Hydrochlorothiazide: Chemical Structure, Therapeutic, Phototoxic and Carcinogenetic Effects in Dermatology

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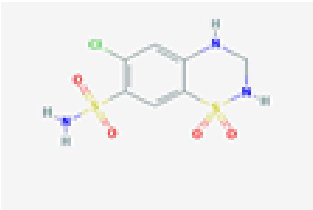
The present paper is a review on hydrochlorothiazide, a diuretic frequently used in therapeutics, also underlining several particularities observed in time and correlated with the results in the literature in what concerns the phototoxic action of this diuretic on skin.

Keywords: hydrochlorothiazide, adverse drug reactions, phototoxicity, carcinogenesis

The chemical formula 6-Chloro-7-sulfamoyl-2H-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide is a slightly white, microcrystalline powder, slightly soluble in water, soluble 1/20 in acetone, slightly soluble in alkaline solutions [1].

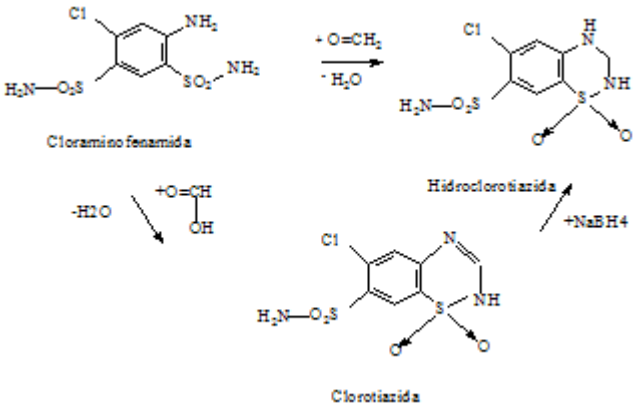


It is obtained directly by treating chloraminophenamide with formaldehyde or paraformaldehyde;

It can also be obtained by treating with formic acid and reducing the intermediate (chlorothiazide) with sodium borohydride.

Experimental part

Obtaining the chemical formula (1)



It is a diuretic, which is a benzothiadiazine class, and acts as a diuretic by preventing the reabsorption of sodium due to the tubular transport mechanisms of sodium. In practice, it prevents sodium reabsorption at the terminal, cortical level of the *Henle* [2]. It is an average efficacious diuretic.

Hydrochlorothiazide is a saluretic, which causes sodium and chloride removal in almost equal amounts. It is indicated in arterial hypertension, all cases where oedema occur, administered orally 25-75 mg per day.

The elimination from the body is in the non-metabolized form of urine, it begins after one hour of administration and is 50% after 5-6 h.

It can lead to potash depletion, so it is recommended to use potassium in a prolonged use, especially during the first weeks of treatment, when more potassium is discharged. Saluretic diuretics that cause hypokalaemia can also produce increased Mg2 + elimination.

Diuretics cross the placenta and pass into breast milk.

Results and discussions

Toxic effects

On the hemato-forming spleen, it can cause leukopenia and thrombopenia; it may have renal and digestive toxic effects; may cause allergic reactions, such as rash.

The treatment does not stop abruptly, as hydrosaline retention and oedema can be accelerated due to secondary sodium-induced hyperaldosteronism induced by sodium depletion with the rebound effect.

An interesting observation is related to the action of hydrochlorothiazide on the skin: allergic reactions, rashes, photosensitisation [3]

It should be emphasized that other diuretic derivatives such as xypamide or indapamide, or furosemide have similar hydrochlorothiazide-like pharmaco-toxic effects and secondary Staphylococcal or other infections can occur on the skin or on other organ [4-6]

Drug-induced photosensitivity is the occurrence of skin-related changes due to the interaction between certain substances and light radiation, the interaction that causes photoactivation of the substance involved. Skin changes occurring in this context may be phototoxic and photoallergic reactions, generally resulting in cutaneous erythema, but it may also involve other forms: lichenoid reactions, pseudo porphyria and lupus-like.

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The substances involved can be administered either as systemic or topical preparations, phototoxic substances being much more common than photoallergents.

Wavelengths in the UV-A spectrum (320-400 nm) are most likely to induce photosensitisation reactions, but for some substances radiation from the visible spectrum or UV-B (290-320 nm) may also be involved.

Mechanisms involved

The substrate of phototoxic reactions is the action of photoactivated compounds on cell membranes or on deoxyribonucleic acid [7,8]. These occur in most people exposed to the drug and in light in sufficient quantity, usually in the form of exaggerated sunburn, often within minutes to hours of exposure.

