Clinical Safety of a Homeopathic Preparation

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Abstract

Background Traumeel® is a homeopathic medication containing 12 botanical substances and 2 mineral substances. It has been sold in the United States since 1986 and in Germany since 1937, and it is available worldwide for use as an anti-inflammatory, analgesic, antiedematous, and antiexudative drug. The indications for its use include temporary relief of symptoms associated with inflammatory, exudative, and degenerative processes due to acute trauma, repetitive or overuse injuries, and minor pain from osteoarthritis, rheumatoid arthritis, gouty arthritis, and ankylosing spondylitis.

Objective To evaluate the clinical safety of Traumeel® oral tablets by measuring changes from baseline to post-treatment in the following: complete blood cell count, liver profile, serum chemistry, bleeding time, coagulation time, and the gastrointestinal system (presence of occult blood in the stool).

Methods The four-week study was performed with one group of 20 volunteers. Baseline measures included case history, physical examination, vital signs, hematology, urinalysis, and a clinical chemistry. Volunteers received the study drug, two Traumeel® tablets sublingually three times per day. Selected laboratory tests were performed once a week. Each subject was required to keep a daily log of study drug intake and report any adverse symptoms following drug ingestion. A final examination of each study participant was performed during the fourth week of the study.

Results Statistical evaluation of the laboratory data revealed no significant ($P>.05$) differences from baseline to post-treatment in this study. All adverse events experienced by the subjects were mild to moderate in severity, transient, and subsequently resolved without intervention despite continued use of Traumeel®. Some examples reported by subjects were stomach discomfort, headache, diarrhea, dizziness, nausea, insomnia, and arm/leg pain.

Conclusion Traumeel® is well tolerated and safe in healthy subjects. There was no significant gastrointestinal toxicity in the form of symptoms or gastrointestinal blood loss. Conventional nonsteroidal anti-inflammatory drugs cause gastrointestinal ulceration and bleeding in some patients and are especially hazardous for patients with diseases or taking medications that interfere with normal coagulation. Traumeel® has anti-inflammatory and analgesic effects and does not inhibit the arachidonic acid pathway of prostaglandin synthesis. It deserves consideration as a safer alternative for patients at high risk for gastrointestinal bleeding with conventional NSAIDs.

Traumeel® is a broad-spectrum, antiedematous, antiexudative, anti-inflammatory analgesic composed of biological and mineral substances, and it is a homeopathic combination medication. It has been used to treat inflammation and a variety of injuries, mainly to stimulate wound healing, provide pain relief, stop bleeding, improve muscle tone, and for a potential antiviral effect. It is a safe alternative to nonsteroidal anti-inflammatory medication.[1] Traumeel® has 12 biological ingredients and 2 mineral substances: *Arnica montana, radix* (mountain arnica), *Calendula officinalis* (calendula), *Hamamelis virginiana* (witch hazel), *Millefolium* (milfoil), *Belladonna* (deadly nightshade), *Aconitum napellus* (monkshood), *Chamomilla* (chamomile), *Symphytum officinale* (comfrey), *Bellis perennis* (daisy), *Echinacea angustifolia* (narrow-leafed coneflower), *Echinacea purpurea* (purple coneflower), *Hypericum perforatum* (St John's wort), *Hepar sulphuris calcareum* (calcium sulfide), and *Mercurius solubilis* (no common name).

The objectives of this study were to explore the nature of adverse events caused by Traumeel® and to research the possible interaction of Traumeel® with biological function and/or gastrointestinal tract occult bleeding. Our primary objective was to document any adverse reactions to the study medication, and the secondary objective was to document any significant variation in physiological parameters.

This study was designed to evaluate the clinical safety of Traumeel® by instructing healthy subjects to ingest the medication on a daily basis. Adverse effects and physiological parameters were evaluated throughout the study. The Human Research Review Committee of the University of New Mexico School of Medicine approved this study on the basis of the final protocol in April 1998.

METHODS

Subject Population

Twenty healthy volunteers from the University of New Mexico Hospital who met the inclusion criteria were enrolled in the study. The volunteers received detailed written information on the trial medication and study procedures. In addition, the participants were informed about the possible risks of the study medication by a physician or nurse, and subjects provided written informed consent. The subjects were informed that they could withdraw from the study at any time by their own discretion. The confidentiality of any medical data collected in the study was maintained respective to applicable federal and state laws and regulations.

Healthy men and women aged 18 to 75 years were eligible to participate. Children, pregnant or lactating women, patients with known allergies to the study drug, and subjects taking any investigational drug within 4 weeks of the start of the study were excluded.

