Clinical Evaluation of Metal Panel Allergens: Aluminum, Copper, Manganese, Molybdenum, Tin, Titanium, Vanadium and Zinc Metal Dose Response Study

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To evaluate the diagnostic performance and safety of metal allergens proposed for inclusion in Metal Panel T.R.U.E. Test. The study will compare the diagnostic performance (primary) and safety (secondary) of ascending patch test doses of aluminum,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON47406

Source
ToetsingOnline

Brief title
Metal Dose Response Study

Condition

- Epidermal and dermal conditions

Synonym
Eczema, Skin Rash

Research involving
Human

Sponsors and support

Primary sponsor: SmartPractice Dermatology|Allergy
Source(s) of monetary or material Support: SmartPractice will be responsible for the funding of this study

Intervention

Keyword: Dermatitis, Inflammation

Outcome measures

Primary outcome

Determination of optimal test allergen dose will be based on the following

criteria:

-The lowest concentration of each dilution series allergen eliciting positive

responses in a minimum of 15 subjects. Positive responses (defined as score of

1+, 2+ or 3+ during at least one reaction assessment visit) may be due to the

dilution series allergen, a corresponding reference allergen or both. If a

significant number of 3+ responses are elicited, the dose will be selected

based on 1+ and 2+ responses.

-Approximately 50% of the 15 positive responses attributed to a dilution series

allergen,

-Moderate to very good concordance (measured using Cohen*s kappa, includes all

subjects who test each allergen) between the dilution series and reference

allergens. [less than 0% no agreement, 0-20% poor, 20-40% fair, 40-60%

moderate, 60-80% good, 80% or higher very good].

Secondary outcome

Determination of allergen safety

-Frequency of tape and polyester chip induced irritation or allergic reactions

at Visits 2 through 6.

-Frequency of subject reported sensations of itching and/or burning for each allergen panel at patch removal.

-Frequency of positive (1+, 2+, 3+) skin reactions for each investigational and reference allergen dose at each post removal visit and overall.

-Frequency of negative, doubtful, irritant, late and persistent skin reactions for each investigational and reference allergen dose at each post removal visit (late and persistent reactions at visits 4, 5 and 6 only).

-Frequency of adverse events. Documentation for all local and systemic adverse reactions classified by the investigator as possibly or definitely related to the study product (e.g., erythema, hyper-pigmentation, hypo-pigmentation, skin thinning or dermatitis flare) will include grade (mild, moderate or severe) and time point (clinic visit).

Study description

Background summary

As a group, metals are the most common contact allergens. Contact allergy to metals such as nickel, cobalt, and chromium is prevalent in the general population. It is estimated that up to 17% of women and 3% of men are nickel allergic, and that about 1 to 2% are allergic to cobalt, chromium, or both. Metal-induced allergic contact dermatitis (ACD) is expressed in a wide range of cutaneous reactions following prolonged or repeated exposure to personal products such as cosmetics, tattoos, detergents, jewelry, piercing studs, leather goods, cell phones, clothing buttons, snaps, zippers, partial dentures, dental braces and restorations. Occupational exposure in the metal and construction industries is also a significant risk factor for metal allergy reports. Apart from the well-known significance of nickel, cobalt, chromium and gold in developing ACD, other metals such as aluminum, beryllium, copper, iridium, indium, mercury, palladium, platinum, rhodium, molybdenum, manganese, zinc, cadmium and titanium have been reported as increasing causes of skin

hypersensitivity.

Because metal contact allergy is increasing there is a need to develop a series of standardized metal patch test allergens utilizing the same allergen delivery technology as used in the T.R.U.E. TEST* product. Metal Panel T.R.U.E. TEST will be indicated for patients in whom the physician suspects contact dermatitis related to:

Cardiac implant (stent, pacemaker, etc.)
Orthopedic implant (knee, hip or other)
Gynecological implant or device
Surgical hardware (plates, screws, wires, pins, rods, expanders, staples)
Dental metal implant
Dental metal appliance, prosthesis or filling
Inflammation associated with an oral metal implant:
Itching, papules or nodules at injection site of aluminum containing vaccination
Dermatitis over site of metal implant
Systemic contact dermatitis
Accelerated restenosis of cardiac stent
Aseptic loosening
Persistent joint pain

Other symptoms may also be associated:

Persistent and recalcitrant dermatitis
Dorsal or patchy hand dermatitis
Leg and foot dermatitis
Facial dermatitis (excluding seborrheic)
Discoid dermatitis
Dermatitis with unusual distribution
Atypical allergic symptoms

Study objective

To evaluate the diagnostic performance and safety of metal allergens proposed for inclusion in Metal Panel T.R.U.E. Test. The study will compare the diagnostic performance (primary) and safety (secondary) of ascending patch test doses of aluminum, copper, manganese, molybdenum, tin, titanium, vanadium and zinc allergens.

