

## 21 Publications



### **In vitro evaluation of phototoxic properties of systemic antipsoriatics**

Sep 7, 2016 • Supplement to the Journal of Investigative Dermatology, Volume 136, Number 9S, Supplement 2, September 2016

A combination therapy with phototherapy at the beginning of a systemic antipsoriatic therapy or in case of only a partial remission can be reasonable. Therefore phototoxic properties of fumaric acid esters (Fumaderm), apremilast (Otezla), methotrexate (Metex), anti-TNF- $\alpha$  agents (adalimumab (Humira), etanercept (Enbrel), infliximab (Humira)), ustekinumab (Stelara) or secukinumab (Cosentyx) were tested using an in vitro photohaemolysis test and different light sources. Human erythrocytes from three donors were incubated with the compounds each at three concentrations and irradiated with light sources rich in UVA (Waldmann UVA 700) or UVB (TL 20W/12 light bulbs), respectively. Doses were 0, 25, 50, 75 J/cm<sup>2</sup> UVA and 0, 0,8, 1,600, 2,400 mJ/cm<sup>2</sup> UVB. Photo-induced hemolysis was calculated as percentage of complete hemolysis. This test demonstrated minor phototoxic properties (< 15% photo-hemolysis) of some of the used systemic antipsoriatics (adalimumab, fumaric acid ester, infliximab, ustekinumab), while the other ones (apremilast, etanercept, methotrexate, secukinumab) showed no phototoxic properties. Therefore combination of all these substances with either UVA-rich or UVB-rich irradiation seems to be possible with regard to the absence of severe phototoxic properties of these substances.

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### **In vitro evaluation of phototoxic properties of systemic antipsoriatics**

Sep 7, 2016 • ESDR Sept 2016 Poster Session

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### **In vitro Evaluation of Phototoxic Properties of Systemic Antipsoriatics.**

Jul 6, 2016 • SciTz Dermatol. 2016. 1(1): 1001

A combination therapy with phototherapy at the beginning of a systemic antipsoriatic therapy with fumaric acid esters, apremilast, methotrexate, anti-TNF- $\alpha$  agents, ustekinumab or secukinumab or in case of only a partial remission is sometimes used. As these chemicals can be absorbed into the skin, photosensitive effects with the clinical symptoms of exaggerated sunburn should be investigated. We assessed phototoxic properties of these substances using an in vitro photohaemolysis test. In this in vitro model of phototoxicity UV-induced damage of erythrocytes and resultant haemolysis is measured. This test exhibited no phototoxic effects. Therefore combination of these substances with either UVA-rich or demonstrated minor phototoxic properties (< 15% photohemolysis) of some of the used systemic antipsoriatics (adalimumab, fumaric acid ester, infliximab, ustekinumab). The other tested drugs (apremilast, etanercept, methotrexate, secukinumab) UVB-rich irradiation is probably safe with regard to the absence of severe acute phototoxic properties of these substances, but an estimation of the long-term risk/benefit ratio of such a therapy cannot be made.

Other author



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### **Photosensitizing properties of compounds related to benzophenone.**

2013 • Acta dermato-venereologica 2013;93(1):30-2.

Benzophenone is a phototoxic compound with absorption maxima in the ultraviolet A (UVA) and ultraviolet B (UVB) range. Many benzophenone derivatives are known to be photosensitizing. On the other hand, 2-hydroxy-4-methoxybenzophenone is used as a photoprotective agent. The aim of the present study was to analyse a range of benzophenone derivatives and thus examine the effects of molecular changes in the benzophenone molecule on phototoxic behaviour. Phototoxicity was tested by an in vitro photohaemolysis test. The tested compounds were benzophenone itself and the derivatives 2-hydroxybenzophenone, 2-aminobenzophenone, 2-benzoylbenzoic acid, 3-hydroxybenzophenone, and 4-hydroxybenzo-phenone, as well as the structurally similar compounds 9-fluorenone, 9-fluorenone-2-carboxylic acid, cyclohexyl phenyl ketone, and 1,4-naphtho-quinone. It was shown that minor changes in molecular structure can result in highly different phototoxic characteristics.

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### **In vitro evaluation of phototoxic properties of proton pump inhibitors, H2-receptor antagonists and statins.**

2012 • Acta dermato-venereologica 2012;92(2):208-10.

