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Environmental Chemical Skin Carcinogenesis Concerning the Development of Melanoma and Keratinocyte Cancer: From Nitrosocontamination / Endogenous Nitrosation in Pharmaceuticals to Photocarcinogenicity in Humans

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Abstract

Nitrosamines have been recognized since the 1930s as carcinogens, and as photolabile compounds capable of undergoing photodegradation, regardless of their carcinogenic potential. While larger studies are gradually being conducted and officially acknowledged, single case reports often provide highly valuable clinical insights, reflecting real-world clinicopathological correlations.

Drugs such as those taken by the patient presented (like ramipril/amlodipine, moxonidine, febuxostat, esomeprazole) share several important characteristics: All five have been discussed in the literature in the context of potential 1) nitrosamine contamination or 2) formation from secondary/tertiary amines under specific (acidic) conditions. For each of them, literature data from recent decades suggest the possibility of systemic distribution with accumulation in peripheral tissues, including the skin.

It should be noted that the FDA's Daily acceptable intake (AI) limits for nitrosamines are largely derived from mutagenicity and carcinogenicity data, including bacterial assays such as the Ames test (using Salmonella typhimurium and/or Escherichia coli strains). However, while these assays are well established for detecting mutagenic potential, they cannot replicate the complexity of the so called dynamic human skin related carcinogenesis. In particular, they may not adequately account for mechanisms such as Nitroso phototoxicity/ Nitroso photocarcinogenicity, were photochemical reactions in peripheral tissues - such as the skin - could occur independently of, or prior to, hepatic metabolic activation of the drugs mentioned.

Consequently, localized ultraviolet-driven chemical reactions and/or independent tissue-specific oxidative or nitrosative stress pathways may not be sufficiently reflected in standard bacterial-based risk models.

More Information

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skin deposition,
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NO formation,
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Nitroso photocarcinogenesis.

Already published national and international data, suggest a pathogenetic association between polymedication intake and the increased skin cancer risk, particularly in chronically treated, polymorbid patients.
In clinical practice, these considerations raise the possibility that photocarcinogenicity - and more specifically, Nitroso Photocarcinogenicity - may be influenced by the combined effects of polymedication, especially in the presence of potential nitrosamine contamination/ endogenous formation (even without contamination).
These processes also depend on individual pharmacokinetic and pharmacodynamic profiles of each drug, as well as on individual variability in metabolism, enzyme activity, and tissue distribution.
Nitroso mediated Photocarcinogenesis may additionally be influenced by nutritional Nitrosogenesis: nitrosamines may be introduced into the body through medication without any availability of external Nitrosamine contamination. If the drugs posses secondary or tertiary amino group, there is a possibility to undergo on that way the so called endogenous Nitrosation/ Nitrosamine formation in the presence of nitrites rich food intake in acidic environment (in the stomach) - leading to the in vivo formation of N-nitrosamines.
Polymedication (ramipiril/amlodipine, moxonidine, febuxostat, esomeprazole) and the subsequent development of cutaneous melanoma and BCC skin tumors located in close proximity, can once again be explained within the conceptual framework of the so called exogenous Nitrosocontamination and the endogenous drug related Nitrosogenesis leading subsequently to the drug related Nitroso- Photocarcinogenesis.