Most of the compounds responsible for phototoxicity have conjugated double bonds or an aromatic nucleus that can absorb radiant energy in their structure. Photoactivation of the compound induces the excitation of the electrons. As excitable electrons return to the more stable configuration, they transfer the energy in excess of oxygen, which leads to the formation of reactive oxygen species (O-, superoxide anion, hydrogen peroxide) that can damage tissue structures. At the same time, the production of pro-inflammatory cytokines and metabolites of arachidonic acid is activated, contradicting the picture of an inflammatory response [9,10].

There is also an exception to this rule: psoralen-induced phototoxicity, which is incorporated into the DNA chain

Photo-allergic reactions have a different substrate: it is a cell-mediated immune response induced by the photo-activated compound, which is why there may be an interval of up to 24-72 h between exposure and the occurrence of lesions. By photo-activation, an intermediary compound that can bind to protein, transporter, cutaneous to generate a complete antigen that is then taken up by Langerhans cells and other types of APC, cells that continue to migrate to local lymph nodes where the antigen to T lymphocytes. The activation and proliferation of T cells is followed, with the triggering of the well-known inflammatory response [11,12].

Clinical appearance is similar to allergic contact dermatitis, but with limited distribution to photo-exposed areas (with the point that severe injuries may extend to sun-exposed regions). Unlike phototoxic reactions, photo-allergic reactions occur only in some people exposed to drugs and light, with a lower prevalence, and the amount of medicine needed to induce the effect is much lower.

Clinical aspects

All types of lesions resulting from photosensitisation occur in the exposed areas of the photo: the face, the neck, the forearms and the dorsal faces of the hands, with the mention that in severe forms the damage can extend beyond them. Certain regions are usually spared: scalp portions covered by hair, retro-auricular, periorbital and sub-montane areas. The widespread nature of the eruption is suggestive of the existence of a systemic photosensitiser, while the localized lesions suggest the use of a photosensitising topical product.

Acute photo toxicity picture: erythema and oedema are present at the onset, occurring within minutes of exposure to light, with blisters and bubbles developing. Healing can be done with reversible hyperpigmentation.

The appearance in chronic photo toxicity usually involves the presence of lichenification (the result of scratching the affected region).A particular clinical aspect of photo toxicity is pigmentation, notably blue-grey coloration due to amiodarone or other drugs (some tricyclic antidepressants, chlorpromazine).

Another particular aspect is the expression of photo toxicity in the nail, in the form of onycholysis: separation of the distal portion of the nail blade from the nail bed, which may be a more subtle clinical indication.

Pseudoporphyria has certain clinical aspects (bullous lesions) and histopathological (subepidermic cleavage) in common with late porphyria, but it differs from this in the absence of hypodermic and slerodermoid modifications and in the fact that there are no abnormalities of porphyrins. The most commonly involved agent is naproxen, but can also be induced by the administration of nalidixic acid, tetracycline, furosemide, dapsone etc. [13].The lichenoid reactions occurring in photo expressed regions consist of papules and erythematous platelets or erythematosus, with or without Wickham striations, most often occurring after administration of chloroquine, hydroxychloroquine, quinine, quinidine, hydrocoltiazide, captopril or enalapril [13].

Lupus-like reactions or drug-induced lupus are clinically similar to the subacute cutaneous eruptive lupus picture, the most commonly involved agents being hydro-chlorothiazide, calcium channel blockers, IECA, griseofulvin, terbinafine, and the like. Often, they associate positivity for anti-histone antibodies (sensitive but non-specific test for drug-induced lupus) [13]. A special care and rigorous blood test should be performed in patients with suspicion of multiple autoimmune syndrome [12].

Photo-allergic skin reactions typically take the form of pruritic eruptions with erythema and vesiculation in the acute phase and erythema, lichenification, and desquamation in the chronic phase. Photo allergic reactions do not associate skin hyperpigmentation.

The differentiation of phototoxic reactions from photo allergic reactions is sometimes difficult to achieve, but in this respect it is useful to corroborate the minute histories with clinical features.

Substances involved more frequently

Most phototoxic reactions are the result of systemic drug administration, while photo allergic reactions are mainly induced by the application of topical products but can also occur after drug administration.

The factors involved in the occurrence of photosensitivity reactions are numerous: the amount of drug administered, the spectrum and skin penetration capacity of light radiation, the thickness and degree of pigmentation of the skin, the state of the immune system. Photosensitivity reactions are common in people with immune deficiency syndromes (e.g., acquired immune deficiency syndrome).

