include reduction in pain, improvement in clinical and/or mechanical evaluations, and evaluation of local and systemic adverse effects. Analysis was conducted at two weeks, after one week's clearance, and again after two weeks. **RESULTS:** For chronic neuralgia associated with arthritis, tendinitis, and bursitis, the test material had a positive effect at temporary pain reduction. Several subjects also recorded improvements in mechanical evaluations from baseline. Withdrawals due to systemic or local adverse reactions were minimal. **CONCLUSION:** A topical emulsion of a strong ammonium solution utilizing quaternary ammonium, enhanced with certain penetration enhancers, is effective for temporary relief of pain associated with arthritis, tendinitis, and bursitis.

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Introduction

Topically applied non-steroidal anti-inflammatory drugs (NSAIDs) are widely advertised and used for acute and chronic painful conditions. Relief from pain is a major impetus for seeking clinical intervention. There are millions of NSAID prescriptions written each year in the United States for the treatment of chronic pain and approximately \$300 million per year spent on over-the-counter topical remedies.¹ Marketing research indicates consumers are skeptical of the efficacy of topical products. There has been growing interest around the world in topically applied NSAIDs in over-the-counter preparations.

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Figure 1. Age distribution.

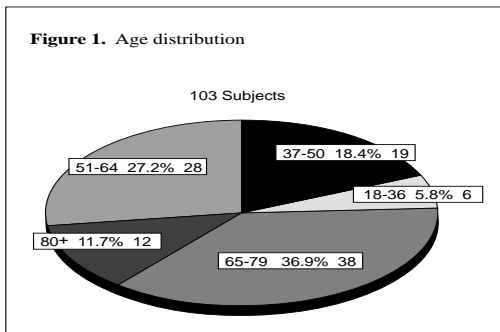


Figure 2. Sex distribution.

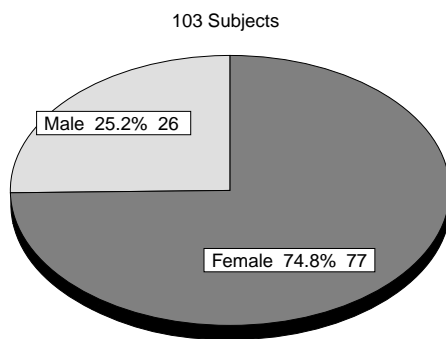


Figure 3. Diagnosis.

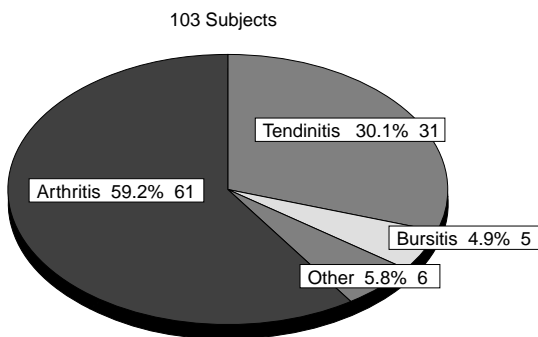
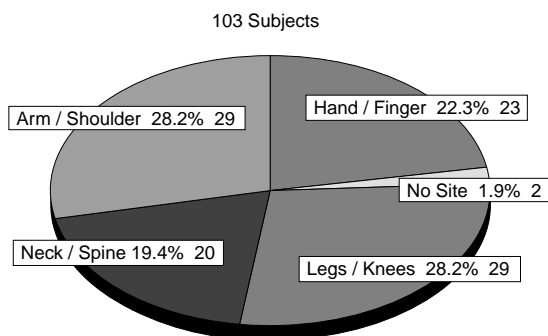


Figure 4. Site of involvement.



The history of the use of ammonium compounds as pain relievers is probably as old as civilization itself. Urea, a natural by-product of metabolism, containing quaternary-like ammoniums, has been used as a topical analgesic and healing adjuvant for burns and cuts, and poultices containing urea compounds have been used to reduce swelling and inflammation.

Methods

Criteria for Inclusion: Subjects were recruited from advertisement to patients of a family practice in Palm Beach County, Florida, and by advertisement in the local daily newspaper.

Subjects included were otherwise healthy individuals presenting with chronic pain (defined as longer than six weeks) secondary to arthritis, or chronic or acute pain of tendinitis or bursitis in at least one joint. Subjects may or may not have been receiving NSAID medications to treat their pain, but were required by the protocol to discontinue all pain medication two weeks prior to beginning the study. Subjects ranged from 24 to 90 years of age. Demographics of age, sex, diagnosis and site of involvement are shown in Figures 1-4, respectively.

Subjects were evaluated for ability to record their responses to daily scheduled dosing of the test materials and for their willingness to complete the entire five weeks of the protocol.

Subjects were screened by the contract research organization, Palm Beach Center for Clinical Investigation, and when selected, were given a physical examination, including baseline mechanical measurements, before being admitted to the study.