Introduction

Numerous medications were known to cause phototoxic reactions long before the mechanisms of drug-mediated Nitrosogenesis and Nitroso-photocarcinogenicity were established [1].
This phototoxicity is characterized by several aspects that remain till recently incompletely understood, including: 1) its sporadic rather than consistent occurrence of side effects and 2) it remains unclear whether the associated toxicity and carcinogenicity are mediated by the active pharmaceutical ingredient itself or by some additional factors.
Additionally, other components present in pharmaceutical products – some or all of them recognized historically and more recently as "photocarcinogens" - may contribute to these effects (2). Such photocarcinogenic compounds are more commonly referred to as nitrosamines [2].
The most important dilemmas and questions related to the Nitrosogenesis theory/ Nitroso related Phototoxicity/ Photocarcinogenicity will be discussed as follows. Important dillemas remain however:
Do some of those drugs exhibit bioavailability within human skin?
Are there available data demonstrating the presence and distribution of systemically administered drugs in the skin, and does this cutaneous bioavailability correlate with plasma drug concentrations?
Have certain drugs been reported to induce phototoxicity in an intermittent rather than consistent manner?
Specifically, does phototoxiciy occur only under particular conditions, such as increased drug bioavailability in the skin and/or then concomitant ultraviolet (UV) exposure is also a precondition and cofactor?
Within this context, how can each individual's medications of the patient presented could be evaluated with regard to its potential association to phototoxicity and Photocarcinogenesis?
We present a case of a patient with three lesions located on the back, later histologically proven to be a haemangioma, pigmented basal cell carcinoma, and nodular melanoma. A possible strong correlation once again appears to exist between skin carcinogenesis and the patient's medical history and long-term systemic therapy, including ramipiril/amlodipine, moxonidine, indapamide, febuxostat, and esomeprazole. The pathogenesis will be explained in a staged pattern, providing for the first time a comprehensive "from A to Z" nitrosamine-related pathogenic pathway, thereby establishing it as an actual reality.

Case Report

A 78-year-old male presented to the dermatology department with three tumorous lesions located on the back. The lesion on the left had been present since childhood, the lesion on the right was first noticed in 2020, and a third lesion located inferior to the others had an unknown duration.
The patient's medical history included antihypertensive therapy with ramipiril/amlodipine 5mg /5mg (once in the morning and once in the evening) since 2017, moxonidine 0.4 mg (once at noon) since 2017, indapamide 1,5 mg (once in the morning) since 2017, febuxostat 120 mg (half a tablet in the morning) since November 2024, esomeprazole 20 mg (once in the morning) since 2018, and eye drops since 2020.
Dermatological examination revealed three tumorous lesions on the back region: 1) a pink-to-violet nodular lesion measuring 1cm x 1cm, clinically suggestive of a haemangioma, 2) a red nodular lesion with irregular borders and overlying dark pigmentation, clinically suspicious for nodular melanoma, and 3) a smaller inferior lesion with an erythematous base, irregular pigmentation, and poorly defined borders, clinically suspicious for pigmented basal cell carcinoma (see Figure 1a,b). Enlarged lymph nodes were not detected.

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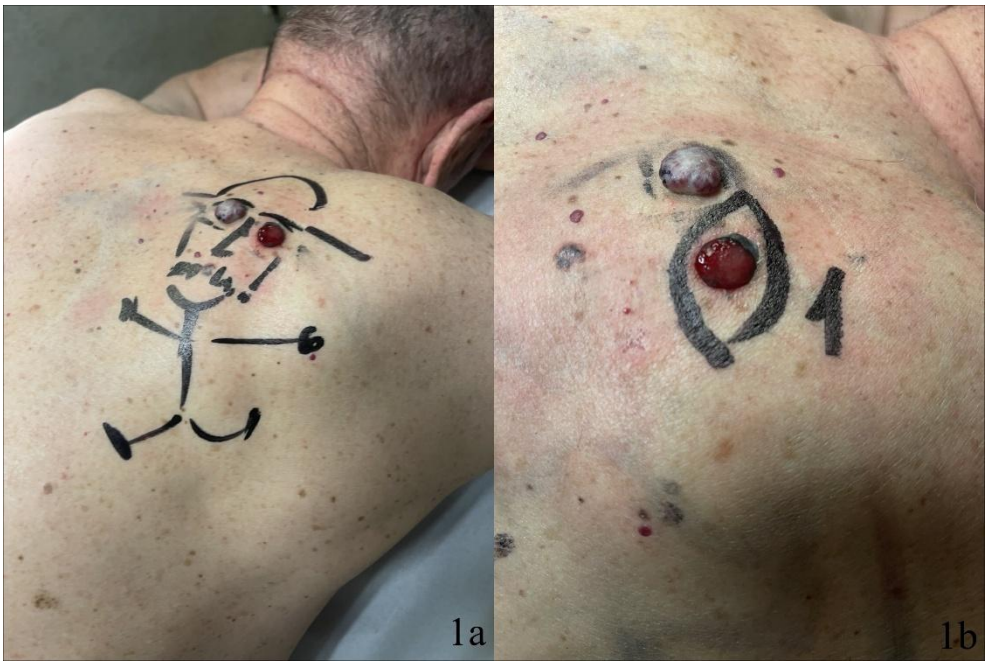