Proton pump inhibitors and H2-receptor antagonists are widely used in the treatment of peptic ulcers and gastric acid-related diseases, because of their acid production inhibitory properties. Another group of frequently pre-scribed drugs, statins are used to significantly decrease the serum levels of cholesterol, thus stabilizing atherosclerotic plaques. Statins, as well as proton pump inhibitors and H2-receptor antagonists, are generally well tolerated. However, there are some case reports of photosensitive side-effects (1–12): ranitidine has been shown to induce increased photosensitivity, whereas pantoprazole, lansoprazole and omeprazole have been associated with the development of cutaneous lupus erythematosus, a known photosensitive skin disease. Furthermore, statins mainly induced chronic actinic dermatitis. We therefore assessed the in vitro phototoxic potential of several proton pump inhibitors, H2 antagonists, and statins, using a photohaemolysis test. This assay is an established in vitro method used in isolated erythrocytes for measurement of possible phototoxic effects. The effects of anti-oxidative substances (e.g. ascorbic acid, Trolox®, a water-soluble derivative of vitamin E) can also be assessed easily.

Other authors



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### **Effect of ultraviolet (UV) A, UVB or ionizing radiation on the cell cycle of human melanoma cells.**

2007 • The British journal of dermatology 2007;156(5):843-7.

**BACKGROUND:** One important component of the cellular response to irradiation is the activation of cell cycle checkpoints. It is known that both ultraviolet (UV) radiation and ionizing radiation (IR) can activate checkpoints at transitions from G(1) to S phase, from G(2) phase to mitosis and during DNA replication. **OBJECTIVES:** To evaluate the effects of irradiation with different wavelengths on cell cycle alterations. **METHODS:** p53-deficient IPC-298 melanoma cells were irradiated with 10 J cm<sup>-2</sup> UVA, 40 mJ cm<sup>-2</sup> UVB, or with 7.5 Gy IR. Cell cycle effects were then determined by DNA/5-bromodeoxyuridine dual-parameter flow cytometry. **RESULTS:** IPC-298 cells irradiated in G(1) with UVA were not arrested at the G(1)/S transition, but at the G(2)/M transition. Despite p53 deficiency, the cells showed a G(1) arrest after UVB exposure. Furthermore, IR did not affect G(1) or S phase, but induced G(2) phase arrest. Hence, the effects of UVA, but not of UVB, on the cell cycle in p53-deficient melanoma cells are comparable with those of IR. **CONCLUSIONS:** UVA and IR induce radical-mediated strand breaks and DNA lesions, and UVB essentially induces thymine dimers that lead to excision repair-related strand breaks. Different cell cycle effects may be a consequence of different types of DNA damage. The results showed that UVB-irradiated p53-deficient cells are arrested in G(1). Irradiation with the solar radiation component UVB can therefore result in a beneficial retardation of tumour promotion in human skin carrying p53-mutated cell clones.

Other authors



### Evaluation of phototoxic properties of fragrances.

2007 • Acta dermato-venereologica 2007;87(4):312-6.

Fragrances are widely used in topical formulations and can cause photoallergic or phototoxic reactions. To identify phototoxic effects, 43 fragrances were evaluated in vitro with a photohaemolysis test using suspensions of human erythrocytes exposed to radiation sources rich in ultraviolet (UV) A or B in the presence of the test compounds. Haemolysis was measured by reading the absorbance values, and photohaemolysis was calculated as a percentage of total haemolysis. Oakmoss caused photohaemolysis of up to 100% with radiation rich in UVA and up to 26% with radiation rich in UVB. Moderate UVA-induced haemolysis (5-11%) was found with benzyl alcohol, bergamot oil, costus root oil, lime oil, orange oil, alpha-amyl cinnamic aldehyde and laurel leaf oil. Moderate UVB-induced haemolysis was induced by hydroxy citronellal, cinnamic alcohol, cinnamic aldehyde, alpha-amyl cinnamic aldehyde and laurel leaf oil. The phototoxic effects depended on the concentration of the compounds and the UV doses administered. We conclude that some, but not all, fragrances exert phototoxic effects in vitro. Assessment of the correlation of the clinical effects of these findings could lead to improved protection of the skin from noxious compounds.