Test Materials: TransDermal Technologies, Inc., the sponsor of the trial, provided both the active and placebo test materials. These test materials were manufactured under U.S.F.D.A. Good

Manufacturing Procedures by ABCO Laboratories of Concord, California. The active test material was an emulsion of quaternary ammonium 27 (a quaternary ammonium chloride compound) in water, enhanced with a permeation enhancer, methylsulfonylmethane (MSM), lemon oil, and other skin protective agents. All open bond sites on the ammonium compound are filled with a fatty acid, making it non-irritating. The placebo was compounded as sorbitan monopalmitate and water. Both test materials were presented as lotions. The active test material was evaluated by the Institute for In Vitro Sciences in Gaithersburg, Maryland, for primary dermal irritation, skin sensitization and toxicity. Materials tested within non-irritating limits.²

Enough material was prepared for two 3-oz. containers of each material to be assigned to each subject. Each container was given a serial number beginning at 98001 and ending with 98103 and designated as either "A" with a red dot or "B" with a blue dot. "A" containers held one form of test material and the "B" containers the other. A corresponding detachable label with identical information was attached to each container. Assignment of "A" or "B" was randomized and recorded in the Master Test Material Log. Once numbered and assigned as "A" or "B," test materials were placed in nested, numbered boxes for assignment to subjects.

As each subject was entered into the protocol, they were assigned as subject number the next available test material number. The detachable label from one of the "A" containers was attached to the subject's patient records retained by the investigator. At the end of Phase I, the test material container was returned to the investigator and replaced in its nest. At the beginning of Phase II the first "B" container was issued. In the event the container was exhausted or lost, it was replaced with the second container in the appropriate "A" or "B"

series for that subject. The study was double-blind so neither subject nor investigator knew which test material was being employed during either phase.

Protocol: Phase I: After the initial physical exam and baseline measurements, subjects were assigned test materials and instructed to apply their first dose in the presence of the investigator. They were given a two-week daily log to be completed for each application of test material, with instructions for use four times daily. At the end of the first two weeks, the subjects were evaluated by the investigator for pain, mechanical measurements, and general status. They then were instructed to return after a wash-out period of no less than one week. On the cross-over visit, the subjects were asked if they had used any medicines for pain, and whether they had undergone any significant changes in their condition during the clearance period. If both answers were negative, they were admitted to Phase II of the protocol. If not, they were discharged.

Phase II: The protocol was identical to Phase I except for the actual content of the test material. After completing the two-week trial, subjects returned for evaluation and discharge.

All subjects who voluntarily or involuntarily withdrew from the protocol were evaluated at discharge for general medical condition.

Measurements: Each subject was evaluated for pain in one joint using a self-marked linear pain intensity scale at baseline and each subsequent visit. The investigator evaluated each subject on the following:

- Swelling
- Tenderness
- Pain at rest
- Pain on motion

A pain rating system was used with 0 = No Pain, 1 = Mild, 2 = Moderate, 3 = Marked, and 4 = Severe.

Figure 5. Types of response.

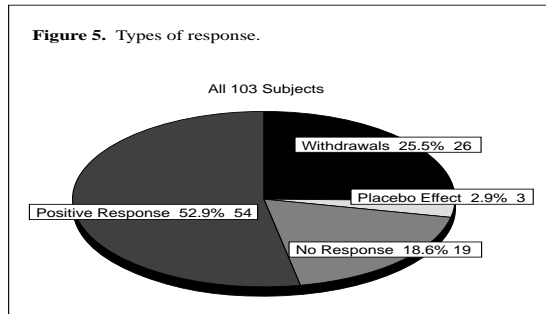


Figure 6. Level of positive response.

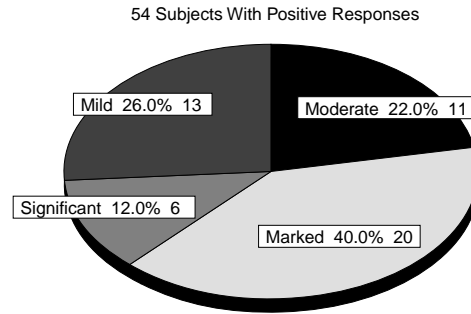


Figure 7. Positive response by age.