Figure 1 a,b: Three Tumorous Lesions on the Back Region:
1) a pink-to-violet nodular lesion measuring 1cm x 1cm, clinically suggestive of a haemangioma (on the left), 2) a red nodular lesion with irregular borders and overlying dark pigmentation, clinically suspicious for nodular melanoma (on the right), and 3) a smaller inferior lesion with an erythematous base, irregular pigmentation, and poorly defined borders, clinically suspicious for pigmented basal cell carcinoma

Routine laboratory tests were unremarkable. Surgical excision of all three lesions was performed under local anesthesia with lidocaine 1%. The lesions were excised with elliptical excisions. The wound defects were closed with single interrupted sutures (see Figure 2a,b).

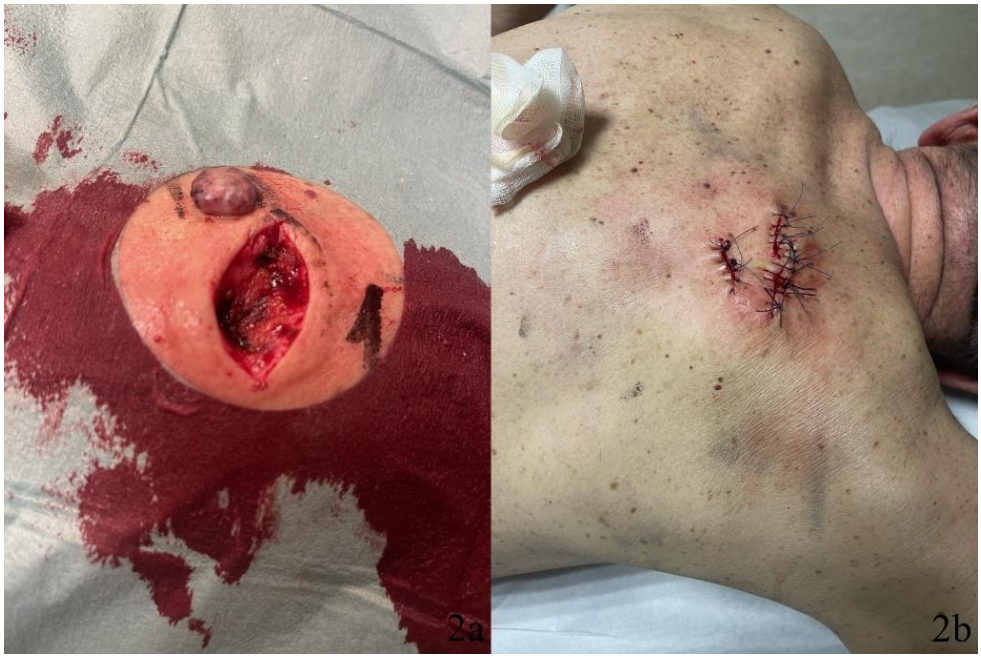

Figure 2 a,b: Surgical Excision of the Suspected Melanoma Lesion
(a). All three lesions are excised and closed with single interrupted sutures (b).

Histopathological examination revealed: 1) cavernous haemangioma, 2) nodular malignant melanoma with a Breslow thickness of 4 mm, Clark level III, high mitotic activity, ulceration, and clean resection margins; and 3) pigmented basal cell carcinoma with clean resection margins. Subsequent reexcision and SLN removal has been planned for the nodular melanoma.

Discussion

In the discussion section, we aim to follow a logical framework and address several key questions concerning the relationship between drug intake, Nitrosamine related Phototoxicity, and Nitroso-Photocarcinogenesis:

Nitrosamines have been recognized since the 1930s as photolabile compounds/to undergo photodegradation/ photodecomposition, regardless of their carcinogenic potential [3]. This characteristic arises from the instability of the nitroso group, as UV irradiation of N-nitrosodimethylamine (NDMA), for example, and other N-nitrosamines induces fragmentation of the N-N bond [3,4].