Other authors



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### Pathophysiology of acne

2007 • Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 2007;5(4):316-23.

Other authors



### Mastocytosis -- clinical picture and diagnosis

2006 • Deutsche medizinische Wochenschrift (1946) 2006;131(28-29):1616-21.

Other authors



### Mastocytosis and Hymenoptera venom allergy.

2006 • Current opinion in allergy and clinical immunology 2006;6(4):284-8.

**PURPOSE OF REVIEW:** Mastocytosis is a rare disease characterized by increased mast cells in skin and/or internal organs. We evaluate the impact of mastocytosis on diagnosis and treatment of Hymenoptera venom allergy. **RECENT FINDINGS:** Patients with Hymenoptera venom allergy who suffer from mastocytosis develop life-threatening sting reactions more often than those who do not. When patients with Hymenoptera venom allergy were systematically examined for mastocytosis, it was found to be represented to an abnormally high extent. Most patients with mastocytosis tolerate venom immunotherapy with no or only minor systemic symptoms. Venom immunotherapy was found to be marginally less effective in patients with mastocytosis than in those without evidence of mast cell disease (defined as absent cutaneous mastocytosis combined with a serum tryptase concentration of <11.4 microg/l). Several deaths from sting reactions were reported in patients with mastocytosis after venom immunotherapy was stopped. These patients should have venom immunotherapy for the rest of their lives. **SUMMARY:** Patients suffering from mastocytosis and Hymenoptera venom allergy are at risk from a particularly severe sting anaphylaxis. They need optimal diagnosis and treatment. In patients presenting with Hymenoptera venom allergy, screening tests by measurement of serum tryptase concentration, and a careful skin examination, are highly recommended.

Other authors



### Contact urticaria to giraffe hair.

2005 • International archives of allergy and immunology 2005;138(4):324-7.

**BACKGROUND:** Immediate-type hypersensitivity to animal proteins is a common problem in people occupationally exposed to animals. **METHODS:** A 19-year-old female working as a voluntary zookeeper in her off-time suffered from hives on her forearms following contact to the fur of a giraffe. For diagnostic evaluation, skin prick tests, assessment of specific serum IgE antibodies, and basophil activation tests were performed. **RESULTS:** Skin prick tests with a standard series of common aeroallergens were positive for various pollens. Prick testing with native materials was positive for extracts of hair from two different giraffe subspecies in the patient, but not in control subjects. By CAP-FEIA, no specific serum IgE antibodies to dander of a large variety of animals were found in the patient. In the basophil activation test, expression of the activation marker CD63 was induced by extract of giraffe hair on the cells from the patient, but not on those from unaffected controls. **CONCLUSIONS:** This patient suffers from an 'exotic' immediate-type contact allergy to giraffe hair.

#### Other authors



### Elevated 17-hydroxyprogesterone serum values in male patients with acne.

2005 • Journal of the American Academy of Dermatology 2005;53(6):955-8.

**BACKGROUND:** Androgen excess may provoke or aggravate acne by inducing seborrhea. In women, androgen disorders are frequently suspected when acne is accompanied by hirsutism or irregularities of the menstrual cycle. In men, however, acne may be the only sign of androgen excess. **OBJECTIVE:** Our aim was to investigate whether male patients with acne display pathologic androgen blood values. **METHODS:** This case-control study at a university dermatology department with referred and unreferred patients investigated male acne patients (n = 82, consecutive sample) in whom the diagnosis of mild to severe acne was made, as well as a control group of men without acne (n = 38). The main outcome measures were androgen parameters including morning values of testosterone, luteinizing hormone, follicle-stimulating hormone, dehydroepiandrosterone sulfate, androstenedione, and 17-hydroxyprogesterone; as well as a corticotropin stimulation test. **RESULTS:** 17-Hydroxyprogesterone levels were significantly higher (P = .01) in acne patients than in the control group, whereas the other parameters did not differ significantly. In addition, the corticotropin stimulation test revealed abnormal 17-hydroxyprogesterone induction values in 10 of 82 patients. **LIMITATIONS:** The analysis is limited to a selection of androgen parameters. **CONCLUSION:** The results suggest that in men irregularities of adrenal steroid metabolism may be a factor contributing to acne.

