A reverse translational pharmacological approach to understand the underlying mechanisms of the reported association between hydrochlorothiazide and non-melanoma skin cancer

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In the last three decades, a number of individual studies and meta-analyses have claimed that most antihypertensive drugs can be associated with an increased risk of a variety of neoplastic diseases \cite{1–5}. This has not been confirmed by meta-analyses of randomized clinical trials or observational studies of longer duration, which have not seen any substantial antihypertensive drugs–cancer association or produced mechanistic evidence of its plausibility \cite{6–8}. An exception, however, could be hydrochlorothiazide (HCTZ) as the reports that in the Danish population, the use of this drug was associated with an increased risk of non-melanoma skin cancers (NMSCs) \cite{9,10}, have been replicated in other populations and settings around the world \cite{11–15}, with few exceptions \cite{16,17}. Furthermore, it has been observed that the association has a clear dose–response relationship, which supports a causal role of the drug, a conclusion that is further strengthened by the evidence, available already years ago, that HCTZ has photosensitizing effects \cite{18–22}. This led the International Agency for research on Cancer to classify HCTZ as potentially carcinogenic in humans \cite{23}. It has more recently led the European Medicines Agency and the US Food and Drug Administration to recommend updating the summary of product characteristics with safety warnings and advice on adequate ultraviolet (UV) protection in patients under HCTZ treatment \cite{24,25}.

Thiazide/thiazide-like diuretics are commonly prescribed for lowering an elevated blood pressure and reduce hypertension-related cardiovascular events and death \cite{26,27}. Their use markedly enhances the blood-lowering effect of all other drugs \cite{28}, for which reason, combinations that include diuretics are recommended by all hypertension guidelines to achieve blood pressure control in most hypertensive patients either after initial monotherapy or by some guidelines, as the initial treatment step \cite{29–31}. The single pill combination of a thiazide diuretic, such as HCTZ at lower daily doses (12.5 or 25.0 mg) and a blocker of the renin–angiotensin system exceeds by far that of any other diuretic almost all over the world. After the reports from the Danish population, use of HCTZ dropped by 44% in Denmark, with even greater rates of discontinuation in younger patients \cite{32}. Although numerical data are not available, a drop has probably occurred in other countries as well. This may seriously undermine the available therapeutic means to fight a condition, which is ranked as the first cause of death and burden of diseases worldwide \cite{33}, emphasizing the need for further studies not only on the carcinogenic risk of this drug but also on the mechanisms of this effect, its predictability in different patients, and the safety boundaries within which the drug can be used. We have recently added information on this issue, by setting up an experimental model that did not limit the observation to acute effects but mimicked the actual human exposure consisting of long-lasting HCTZ exposures and multiple UV irradiations. Human keratinocytes (HaCaT) were irradiated twice a week for 9 weeks with UVA (10 J/cm\textsuperscript{2}) in the presence or absence of HCTZ (70 ng/ml) and compared with untreated cells or to cells exposed only to HCTZ. To establish a model with translational relevance for human exposure, the UVA dose applied approximated a human exposure of approximatively 1 h of midsummer sun \cite{34}, and in the absence of data on skin levels, the concentration was selected on the basis of the average human plasma levels after oral administration of 12.5 mg of HCTZ \cite{35,36}. We demonstrated that the chronic combined exposure to UVA and HCTZ induced dysplastic changes in human keratinocytes, increased genotoxic damage, apoptosis resistance and inflammation, and activated the oncogenic pathway Wnt, thus reproducing some of the molecular alterations observed in human NMSCs \cite{37} (Fig. 1). It was also clear that in absence of UVA, HCTZ did not exert any pro-carcinogenic effect. This adds to current knowledge of the steps through which HCTZ increases at cellular level the risk of NMSCs and further shows that in absence of UVA, the drug is well tolerated and that this is most likely the case if exposure to UVA is avoided by...
appropriate photoprotective measures, a principle that applies, however, not only to HCTZ users but also to the general population. Finally, this work emphasizes that a bidirectional research approach that integrates clinical data with experimental evaluations might be valuable to understand the biological plausibility of epidemiological observations, including those related to drug safety. This was also well exemplified by the studies exploring the link of thiopurines and voriconazole with skin cancer [38,39].

An important but unfortunately unanswered question is whether HCTZ can be replaced by other drugs [40] with similar blood pressure-lowering mechanisms to preserve the multimechanistic approach that makes combination treatment particularly effective [41]. As photosensitivity is not a unique feature of HCTZ, carcinogenic influences may in principle not be excluded also for other thiazides or thiazide-like antihypertensive drugs [42]. However, human and experimental studies in the field are scarce. The thiazide bendroflumethiazide was phototoxic in a cell culture model whereas chlortalidone and indapamide did not induce phototoxicity in this assay [43]. Case–control studies in Denmark and UK showed that the thiazide-like indapamide was not associated with NMSCs but with an increased risk of malignant melanoma [9,44,45] whereas bendroflumethiazide was not associated with the risk of any type of skin cancer [8,46]. To our knowledge, whether the thiazide-like diuretic chlortalidone increases the risk of skin cancer is still to be determined. Additional pharmaco-epidemiological studies as well as experimental pharmacological evidence for or against the photocarcinogenic effects of other thiazide or thiazide-like antihypertensive drugs would be valuable.

To date, health authorities do not recommend stopping HCTZ as the risk–benefit is in favor of the cardiovascular benefits but recommend patients taking HCTZ to be informed of the risk of NMSC and to regularly check their skin, limit UV exposure and use adequate protections [24,25]. Health authorities also recommend that in patients with history of skin cancer, the use of HCTZ may be reconsidered [24].

In conclusion, in line with the recommendation of health authorities, for patients under appropriate blood pressure control with HCTZ, the switch to other treatments, whose pro-photocarcinogenic effects are not yet well established, should be carefully evaluated on the basis of the risk–benefit ratio.

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Conflicts of interest

There are no conflicts of interest.

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