



## COMMENTARIES

# Safety of Hydrochlorothiazide in the Real World: A Commentary on the Italian Medicines Agency (AIFA) Pronouncements

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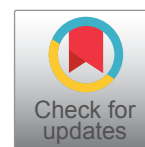
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## Background

Thiazide diuretic drugs are the most commonly used molecules for the treatment of systemic hypertension. Despite their established role in the treatment of this disease, well recognized by the guidelines of national (such as the Italian Society of Cardiology - SIC - for example, which incorporates the directives of the European Society of Cardiology - ESC -) scientific societies [1,2] - including those that operate specifically in the setting of the General Medicine [3,4] - that international scientific societies [5-8], with recognized effect and good class of recommendation, nevertheless in recent times new advice has arisen from studies present in the literature that have undermined its safety and warned the clinician of the dangers concerning their use. In particular, our attention focused on a molecule such as hydrochlorothiazide.

## Known Adverse Events of Hydrochlorothiazide

Several evidences have shown that hydrochlorothiazide therapy in chronic renal disease with advanced grade of kidney insufficiency leads to deleterious effects, as the adverse effects of this therapy are reported (worsening of renal function, depletion of water

volume, hyponatremia, hypercalcemia, hyperglycemia, dyslipidemia) [9]. Regarding the electrolyte imbalances, thiazide-induced hyponatremia is certainly an important medical condition, that is regularly present in the internal medicine departments and it causes substantial morbidity to frail patients, often elderly, who are taking hydrochlorothiazide, in subgroups of patients [10,11]. Equally not yet well understood is the mechanism by which hydrochlorothiazide interferes with the glucose homeostasis [12-14]. There is also a whole range of side effects, fortunately rarer, but described in the medical literature, ranging from the appearance of lupus [15], interstitial lung disease [16], even severe allergic states [17], pulmonary edema [18-20], all conditions linked to immunological changes induced by the molecule itself. The effect on the sense organs (hypoacusis) is more known and less rare (although investigated with low frequency, especially in the elderly subjects), with various reports from the organs of vigilance drug, for which there are well defined indications for the diagnosis of this adverse event (Austin Bradford-Hill criteria, Naranjo criteria), well applied in pharmacovigilance [21,22].

## Pharmacovigilance in Italy

With regard to this aspect, it is worth mentioning



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a recent intense vigilance drug activity for cutaneous hydrochlorothiazide adverse events. We recall that pharmacovigilance is the set of activities whose objective is to provide, on an ongoing basis, the best possible information on the safety of medicines, thus allowing the adoption of appropriate measures and in this way ensuring that the drugs available on the market, in the conditions of authorized use, a favorable benefit risk ratio for the population. There is a "Pharmacovigilance" section of the Italian Drug Agency (Agenzia Italiana del Farmaco - AIFA) dedicated to General Practitioners (GPs) and to the Pediatricians. The service is bidirectional, i.e., the GPs/Pediatricians can (directly) send the adverse drug reaction (ADR) report to the pharmacovigilance network of AIFA, that will insert it within the scheduled time on the National Pharmacovigilance Network. In the opposite direction, the doctor will be able to receive letters by mail from the body (a collection of such letters exists on the site of AIFA <http://www.agenziafarmaco.gov.it/it/nii>). Towards the end of 2018, AIFA sends one of these letters to doctors about hydrochlorothiazide and its skin effects [23]. Also the latter have long been reported in the literature and very heterogeneous from the clinical point of view, going from lichenoid dermatitis to skin eruptions similar to pityriasis rosea to erythema multiforme to the vasculitic reaction [24-27]. Recently, however, the attention of epidemiologists has focused on drug-induced oncogenesis. The photosensitizing action of hydrochlorothiazide, in fact, combined with the generation of free radicals, is known to have a damaging action on the skin in a cancerizing sense [28]. Oxygen free radicals, in fact, generated by exposure to ultraviolet rays and enhanced by hydrochlorothiazide, cause DNA damage with alterations of nitrogenous bases and formation of thymine dimers that have cells on the skin, active labile cells replication, an oncogenic effect [29,30]. In addition to the skin squamous cell carcinoma, in the year 2013 a study put this drug in relation with other skin cancers, such as the cutaneous T-cell lymphomas [31], without clarifying a true causal link but postulating a possible genotoxic action, similar to that on other skin cells [30]. A more recent Danish study, investigating the non-melanomatous tumors in the Danish Cancer Registry, focusing on over 70,000 cases of basal cell carcinoma and over 8,600 patients with squamous cell carcinoma, respectively compared with control populations of over 1,400,000 and over 170,000 subjects, found that the high use of hydrochlorothiazide (at the cumulative dose equal to 50,000 mg - corresponding to 12.5 mg of this drug taken daily for about 11-years or higher) was associated with an adjusted odds ratio (OR) to 1.29 (with a 95% confidence interval - CI - 1.23-1.35) for basal cell carcinoma and 3.98 (95% CI: 3.68-4.31) for carcinoma a squamous cells, with a cumulative dose-response relationship for both of these tumor forms [32]. The

use of other types of diuretic and other antihypertensive drugs was not associated with non-melanomatous skin tumors. Another study showed a possible association between labial squamous cell carcinoma and the exposure to this thiazide, in 633 cases compared to 63,067 controls, with a cumulative dose-response relationship with adjusted OR of 2.1 (95% CI : 1.7-2.6) which increased up to OR 3.9 (3.0-4.9) for patients who used it at high dose (~ 25.000 mg) and a OR 7.7 (5.7-10.5) for the highest cumulative dose (~ 100,000 mg) [33]. Finally, a recent study, conducted with the evaluation of different databases (PubMed, EMBASE, Cochrane Library), would confirm the association with increased risk of skin cancers, especially squamous cell carcinoma (underlining the need for further studies to confirm the results) [34]. The AIFA report concluded the report by inviting the physicians to the following prescriptive behaviors and to adopt the following precautions: information on the risk of non-melanoma skin cancers for patients taking hydrochlorothiazide, alone or in combination with other drugs, with the regular control and self-control of the skin for the early identification of any new lesions or changes to existing lesions, with notification to your doctor of any suspected skin lesion; examination of suspected skin lesions both from a clinical but also histological point of view, using the bioptic exam; warning patients about the limitation of exposure to sunlight/UV rays, with the use of adequate protection when exposed to sunlight/UV rays, to minimize the risk of skin cancers; careful evaluation and discernment on the prescription/use of hydrochlorothiazide in patients who have had a previous skin cancer.

## Conclusions

Recent studies showed the presence of a cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancers. There was a statement with an information note issued by the European/Italian monitoring and surveillance organizations (European Medicines Agency - EMA - and AIFA). There is a need for the integration of pharmacological-epidemiological data and those data coming from the registers, the various databases and the studies already present in the literature with data collected in the real world, both in the academic environment but even more so in the field, especially from the databases in possession of general practitioners, to have as far as possible an objective picture of the situation.

## Contributors

Magro VM was the primary researchers and wrote the manuscript. Coppola C, Caturano M, Boccalone E and Scala G provided research and editing assistance to the manuscript. Magro VM, Coppola C, Caturano M, Boccalone E, Scala G and Verrusio W contributed to overall article design, data collection as well as revising

and approving the manuscript.

## Conflict Interest and Disclosures

None declared.

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