#### Other authors



**Evaluation of phototoxic properties of antimicrobials used in topical preparations by a photohaemolysis test.**

2005 • Acta dermato-venereologica 2005;85(1):13-6.

Antimicrobials are widely used in topical formulations as preservatives or as therapeutically active agents. Photosensitization by such compounds has not yet been studied systematically. To identify possible phototoxic properties, antimicrobials (benzyl alcohol, bronopol, chloracetamide, clioquinol, diazolidinyl urea, ethylenediamine dihydrochloride, formaldehyde, glutaraldehyde, imidazolidinyl urea, sodium benzoate, propylene glycol) were evaluated in vitro by means of a photohaemolysis test using suspensions of human erythrocytes. Irradiations were performed with UVA- and UVB-rich light sources. In the presence of bronopol or clioquinol, there was photohaemolysis up to 78.1% or 48.5% with UVA and up to 100% or 34.3% with UVB, respectively. The phototoxic effect depended on the concentration of the compounds and the UV doses administered. None of the other substances tested caused significant photohaemolysis. It is concluded that bronopol and clioquinol exert phototoxic effects in vitro and thus might also cause photosensitization when used on the skin. The clinical significance of this has to be established by further work.

Other authors



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**Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol.**

2005 • The Journal of investigative dermatology 2005;124(2):304-7.

DNA damage caused by ultraviolet (UV) irradiation is considered the main etiologic factor contributing to the development of skin cancer. Systemic or topical application of antioxidants has been suggested as a protective measure against UV-induced skin damage. We investigated the effect of long-term oral administration of a combination of the antioxidants ascorbic acid (vitamin C) and D-alpha-tocopherol (vitamin E) in human volunteers on UVB-induced epidermal damage. The intake of vitamins C and E for a period of 3 mo significantly reduced the sunburn reaction to UVB irradiation. Detection of thymine dimers in the skin using a specific antibody revealed a significant increase of this type of DNA damage following UVB exposure. After 3 mo of antioxidant administration, significantly less thymine dimers were induced by the UVB challenge, suggesting that antioxidant treatment protected against DNA damage.

Other authors



**Tobacco smoke is phototoxic.**

2004 • The British journal of dermatology

Both cigarette smoke and ultraviolet (UV) radiation are known to cause changes of the skin which can be regarded as premature ageing. OBJECTIVES: To assess the theory that the effects of these two exposures could be linked by a phototoxic action of cigarette smoke. METHODS: A photohaemolysis test was used, in which human erythrocytes were incubated with cigarette smoke condensate, followed by UV irradiation and measurement of exposure-dependent haemolysis. RESULTS: Cigarette smoke condensate was clearly phototoxic. Photohaemolysis depended on the concentration of the condensate and UV dose and was more pronounced after exposure to UVA-rich than UVB-rich radiation. CONCLUSIONS: Phototoxicity may be a mechanism by which cigarette smoking causes premature skin ageing. An enhancing effect on photocarcinogenesis has also to be considered.

Other authors



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### **Congenital adrenal hyperplasia and acne in male patients.**

2003 • The British journal of dermatology

Seborrhoea is one pathogenic factor for acne. Androgens induce sebum production, and excess androgen may provoke or aggravate acne. In women an androgen disorder is frequently suspected when acne is accompanied by hirsutism or menstrual irregularities. In men acne may be the only symptom of androgen excess. We report three male acne patients in whom hormonal screening revealed irregularities of androgen metabolism suggestive of late-onset congenital adrenal hyperplasia and who benefitted from low-dose glucocorticoids. Disorders of androgen metabolism may influence acne not only in women, but also in men, and these patients may benefit from low-dose glucocorticoid therapy.

Other authors



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### **Systemic vitamin C and vitamin E do not prevent photoprovocation test reactions in polymorphous light eruption.**

2000 • Photodermatology, photoimmunology & photomedicine

The possible influence of oxidative stress is discussed in the pathogenesis of polymorphous light eruption (PLE). A double-blind, placebo-controlled study of prophylactic treatment with systemic administration of vitamin C (3 g/d) and E (1500 IU/d) for 8 days was undertaken in 9 patients with PLE (verum, n=4; placebo, n=5). Evaluation of the maximal effects after photoprovocation before and after intake of the antioxidants revealed a reduction of most skin reactions (overall skin reaction, papules/vesicles) in both groups with marked differences in the placebo group. The antioxidants in the doses given and over the time period used did not influence the development of PLE, but might interfere with immunosuppressive effects of repeated photo provocation tests.