More common photosensitizers include [14]:

- Antibiotics (tetracyclines, quinolones, sulfonamides);
- Antihistamines (diphenhydramine);
- Antimalaric acid (quinine, chloroquine, hydroxy-chloroquine);
- Chemotherapeutics (5-fluorouracil, dacarbazine, vinblastine);
- Antiarrhythmic drugs (amiodarone, quinidine, diltiazem, nifedipine);
- Diuretics (hydrochlorothiazide, furosemide);
- Antidiabetics (sulfonylurea);
- AINS (piroxicam, naproxen)
- Compounds used in photodynamic therapy (5-aminolevulinic acid and 5-aminolevulinic acid) [15]:
- systemic retinoids (isotretinoin, acitretin);
- Antidepressants and neuroleptics (chlorpromazine, imipramine, desipramine).

And among topical products with photo allergy potential we mention:

- Some organic solar filters (PABA, oxybenzone, salicylates, cinnamate, benzophenone, etc.) [14];
- Certain antiseptics (chlorhexidine, hexachlorophene);
- Perfumes and perfumed products (notably musk, bergamot, lavender).

A special mention is 5-aminolevulinic acid or 5-aminolevulinic acid. In the last decade, photodynamic therapy (PDT) has increasingly gained ground in the treatment of actinic keratoses and basal cell carcinoma. What is the principle on which this therapeutic approach is based? Applying 5-aminolevulinic acid (which is intracellularly metabolised to protoporphyrin IX, photosensitizer) or 5-aminolevulinic acid methyl ester followed by exposure to a blue (410-420 nm) or red (570-670 nm). Under the action of light, protoporphyrin IX is activated, generating free radicals and reactive oxygen species with cytotoxic action, which causes the destruction of the tissues with excessive proliferation. A common side effect of photodynamic therapy is represented by local phototoxic reactions with auto limited evolution [11,13].

One should not be overlook the possibility that symptoms have been triggered by contact with plants and / or vegetables containing photosensitizing substances, such as lemons, mango, celery, passion fruit, carrots, figs or parsley.

Management of photosensitization reactions has three pillars:
- Identification and avoidance of the etiological agent;
- Photo protection;

As mentioned, photo protective products may be causative agents of photosensitization reactions [14]. If this hypothesis is invalidated, photo protectants can and should be used, with the mention that it is preferable to those containing UV-A filters (avobenzone, titanium dioxide, zinc oxide) and it is not recommended to choose according to SPF (because SPF correlates with the degree of protection against UV-B, and most photosensitization reactions are the result of exposure to UV-A)[15]. Also, do not forget the more effective physical protection methods: clothes, hats, etc.

-Symptomatic treatment;

It consists mainly of the application of cold compresses and medium or high potency topical corticoids, and in more severe cases systemic corticosteroids can be used.

Some vegetables and plants can cause sensitivity [15] if they come into contact with the skin exposed to the sun. Mango peel, lemon juice, pastry or celery can cause temporary skin discoloration in sun-exposed areas. Here's a list of fruits and vegetables that are phototoxic:
- Lime
- Celery
- Carrot
- Figs
- Parsley
- Parsnip

In addition, cigarette smoke is phototoxic [16] - it becomes more harmful in the presence of UV rays and causes more skin cell damage than cigarette smoke or UV rays would otherwise cause. The worst thing you can do for the skin is to smoke at the beach! Wrinkles caused by smoking may not appear for a decade after the first smoke, but the damage occurs with each cigarette smoked. A study conducted in 2013 on 79 pairs of identical twins, of which only one of the twin smokers (or smoked at least five years longer than the other), revealed striking differences in their girls. A group of evaluators who did not know which of the twins was smoker gave the smallest scores to twin smokers in terms of circles, naso-labial creases, goitre and upper lip wrinkles.

Once the photosensitivity and perhaps the diuretic effect with implications on the hydro lipid barrier at the skin, especially the facial, the use of such drugs may have implications for the evolution of photosensitive dermatoses such as Rosacea, or factors involved in its development such as Demodex Folliculorm or its endosymbions belonging to the cutaneous microbioma [17-23].