To determine if subjects who have not had previous patch testing are allergic to any of the most common metal allergens; nickel, cobalt chromium and gold.

Study design

This is a prospective, multi-center, double-blind randomized design. A 48-hour application (approximate) of investigational allergen panel(s), an excipient control and corresponding reference petrolatum allergen(s) will be applied to the skin of human subjects to test for potential positive allergic responses. Test sites will be evaluated at 3-4, 7-8, 10-14 and 19-23 days after application. The chosen evaluation times are consistent with generally accepted international patch test guidelines and are designed to prevent missed late reactions and false negatives. The final clinic visit (day 21) allows the investigator to evaluate any late or persistent localized reactions. The investigator may choose to perform this visit via telephone if there are no residual reactions. If there are persistent escalating reactions noted at Visit 6, the investigator will determine and record follow up action.

Intervention

Ascending patch test doses and a reference allergen will be applied to the upper backs of the study subjects and removed after two days. Test site skin reactions will be evaluated at least four times which is consistent with generally accepted international patch test guidelines designed to prevent missed late reactions and false negatives.
During the first 2 days of the study, test sites and patch test panels must remain dry and protected. Activities that involve excess moisture (sweat or water), movement, or sun exposure must be avoided. After panel removal, and until the final 3-week visit, subjects must protect test sites from sun, irritation, medicaments, and foreign or harsh substances.

Investigational panels will be produced with ascending doses of allergen and an excipient control. These dose ranges were selected based on published studies of patch testing with the metals and available non-standardized patch test products currently available in the U.S. and Europe.

Investigational allergen panels are packed and labeled by the manufacturer SmartPractice Denmark ApS. Products are labeled with allergen batch codes and expiration dating. Commercially available reference allergens may be used or the reference allergen syringes may be prepared and labeled by the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden.

All investigational products used in this study must be accounted for. Records must show amount and date of delivery of all test materials to each local investigator. Likewise dates, amount, and signatures should document return of unused test tapes. Product deliberately and/or accidentally destroyed by the investigator must also be documented.
The use of the investigational product for the individual subject, including the subject number, date of application of the test panel, and date of removal of the test panel will be documented in the Case Report Form

Study burden and risks

The patch test is considered to be a safe and optimum method to identify the cause of allergic contact dermatitis when performed and interpreted correctly. Evaluations regarding the safety of the T.R.U.E. Test product has been based primarily on the scientific and medical literature in addition to clinical trials conducted by Smart Practice and SmartPractice Denmark (previously Mekos Laboratories AS). After many years of extensive patch testing, no data has evolved to indicate there are any significant safety concerns or long-term adverse effects to human tissue other than the expected allergic response in a sensitized individual.

The elicitation of a specific immunologic inflammatory response at the test site (forearm or back) on re-exposure to a specific allergen, is the expected reaction and the basis for this diagnostic patch test method. This response is expected to manifest 24 to 72 hours in a previously sensitized individual. Patch testing aims to reproduce (on a small scale) the eczematous response of the patient when in contact with the suspect allergen(s).

Patch tests are typically applied to the skin of the upper back. The humidity of the skin hydrates the allergen, allowing it to migrate into the skin, thereby reaching the cells of the immune system. The test is removed after 48 hours and read at 72-96 hours after the application, when the allergic responses are fully developed and mild irritant reactions have faded. Additional readings at 1 week and 21 days after panel placement are also advised in some cases.
Site reactions are graded according to standard patch testing guidelines established by the International Contact Dermatitis Research Group.

The following reactions, although exceedingly rare, have been reported. Unless all 3 SUSAR criteria are met, these reactions will be reported as adverse events.
-Active Sensitization: A positive reaction observed 7-14 days after application, with no preceding reaction. The positive reaction must meet the criteria for an allergic reaction (papular or vesicular erythema and infiltration), to help distinguish between a false-positive and sensitization.
-Bacterial or Viral Infections: An inflammation due to a skin infection.
-Ectopic Flare: A positive patch test reaction accompanied by a flare of an existing or pre-existing dermatitis that was caused by the test allergen.
-Excited Skin Syndrome (Angry Back): A state of skin hyper-reactivity induced by dermatitis on other parts of the body or by a strong positive skin-test reaction in which other patch test sites become reactive, especially to marginal irritants.
-Immediate Contact Urticaria (ICU): Some allergens can cause ICU (balsam of Peru, cinnamic aldehyde, neomycin, bacitracin) with the typical wheal and flare appearing 30- 40 minutes after application. The reaction only occurs in