A study by Kwon et al. [5] published in 2012, demonstrated that photolysis of NDMA leads to the formation of oxidized products, namely NO(2)(-) (nitrite) and NO(3)(-) (nitrate), and revealed the presence of a key reactive species produced during this process. The authors described an Unknown Reactive Species (URS) exhibiting OH-like reactivity, which may contribute to the formation of both NO(2)(-) and NO(3)(-) during the photochemical decomposition of NDMA [5].

Now we know that the subsequent photodegradation/ photodecomposition of nitrosamines is accompanied by the release of nitric oxide (NO), which interacts with reactive oxygen species (ROS) and thereby act as a key mediator of cutaneous carcinogenesis, contributing to both melanoma and keratinocyte-derived skin cancers [6,7].

Recent molecular biology studies have demonstrated the role of nitrosative stress involving p53 signaling in the pathogenesis of melanoma with or without UV exposure [8,9].

A chronic inflammatory microenvironment promotes the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which disrupt normal cellular signaling pathways [8]. These reactive species induce DNA damage, leading to genomic instability and facilitating the survival and progression of malignant cells (8). Aberrant expression of nitric oxide synthases (NOSs), particularly inducible NOS (iNOS), results in sustained NO production- potent mutagenic carcinogen - and persistent nitrosative stress [8].

Ekmekcioglu et al [10] reported that iNOS expression may serve as a prognostic factor, with NO acting as a critical mediator of an aggressive tumor phenotype in human metastatic melanoma.

The role of nitric oxide in basal cell carcinoma is not as well established [6] as in melanoma, breast or colon cancer [11].

However, nitrosamines are recognized as nitric oxide donors following their decomposition after systemic absorption and ultraviolet irradiation, a property that may be regarded as procarcinogenic [6,11].

N-nitrosoprolinecan exert genototxic effects and induce DNA mutations even prior to metabolic activation [12].

Similarly, N-nitrosomorpholine, found in the drug molsidomine, has been shown to be genotoxic following ultraviolet irradiation without the need for metabolic activation [13].

In practical terms, available laboratory and in vitro data indicate that these compounds can exert genotoxic effects without requiring hepatic metabolic activation [12,13].

This effect may occur through activation of photocarcinogenic pathways in keratinocyte-derived tumors or through direct induction of cellular stress involving p53 [14].

In practice, nitrosamines appear to function as bicarcinogens:

1) their involvement in both melanocytic and non-melanocytic skin tumors may be explained by the so called Nitroso Photocarcinogenesis; and

2) by Nitrosogenesis via direct nitrosation of p53 [8].

These two main mechanisms represent the principal pathways underlying nitrosamine-associated photocarcinogenesis and direct carcinogenicity.

In all likelihood, the elimination of nitrosamines from pharmaceutical products, in any form, could result in a substantial reduction in drug-induced phototoxicity and photocarcinogenicity.

With regard to polymedication and its relationship to skin cancer, as well as the absence of consistent phototoxic reactions during drug exposure, our clinical observations suggest the following: the concurrent use of common prescribed medications in polymorbid patients is frequently associated with hepatic metabolism via shared enzymatic pathways.

In the presence of competitive inhibition between the involved medications, there is a real possibility that the bioavailability of certain nitroso forms of a drug may increase in the systemic circulation due to the delayed hepatic metabolism for example.

This, in turn, may be associated with enhanced tissue availability. Such tissue accumulation of the nitrosamines in its non-metabolically activated form, bypassing hepatic metabolism, could subsequently occur in the skin. In practical terms, this represents the

deposition of nitrosamines in combination with the active compound.

Cancer-inducing capacity is a term used in pharmaceutical toxicology to describe a property of mutagenic drug compounds that are capable of causing genomic damage through the formation of DNA adducts, ultimately leading to malignant cellular transformation [15]. Genotoxic carcinogens may pose a cancer risk to humans even at very low exposure levels [15].

In contrast, non-genotoxic carcinogens induce mutations through indirect mechanisms such as hormonal modulation, cytotoxicity, increased cell proliferation, or epigenetic alterations [15]). These agents are generally considered to have a threshold dose below which exposure is regarded as "acceptable" [15]. However, the distinction is not always straightforward, as certain compounds may have negative results in in vitro bacterial mutation assays while demonstrating positive results in the in vivo transgenic rodent gene mutation models [15].