Other authors



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### **Acne fulminans in late-onset congenital adrenal hyperplasia.**

1999 • Lancet

Acne may be the only clinical sign of androgen excess in men. We report a boy with acne fulminans and androgen excess due to late-onset congenital adrenal hyperplasia.

Other authors



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### **Association between actinic keratoses and potentially photosensitizing drugs.**

1999 • The New England journal of medicine

Other authors



### Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E).

1998 • Journal of the American Academy of Dermatology

UV radiation causes acute adverse effects like sunburn, photosensitivity reactions, or immunologic suppression, as well as long-term sequelae like photoaging or malignant skin tumors. UV radiation induces tissues to produce reactive oxygen species, eicosanoids and cytokines. Inhibition of these mediators might reduce skin damage. Antioxidants such as ascorbic acid and d-alpha-tocopherol have been found to be photoprotective in some in vitro studies and animal experiments. OBJECTIVE: Our purpose was to assess the protective effect of systemic vitamins C and E against sunburn in human beings. METHODS: In a double-blind placebo-controlled study, each of 10 subjects took daily either 2 gm of ascorbic acid (vitamin C) combined with 1000 IU of d-alpha-tocopherol (vitamin E) or placebo. The sunburn reaction before and after 8 days of treatment was assessed by determination of the threshold UV dose for eliciting sunburn (minimal erythema dose [MED]) and by measuring the cutaneous blood flow of skin irradiated with incremental UV doses against that of nonirradiated skin. RESULTS: The median MED of those taking vitamins increased from 80 to 96.5 mJ/cm<sup>2</sup> ( $p < 0.01$ ), whereas it declined from 80 to 68.5 mJ/cm<sup>2</sup> in the placebo group. Cutaneous blood flow changed significantly ( $p < 0.05$ ) for most irradiation doses with decreases in those given vitamins and increases in the placebo group. CONCLUSION: Combined vitamins C and E reduce the sunburn reaction, which might indicate a consequent reduced risk for later sequelae of UV-induced skin damage. The increase of sunburn reactivity in the placebo group could be related to "priming" by the previous UV exposure.

Other authors



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### Phototoxic lysis of erythrocytes from humans is reduced after oral intake of ascorbic acid and d-alpha-tocopherol.

1997 • Photodermatology, photoimmunology & photomedicine

Ultraviolet (UV) radiation causes hemolysis of human erythrocytes in the presence of photosensitizers. This can be used as an in vitro model for evaluating photosensitizing properties of substances. Antioxidants such as ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E) have been found to be photoprotective in such test systems. We assessed the effect of combined systemic intake of both ascorbic acid and d-alpha-tocopherol by human volunteers on phototoxic in vitro lysis of their erythrocytes. In a double-blind placebo-controlled study, 10 subjects took daily 2 g ascorbic acid combined with 1000 IU d-alpha-tocopherol, and 10 took a placebo. Blood was taken before and after 7 days of treatment, erythrocytes were prepared and then incubated with 10(-3) mol/l fenofibrate, a photosensitizer acting in the UVA and UVB region. The suspensions were exposed to radiation rich in UVA (up to 40 J/cm<sup>2</sup> UVA) or to radiation rich in UVB (up to 1.6 J/cm<sup>2</sup>). Photohemolysis of the samples was calculated as a percentage of complete hemolysis. At the end of the treatment phase, in the placebo group photohemolysis was not significantly reduced compared with the initial values at all irradiation doses except for 1.6 J/cm<sup>2</sup> UVB (96% vs 79%;  $P < 0.01$ ). In the group taking vitamins, photohemolysis was significantly reduced at nearly all UV doses, most impressively after moderate UVA irradiation (20 J/cm<sup>2</sup> UVA: 86.5% vs 14.5%;  $P < 0.01$ ). It is concluded that the results of the photohemolysis test are influenced by the antioxidative status of the cell donor and that ascorbic acid and d-alpha-tocopherol also may protect against phototoxic damage in vivo.

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## 3 Languages

Deutsch • Englisch • Niederlande