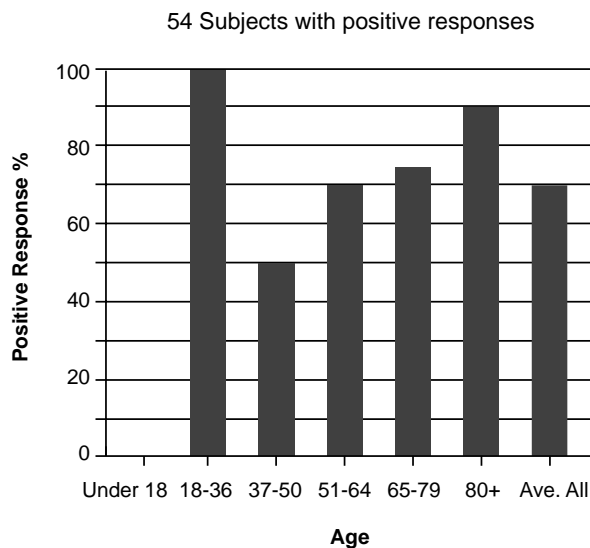
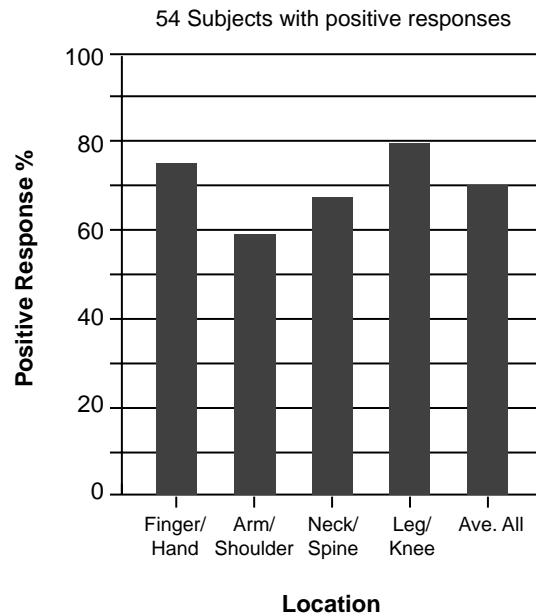


Figure 8. Summary response by location.



Depending on the site of involvement, each subject was further evaluated for grip strength using a hand dynamometer, pinch force using a pinch gauge, range of motion measured in degrees using small and large goniometers, degree of swelling of the involved joint in centimeters, time to walk 50 feet, and duration of morning stiffness. The same joint was monitored throughout the trial.

Subjects were instructed to keep a daily log, including a before-and-after-application-Linear-Pain-Intensity scale and a check box for how soon they noticed relief. A weekly summary was included which asked for general evaluation of overall wellness and

effectiveness of the test material being evaluated.

Ethics: The protocol for the study was submitted to the Institutional Review Board at Humana-JFK Medical Center in Atlantis, Florida. It was approved for study on March 3, 1998, with no substantive corrections except a referral to federal law and an IRB contact being added to the "Subject Informed Consent Release."

A "Study Source Document" was completed for each subject in the trial with complete medical documentation. Subjects were given time at initial screening and at each evaluation to ask questions and were provided

with contact numbers so the investigator and/or sponsor could be reached at any time. Subjects were informed they could discontinue treatment at any time and that such a decision would not affect their care.

Analysis

The following statistics were prepared:

- Overall improvement defined as reduction of pain and/or improvement of mechanical measurements within subjects, in active versus placebo test materials.
- Analysis of variance on overall improvement – active versus placebo (99% confidence interval).
- Number of subjects with positive response to placebo and no response to active test materials.
- Comparisons of overall results by age and site of pain.
- Elapsed time to relief.

Results

Of 103 subjects who began the trial, 77 completed the protocol. Of the 77 subjects completing the trial, 54 subjects (70%) received positive results. Of 26 withdrawals, 13 (50%) withdrew while on placebo. Of the remaining 12 withdrawals, 5 indicated in their logs the material was working for them.

Subjects' response was rated on a scale of 1 = mild response, 2 = moderate response, 3 = significant response, and 4 = marked response. The level of positive responses in various categories is described in Figs. 5-8.

The mean response was $1.92 \pm .002$. The confidence interval that the null hypothesis (that the active material was no more effective than placebo at relieving pain associated with arthritis, bursitis or tendinitis) is true,

is less than 0.01; so the null hypothesis is rejected.

Figures 7 and 8 are an analysis of the 54 subjects with positive responses. The percentages are based on the number of positive responses (54) divided by the number of subjects who completed the trial (77), grouped by age and site of involvement.

Discussion

These results indicate a topically applied quaternary ammonium compound is significantly more effective than placebo, with 70 percent of the subjects receiving some measurable improvement and 40 percent receiving marked relief. The positive response to placebo was 3 out of 77 subjects (4%). Comparable response to placebo in other trials of topically applied NSAID drugs have yielded placebo effects as high as 40 percent.³ Less than 2 percent of the subjects reported minor side-effects, which were self limiting. A number of subjects in this trial reported dramatic relief from what had heretofore been intractable pain of years' duration. Subjects who reported positive results who had used other oral or topical medications rated the test material "as good as" or "better than" their previous medications.

The only consistent area of poor performance was for treatment of acute shoulder tendinitis in younger subjects, for which the test material had virtually no effect. Generally, the test material seemed to work either markedly well for younger subjects (less than age 51) or not at all.

Subjects reported the mean time to onset of relief was 20 minutes from application, and the duration of their relief from a single application ranged from two hours to all day, averaging over four hours.

The most interesting results were:

- Older subjects experienced the most relief – increasing with age to over 80 percent positive response at age 80 and above – we are ignoring the 100 percent response in the 18-36 age group because this group was too small to constitute a valid sample.

- Fingers / hands / wrists and legs / knees / ankles received more than the average 70 percent positive response rate.

Acknowledgements

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