Potent human mutagens, known as N-nitrosamines, may contaminate drug products or be formed endogenously from nitrosatable drug precursors [16]. Of greater concern than preexisting nitroso-impurities in drugs and food are the mutagenic N-nitroso derivates generated in vivo from N-nitrosable drug precursors through their interaction with dietary nitrites in the acidic environment of gastric juice [16].

In a study by Ozhan et al [17], 28 orally administered drugs considered potentially nitrosatable were evaluated under simulated gastric conditions in the presence of nitrite. The genotoxic activity of the resulting drug-nitrite interaction products were assessed using the umu-test with Salmonella typhimurium TA 1535/pSK1002, both with and without metabolic activation [17]. The findings demonstrated that 22 of the nitrosation products exhibited genotoxicity to varying degrees [17]. These intermediates undergo enzymatic bioactivation to reactive species or directly alkylate DNA, leading to mutagenesis even at nano-level exposures [16].

In the subsequent discussion we will examine the patient's current medications and drug classes in relation to their possible carcinogenic potential, based on available international data and our clinicopathological observations:

ACE inhibitors related phototoxicity and photocarcinogenicity and the link to the Nitrosocontamination

An important retrospective analysis by Nardone et at [18] reported an association between the use of ACE inhibitors, and not only, and the subsequent development of malignant melanoma and non-melanoma (basal cell carcinoma and squamous cell carcinoma) skin cancers.

The odds ratio (OR) for basal cell carcinoma among ACE inhibitor was: unadjusted OR (95% CI) 2.09 (1.87-2.34) and adjusted OR (95% CI) 2.23 (1.78-2.81);[18].

For malignant melanoma, the estimated unadjusted OR (95% CI) was 2.42 (2.00-2.95) and in the adjusted model 1.71 (0.97-3.00) [18].

Notably, data presented in the study indicate that the adjusted for melanoma was slightly higher in patients treated with ACEi (OR 1.71) compared with those receiving ARBs (sartans) (OR 1.24) [18].

Another international study evaluating photosensitizing antihypertensive medications and the subsequent skin cancer risk among postmenopausal women reported a significant association between several antihypertensive drug classes and an increased incidence of non-melanoma skin cancer (NMSC) [19].

Specifically, the use of ACE inhibitors (1.09 [1.01-1.18]), calcium channel blockers (1.13 [1.05-1.22]), diuretics (1.20 [1.12-1.27]), loop diuretics (1.17 [1.07-1.28]), and thiazides (1.17 [1.03-1.33]) was each associated with higher risk of NMSC [19].

The risk increased with the use of multiple antihypertensive agents and with longer duration of treatment [19].

An elevated risk of melanoma was also observed in association with antihypertensives use overall (1.15 [1.00-1.31]), angiotensin-II receptor blockers (1.82 [1.05-3.15]), and diuretics (1.34 [1.13-1.59]) [19].

Notably, effect modification by solar radiation exposure was identified, indicating a significant interaction between antihypertensive drug use and melanoma incidence [19].

Despite the availability of international data from large epidemiological studies, single case reports remain highly valuable, as they show clinicopathological correlations observed in daily clinical practice and help bridge population-level evidence with individual patient outcome.

The association between ACE inhibitors use and the development of basal cell carcinoma [20,21] and melanoma [22] has been previously reported in the literature.

Ramipril undergoes presystemic (first-pass) metabolism following oral administration and acts as a prodrug that is converted in the liver to its active metabolite, ramiprilat, via hepatic esterases [23]. It does not exhibit clinically relevant cytochrome P450 (CYP)-mediated drug-drug interactions [23].

Historically, the main source of N-nitrosamines was the use or carryover of sodium nitrite during API synthesis and drug product manufacturing [24]. Additional sources included recycled or contaminated raw and starting materials, carryover or cross-contamination of nitrosamine intermediates, degradation processes and certain packaging materials [24]. More recently, attention has shifted toward exogenously administered

secondary or tertiary amines, which under specific conditions can undergo photodecomposition, contributing to skin cancer [6,7].