Other exclusion criteria included inability to comply with the trial protocol, concomitant diseases, adverse events due to use of a birth control pill, and use of illegal substances. Subjects taking drugs or other therapies with comparable/interactive effects to the study drug or synthetic medications or herbal substances were asked to stop the regimens at least four weeks before participation in the study.

Medication

The study medication was first dispensed during the baseline visit. The subjects were instructed to take two Traumeel® tablets (300 mg each) sublingually at 8:00 AM, noon, and 5:00 PM every day, for a total of 28 days. A research coordinator reminded each subject to take the medication at the designated times. Subjects were instructed to take the medication at least 10 minutes before eating or drinking. The usual therapeutic dose of Traumeel® is one tablet three times per day. The number of tablets given to the subject was compared with the remaining tablets to assess compliance. Each subject's daily log was inspected to evaluate compliance. No concomitant medications were allowed throughout the study except for birth control pills.

Assessments

The first visit to the study center was the baseline screening visit, during which each subject's medical history was taken, including history of cardiovascular; head, eyes, ears, nose, and throat; pulmonary; gastrointestinal; endocrine; musculoskeletal; neurologic; renal; hepatic; and psychiatric diseases. A history was also taken of allergic reactions, past alcohol and drug abuse, and current medications. A physical examination with vital signs was performed at baseline and post-treatment. A serum sample to determine prothrombin time (PT), partial thromboplastin time (PTT), complete blood cell count, liver and kidney profile, and clinical chemistry, and a stool sample to test for occult blood were collected during this visit. A urine pregnancy test was also administered to all female subjects. At this first visit, informed consent was discussed and signed.

Variable	Baseline	Post-treatment	t Test
Hematocrit, %	42.8 ±3.3	42.7±3.2	0.19
Hemoglobin, g/dL	13.9±2.6	14.3±1.3	0.92
Neutrophils, x109/L	3.56±1.1	3.68±1.4	0.52
Platelets, x109/L	259.9±50.2	255.4±44.7	0.99
Red blood cells, x1012/L	4.98±0.44	4.92±0.47	1.83
White blood cells, x109/L	5.9±1.3	5.0±1.5	0.94

** All data are presented as mean ± SD.*

*Table 1: Hematological Laboratory Measurements at Baseline and Post-treatment**

Participants were required to fast for eight hours prior to each visit after 7, 14, 21, and 28 days had passed for individual weekly follow-up. During the subsequent follow-up visits, serum and stool samples were collected to evaluate any physiological changes due to ingestion of the study medication. The following measurements were performed: blood pressure (systolic and diastolic), heart rate measurements in sitting position, respiratory frequency, oral body temperature. Laboratory analyses were performed at the University of New Mexico Hospital Laboratory, 2211 Lomas Boulevard NE, Albuquerque, NM 87131. Hemoglobin, hematocrit, red blood cells, white blood cells with differential count, neutrophils, and platelet counts were measured at baseline and each follow-up visit. Creatinine, fasting glucose, sodium, potassium, albumin, γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and direct bilirubin measures were also performed at baseline and each follow-up visit. Analyses of PT and PTT were performed at baseline, week 2, and the final visit.

Each subject's daily log was evaluated for occurrence of adverse events and study drug compliance. During the final visit, a physical examination recheck was performed on each subject. There were no dropouts or premature terminations of subject participation in the study.

Adverse Events

Adverse events included all disturbances of general health status, subjective and objective disease symptoms (including relevant changes of laboratory values), intercurrent diseases, observed in the context of the trial irrespective of a possible causal relationship with administration of the study drug. Each subject reported adverse events in the daily diary provided by the investigator. Interim analysis was made at 7, 14, and 21 days by examination of the patient diary.

Regardless of causal relationship, all adverse events reported by subjects or observed by the investigator were recorded on the Adverse Events Data Sheet. Severity of the adverse event was ranked on a scale from 1 to 4: 1=mild; 2=moderate; 3=severe; and 4=life-threatening. Relationship of each adverse event to the ingestion of the study drug was ranked on a scale from 1 to 5: 1=unrelated; 2=remote; 3=possible; 4=probable; and 5=related. Action taken to relieve the adverse event was categorized from 1 to 4: 1=no action taken; 2=discontinued drug; 3=treatment required; and 4=hospitalization required. Finally, the outcome of the adverse event was ranked as 1=event resolved or 2=event or reaction continues. Had any serious adverse events occurred they would have been reported immediately by the primary investigator to the Scientific Department of HEEL Inc., the manufacturer of the drug.