individuals who are pre-sensitized. Non-allergic urticaria is possible in non-sensitized individuals and is less serious because the systemic reactions are not evoked. Most non-allergic reactions remain local while ICU may produce generalized urticarial lesions. Most urticarial reactions, reported in conjunction with patch testing, are due to higher concentrations of the allergen (e.g. 5% pet).
-Koebner Phenomenon: A positive patch test reaction in a patient with active psoriasis or lichen planus may reproduce these dermatoses at the patch site during the weeks after testing. Symptoms are cleared with topical corticosteroids.
-Necrosis, Scarring and Keloids: Testing with strong irritants (acids, alkalis or chemicals of unknown composition) may produce such adverse events but are considered extremely rare.
-Pressure Effect: Application of a patch test in certain individuals, which produces an edematous area that is typically most intense at the margins. Dermatographic individuals are more likely to develop this reaction.

Contacts

Public
Selecteer

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US
Scientific
Selecteer

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

a. 18 years of age or older.
b. Past positive patch test result within the past 10 years (to one of the dilution series metals being tested on this study), a strong suspicion of metal contact allergy, or known or suspected infection of the skin, joints and other sites associated with metal exposure as listed in the Qualification Questionnaire.
c. Unable to become pregnant or willing to use an acceptable method of contraception to prevent pregnancy if female of childbearing potential (Inability to become pregnant would include all male subjects and female subjects who are postmenopausal for at least 1 year, or surgically sterile- have had a hysterectomy, bilateral ovariectomy, uterine ablation or bilateral tubal ligation. Acceptable methods of contraception include: 1) systemic birth control; 2) double barrier method; 3) IUD; 4) vasectomized partner; or 5) abstinence from sexual intercourse. Subject must agree to use acceptable contraception for the duration of the entire study.)
d. Understands and signs the approved Informed Consent form which is consistent with all institutional, local and national regulations.

Exclusion criteria

a. Breastfeeding or pregnant (as determined by urine pregnancy test) or intending to become pregnant during the course of the study.
b. Topical treatment with corticosteroids or other immunosuppressive agents on or near the test area 14 days prior to inclusion through the end of the subject*s participation in the study.
c. Systemic treatment with corticosteroids (equivalent to > 10 mg prednisone) or other immunosuppressive agents 14 days prior to inclusion through the end of the subject*s participation in the study. Inhaled treatments and steroidal nose or eye drops are permitted.
d. Treatment with ultraviolet (UV) light (including tanning) during the 3 weeks prior to inclusion through the end of the subject*s participation in the study.
e. Acute dermatitis outbreak or dermatitis on or near the test area on the back.
f. Known or suspected infection of the skin, joints or other site(s) associated with metal exposure
g. Condition such as; fibromyalgia, chronic fatigue, depression, cognitive impairment, flu-like symptoms, diarrhea and/or headache without at least one of the symptoms related to metal exposure listed in Section 10.1 under physical examination.
h. Condition such as; psoriasis, dermatitis herpetiformis, mycosis fungoides or cutaneous T-cell lymphoma that may confound the evaluation of allergic contact dermatitis.
i. Inability to comply with patch test study requirements including multiple return visits and activity restrictions (e.g., protecting test panels from excess moisture due to showering or

vigorous activity).
j. Participation in a clinical trial of an investigational drug, treatment or device during this study or 3 weeks prior to inclusion in this study.
k. An opinion of the Investigator that deems the potential subject to be non-compliant, unable to return for study visits or complete the study as detailed in the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2018
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aluminum chloride
Generic name:	Aluminum chloride
Product type:	Medicine
Brand name:	Aluminum lactate
Generic name:	Aluminum lactate
Product type:	Medicine
Brand name:	Ammonium molybdate
Generic name:	Ammonium molybdate
Product type:	Medicine
Brand name:	Copper sulfate

Generic name:	Copper sulfate
Product type:	Medicine
Brand name:	Manganese chloride
Generic name:	Manganese chloride

Ethics review

Approved WMO Date:	29-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002678-19-NL
ClinicalTrials.gov	NCT02615249
CCMO	NL57210.029.16

Study results

Date completed:	11-06-2019
Actual enrolment:	20

Summary results
Trial is onging in other countries