The presence of secondary amines during synthesis introduces a potential risk for nitrosamine formation - ramipril contains a secondary amine, which makes it susceptible to nitrosation and the formation of N-nitrosoramipril [25].

Nitrosamines can also be formed in vivo when the drug is exposed to nitrosating agents (nitrites) under acidic conditions prior to hepatic metabolism [16].

A study by Schlingemann et al [26] reported that 40.4% of the analyzed active pharmaceutical ingredients (APIs) and 29.6% of the identified API impurities possess structural features consistent with potential nitrosamine precursors. The analysis demonstrated that many of these molecular structures could form complex API-related nitrosamines (nitrosamine drug substance related impurities (NDSRIs), as well as smaller potent nitrosamines such as N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) [26].

According to the FDA, N-nitroso-ramipril is classified under potency category 5, with recommended AI limit of 1500 ng/day [27]. Because of this exactly, Ramipril can be viewed as bicarcinogen:

- In the first scenario, nitrosamine-containing compounds may be ingested prior to hepatic metabolism, raising concerns regarding their subsequent or potential photocarcinogenic effects after skin deposition and UV radiation exposure.
- In the second scenario, although the prodrug (ramipril) is primarily activated in the liver, it possesses sufficient cell membrane permeability to allow systemic distribution to peripheral tissues, including the skin [28]. If nitrosamine impurities are present, exposure to UV radiation in the skin may induce photodecomposition of these compounds, leading to the generation of nitric oxide, which subsequently interacts with ROS, promoting skin carcinogenesis [6,7].

This sequence of events - from oral drug intake to skin cancer formation – seems to be part of the process, which could be called or defined as Nitroso-Photocarcinogenesis [6,7].

According to Becker et al [29], lisinopril - an ACE inhibitor - was shown to additionally stimulate MV3 melanoma cell migration and invasion by increasing the expression and secretion of matrix metalloproteinase-2 (MMP2).

Ramipril, another drug of the ACE inhibitor class, has been reported as a potential culprit drug in the development of basal cell carcinoma and dysplastic nevi [30].

Mutagenic N-nitroso derivates produced in vivo from N-nitrosatable drug precursors interacting with dietary nitrite in acidic conditions are considered more "problematic" than drug- and food-related impurities [16]. Food is frequently enriched with nitrate and nitrite additives, thereby serving as source of substrates for endogenous nitrosation [31].

The paper by Regulska et al [16] evaluated the mutagenic potential of nitroso derivates using in silico simulation, followed by an experimental nitrosation assay designed to model endogenous reactions. The resulting post-nitrosation mixtures were then assessed using a bacterial reverse mutation (Ames) test using Salmonella typhimurium strains, both with and without metabolic activation [16]. In that study, the samples did not induce point mutations in the test bacteria, regardless of the cytochrome-mediated metabolic activation, making endogenous nitrosation unlikely the reason for increased cancer incidence [16]. A major limitation of this and similar international studies is that such experimental systems do not adequately simulate real-time human physiology.

N-nitroso ramipril was predicted to exhibit inhibited nitrosamine bioactivation due to steric hindrance and branching at the alpha position [32]. It was reported as non-genotoxic in an in vivo liver assay and non-mutagenic in other in vivo models [32]. To confirm exposure and evaluate concentration levels, blood samples were collected from the tail of mice and analyzed using a specific technique [32]. The absence of mutagenicity or genotoxicity of nitrosamines in the blood is indeed correct [32]. However, the nitroso form may appear non-mutagenic in the blood, yet become mutagenic or genotoxic after photodecomposition within the skin [6,7].

A study by Regulska et al [33] suggested that the dry air degradation product of ramipril (RAM) may be associated with an increased cancer risk, potentially through the formation of reactive, mutagenic nitroso-metabolites and the induction of genomic damage at high concentrations. Nitroso-metabolites of the ramipril diketopiperazine (DKP) derivative can be formed in vivo following hepatic metabolic activation [33]. These metabolites were evaluated as mutagenic in the Ames test, with the conclusion that no safe exposure level of DKP nitroso-metabolites could exist [33].

However, current assays may be insufficient to fully assess photogenotoxic or photocarcinogenic potential, and more targeted models - particularly involving human skin exposure - are required.