Variable	Baseline	Post-treatment	t Test
Albumin, g/dL	4.05±0.22	4.06±0.25	0.18
Alkaline phosphatase, U/L	61.8±15.2	64.0±14.6	0.79
Aspartate aminotransferase, U/L	29.7±8.4	31.4±9.6	0.94
Alanine aminotransferase, U/L	21.3±8.3	24.6±11.9	1.68
Calcium, mg/dL	9.04±0.24	9.12±0.27	1.22
Creatinine, mg/dL	0.895±0.16	0.910±0.14	0.77
Direct bilirubin, mg/dL	0.20±0.0	0.20±0.0	...
Total bilirubin, mg/dL	0.96±0.41	0.88±0.30	1.36
Gastrin, pg/mL	50.2±22.4	67.5±45.7	1.81
γ-Glutamyltransferase, U/L	32.2±18.1	34.7±27.4	0.98
Glucose, mg/dL	88.2±12.6	87.2±8.6	0.33
Potassium, mmol/L	4.05±0.25	4.00±0.20	0.71
Magnesium, mg/dL	2.0±0.14	2.9±3.9	1.02
Sodium, mmol/L	140.4±1.8	140.3±1.5	0.48
Phosphorus, mg/dL	4.6±6.3	3.2±0.58	0.89
Uric acid, mg/dL	4.8±1.1	5.0±1.5	1.28

** All values are presented as mean ± SD. Ellipses indicate t test was not conducted to evaluate changes.*

*Table 2: Clinical Chemistry Results at Baseline and Post-treatment**

Statistical Analysis

The independent variable was treatment by the study drug taken over the course of 28 days. The dependent variables were the laboratory test variables, adverse events, severity of adverse events, relationship of adverse events to administration of the study drug, action taken to resolve the event, and outcome of the adverse events. The study conditions were standardized throughout the group. The sample size (n=20) was decided by the sponsor, Heel Inc., 11600 Cochiti Road SE, Albuquerque, NM 87123. The study was a within-subjects design and was not blinded.

All adverse events were listed together with information on onset, duration, severity, relationship to drug, and outcome. Frequency statistics were run to evaluate the frequency of adverse events, their severity, their relationship to study medication, any action taken to resolve them, and the outcomes of the events. A paired samples t test was used to evaluate changes that occurred in the physiological variables from baseline to post-treatment. The biometrical evaluation was performed using a personal computer with the SPSS statistical software package (SPSS Inc, Chicago, IL). The study conformed to the principles of the Declaration of Helsinki as well as with German drug law and the requirements thereof.

RESULTS

According to the trial protocol, all subjects were placed into the treatment group and received Traumeel® tablets sublingually three times per day for 28 days. Vital signs were monitored weekly throughout the study. Blood pressure, respiratory rate, heart rate, body temperature, weight, and height were also measured in conjunction with vital signs. All subjects' vital signs remained stable throughout the study.

Laboratory Values

The hematological laboratory values measured at baseline and post-treatment are compared in Table 1. The clinical chemistry laboratory values measured at baseline and post-treatment are compared in Table 2. Analysis of PT and PTT revealed no significant differences from baseline to post-treatment in all subjects (t_{19}=1.18; P>.05). Stool samples were negative for occult blood throughout the study for all subjects.

Adverse Events

A total of 11 subjects of 20 reported 36 adverse events after ingestion of the study medication. Headache was the most commonly reported adverse event (n=15). Other common events included diarrhea and stomach discomfort/bloating (n=6), feelings of nausea and perceptions of "feeling buzzed" (n=2). The least frequently reported adverse events (n=1) were right arm pain, puffy eyelids, insomnia, thigh pain, and dizziness.

All these events were considered to be mild (n=30; 83.3%) or moderate (n=6; 16.7%) in severity. No action was taken to relieve these symptoms. Also, every adverse event experienced by the 11 study participants was transient and resolved despite continuation of the study drug. The majority (n=22; 61%) of adverse events were considered to be remotely related to the study medication, while 33% of the events (n=2) were considered to be possibly related to the study medication. Only 2 cases (6%) were completely unrelated to the study drug. No adverse event was considered probably or definitely related to ingestion of the study medication.

Comment

The purpose of this research was to evaluate the clinical safety of Traumeel®,

an investigational homeopathic anti-inflammatory analgesic. All the events experienced by the subjects were reported as being mild to moderate in severity, unrelated to possibly related to ingestion of the study medication, and subsequently resolved without intervention despite continuation of the drug.

In conclusion, with respect to the data, the use of Traumeel® was very well tolerated by participants in this study. No severe toxic effects were observed and there was no evidence of gastrointestinal bleeding. Conventional non-steroidal anti-inflammatory drugs cause gastrointestinal ulceration and bleeding in some patients and are especially hazardous for patients with diseases or taking medications that interfere with normal coagulation. Traumeel® has anti-inflammatory and analgesic effects and does not inhibit the arachidonic acid pathway of prostaglandin synthesis. It deserves consideration as a safer alternative for these patients.

Reference

1) PDR 53rd Edition, 1999:1287.

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