A strong association between use of the diuretic hydrochlorothiazide (HCTZ) and squamous cell carcinoma (SCC) of the lip [24-26] has been recently reported The authors found a clear dose response pattern, with an estimated 7-fold increased risk of SCC lip cancer with cumulative use of 100 ≥100.000 mg HCTZ. These findings were in line with the results of previous studies from the United States and the recent classification of HCTZ as 'possibly carcinogenic to humans' (Group 2B) by the International Agency for Research on Cancer (IARC) [23]. As HCTZ is among the most widely used drugs in the US and Western Europe, [24] a carcinogenic effect of HCTZ would have a considerable impact on public health. Few studies have investigated the association between thiazide use and NMSC risk [27-29]. Although the study results have been inconsistent, they indicate that HCTZ use increases the risk of NMSC.

The authors were interested in examining the association between HCTZ use and NMSC risk more extensively, and to evaluate the individual effect of HCTZ [25]. Specifically, they used detailed data from the Danish registries to examine the association between HCTZ use and the risk of basal cell carcinoma (BCC) or SCC of the skin. The specificity of HCTZ use with increased risk of BCC and SCC supports the potential causal association between HCTZ use and NMSC risk. In conclusion, given the considerable use of HCTZ worldwide and the morbidity associated with NMSC, a causal association between HCTZ use and NMSC risk would have significant public health implications. The use of HCTZ should be carefully considered, as several other antihypertensive agents with similar indications and efficiency are available, but without known associations with skin cancer [30,31].

We would like to congratulate the authors on their work [24], which, with the large population analysed, has the potential to contribute to answering the question of risk of non-melanoma skin cancer (NMSC) with hydrochlorothiazide (HCTZ) use. Certain questions arise from the reading of this work, which we would request to clarify, because such studies would change our practice in future years.

1. The authors did not clarify whether HCTZ exposure was continuous, (by virtue of indication) or intermittent. We note that NMSC is not ONE cancer, but a diverse group of cancers, from rare (Merkel cell carcinoma) to uncommon (Mycosis fungoides) to more common (SCC, BCC, Keratoacanthoma), thus, we take issue with the assertion that *NMSC is the most common cancer in humans*. Their citation of the bibliography or the bibliography [32] itself may be wrong, as NMSC *and* melanoma are together the commonest skin cancer. [33].

2. The authors focused on only basal cell carcinomas (BCCs) and squamous cell carcinomas (SCC). While very infrequent, other NMSC such as mycosis fungoides, were not reported. It is unlikely that such cases did not show in the study population over the (2004-2012) period. Such a comparison could help support or refute the hypothesis of photocarcinogenesis put forward by the authors.

3. The authors required cases to have no previous skin or other cancer diagnoses prior to the first diagnosis of BCC or SCC [24] however, they make no mention of precancerous lesions like actinic keratosis. Their subsequent development into NMSC may have ultimately impacted on their statistical analyses. Is it possible to clarify this issue?

4. Interestingly, there was no data, nor mention of melanomas, a group of pathologies also associated in some studies with other medication-induced photocarcinogenesis [34-36]. Such data could refute the authors' hypothesis.

5. Based on their conclusions, do the authors believe that there may be a need for warnings on carcinogenic risk to be placed on the medication boxes and in the information leaflets? Also, should prescribing physicians now be required to clarify this issue to patients in the process of consenting them for therapy?

6. While patients with prior azathioprine, cyclosporine and mycophenolatemofetil therapy were excluded, patients with prior methothrexate and systemic corticosteroid therapy appear not to have been considered. Maybe in future studies this point of view should be clarified.

7. The effect of sun exposure in their study population was not accounted for. How could they then explain what not living in Denmark (continuously?) for 10 years prior to the index date have to do with risk of NMSC?

It is also worthwhile to discuss the role of action in a carcinogenic sense, especially on the field of some patients, or in areas interpreted as locus minoris resistentiae, Wolf isotopic response or Koebner type 5 phenomenon by some authors in recent articles [37,38].

Conclusions

Finally, as a conclusion, the beneficial role of Hydrochlorothiazide should be counterbalanced by its adverse effects, especially by its possible role in cutaneous photocarcinogenesis, similar to other drugs of common use - tetracycline, dermatocorticoids (topical or systemic), beta blockers, NSAIDs including those of the old generation such as Aspirin or the new generation -Arcoxia), used especially for various associated pathologies or comorbidities [39-47]. Future research directions can be expanded to other areas and will be performed with the informed consent of the patients and with consideration to medical research ethics [48,49] As such, other therapeutic methods, sometimes alternatives or complementary therapies, that may influence positively the control of various conditions without increasing increased risks to the health of patients in the short or long term [50-54].

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