Our thesis, however, remains that once nitrosated compounds are exogenously ingested or endogenously formed, they may circulate systematically, reach peripheral tissues - including the skin - and, upon ultraviolet irradiation, undergo photodecomposition [6,7]. This process could generate reactive intermediates capable of contributing to

photocarcinogenesis independently of the classical bacterial mutagenicity pathways.

Calcium channel blockers related phototoxicity ,Nitroso contamination and skin related Nitroso-Photocarcinogenesis

Amlodipine is metabolized in the liver via the cytochrome P450 system, specifically through CYP3A4 and CYP3A5, with approximately 90% of the drug transformed into inactive pyridine metabolites [34]. Consequently, concominant use of medications that inhibit CYP3A4 may increase systemic amlodipine exposure, potentially leading to higher-than-anticipated plasma concentrations and, if nitrosamine impurities are present, an increased mutagenic burden. In the case of amlodipine, the molecule contains a secondary amine located within the 1,4-dihydropyridine ring [35] that may act as a potential nitrosatable site. In the presence of nitrite - particularly in an acidic environment such as the stomach - there is a possibility of nitrosation, leading to the formation of nitroso-amlodipine (even without an external contamination) [6,7].

Following oral administration, amlodipine and its metabolites are systemically distributed and can reach peripheral tissues, including the skin's epidermis [35,36]. If a nitroso compound is present - either as an impurity or formed endogenously - cutaneous deposition could occur and under UV light, such compounds may undergo photodecomposition, and potentially generate NO- and ROS-related species, which will further contribute to oxidative DNA damage and skin cancer development [6,7].

An increased risk of basal cell carcinoma associated with calcium channel blockers (OR 1.09) was reported by Kappelin et al [37].

In another analysis, calcium channel blocker use was associated with a higher risk of non-melanoma skin cancer overall 1.13 (1.05-1.22) [19].

Notably, neither article addresses two important considerations: 1) the potential of these medications to form nitroso compounds (either as impurities or via endogenous nitrosation) [6,7], and 2) their inclusion in FDA's list regarding drugs with identified or potential nitrosamine-related carcinogenic risk [27].

According to the FDA, N-nitroso-amlodipine has been identified as a preformed external contaminant and is classified within potency category 5, with recommended AI limit of 1500 ng/day [27].

Calcium channel blockers, particularly amlodipine, have been implicated as potential contributing factors - especially in the setting of polymedication - in the development and progression of skin cancers, including keratinocyte cancers and cutaneous melanoma [38-40].

Moxonidine is an antihypertensive agent that undergoes limited hepatic first-pass metabolism, with only 10-20% off the drug metabolized in the liver [41,42]. It exhibits minimal to no significant involvement with the P450(CYP) enzyme system [41,42].

Moxonidine contains secondary amine functional group, which represents a potential site for nitrosamine impurity formation under certain conditions, such as N-nitroso-moxonidine [43]. Based on its pharmacokinetic profile, a proportion of moxonidine may distribute to peripheral compartments prior to hepatic metabolism, including the skin, rather than remaining in the plasma [44,45].

Moxonidine has been reported, although rarely, to induce cutaneous adverse reactions, including allergic skin reactions, pruritus, and, in isolated cases, angioedema [46,47], which can hardly be categorized solely within the framework of polymedication. If present in the skin - subsequent UV exposure could probably promote photodecomposition and subsequent skin carcinogenesis [6,7].

Moxonidine, particularly in the context of polymedication, has been reported in association with the development of keratinocyte cancers [48,49], as well as melanoma and dysplastic nevi [50].

Thiazide like diuretics, endogenous Nitrosogenesis and subsequent development of Nitroso Photocarcinogenicity

Indapamide is an antihypertensive agent belonging to the thiazide-like diuretics and is almost completely absorbed after oral administration [51]. It is primarily metabolized in the liver via CYP3A4, with minor contributions from CYP2C19 and CYP2C8 [52].

Calcium channel blockers such as felodipine, nifedipine, and nitrendipine- also metabolized by CYP3A4 - have been reported to inhibit indapamide metabolism, potentially increasing its plasma concentration [53]. Although amlodipine is not mentioned as a possible metabolic competitor, it is likewise metabolized by CYP3A4; therefore, concurrent administration may potentially result in competitive enzyme utilization and higher-than-expected plasma levels of one or even both agents.

Indapamide contains a secondary amine functional group [52] which makes it susceptible to nitrosation and the potential formation of N-nitroso-indapamide [53]. Following oral intake and gastrointestinal absorption, the drug enters the systemic circulation and reaches the peripheral tissues, including the skin [54].

Indapamide in combinated medication with perindopril has been reported to induce cutaneous photosensitivity upon exposure to UV light [55]. Another reported photosensitivity reaction was a reaction limited to the nail - a case of photoonycholysis induced by the use of indapamide [56].

Phototoxicity induced by oral antidiabetics and diuretics, such as indapamide, has been reported, with investigations demonstrating swelling of mitochondria and endoplasmic reticulum, and aggregation of euchromatin when cells are irradiated in the presence of photosensitizing agents [57].

Although indapamide itself has not been officially reported as nitrosamine-contaminated drug, another agent from the same pharmacologic class - chlorthalidone [40] - has been discussed in the context of the polymedication-carcinogenesis axis, particularly cutaneous melanoma.

Febuxostat is a medication commonly used for the long-term management of chronic hyperuricemia [58]. It is metabolized predominantly by hepatic enzymes, including CYPs1A2, CYP2C8, CYP2C9, as well as non-CYP-mediated pathways [58].

Given the partial involvement of CYP2C8 in the metabolism of both febuxostat and indapamide, concurrent administration may possibly result in competitive inhibition at the enzymatic level, potentially increasing the plasma concentration of one or both drugs. In such a scenario, indapamide - due to its secondary amine functional group - may accumulate to a greater extent in the systemic circulation, subsequently distribute to the skin, and, upon ultraviolet exposure, undergo photodecomposition. This process may generate reactive oxygen species which are recognized contributors to cancer initiation, promotion, and progression [6,7].

Although febuxostat itself does not structurally contain secondary or tertiary amines and has not been associated with nitrosamine impurities, it may indirectly potentiate carcinogenic risk by altering the metabolic clearance and systemic accumulation of co-administered medications within a polymedication regimen.

Esomeprazole is a proton pump inhibitor (PPI) that is extensively metabolized in the liver, primarily via CYP2C19 and, to a lesser extent, CYP3A4 (59). It is also a metabolism-dependent inhibitor of CYP2C19, which may influence the clearance of concomitantly administered drugs [59]. In this context, esomeprazole could potentially affect the metabolism of indapamide (partially metabolized by CYP2C19) and amlodipine (metabolized mainly by CYP3A4, with minor CYP2C19 involvement) [59]. By increasing the plasma concentrations of more than one co-administered drug - particularly through dual enzymatic pathways in the case of amlodipine - it may contribute to a higher cumulative systemic exposure.

From a theoretical standpoint, elevated plasma levels of these agents could enhance tissue deposition, including in the skin, where nitrosamine impurities (n-nitroso-amlodipine) or secondary amine-containing compounds (with the potential to form N-nitroso-indapamide) may undergo photodecomposition under ultraviolet exposure, thereby promoting photocarcinogenic processes.

After absorption in the small intestine and systemic distribution [60], PPIs have been associated with cutaneous adverse reactions, including photosensitivity [61] and drug-induced cutaneous lupus erythematosus [62]. Cutaneous toxicity in a case of severe exfoliative dermatitis caused by esomeprazole was reported [63].

Esomeprazole itself contains a secondary amine functional group, which under certain conditions - such as exposure to dietary nitrites in an acidic gastric environment - may potentially form N-nitroso-esomeprazole [64].

The possible connection with endogenous gastric nitrosation, subsequent systemic absorption, deposition in the skin [61-63], photodecomposition under ultraviolet exposure, and the release of nitric oxide [6,7] has also been regarded as the most probable explanation for cutaneous Nitroso-Photocarcinogenesis.

International data are concerning in that, although esomeprazole is not currently listed among drugs identified as contaminated with nitrosamines, prolonged PPI use (exceeding three months) has been associated in some studies with an increased overall cancer risk [65]. Additionally, pantoprazole, another PPI, has been discussed in the literature within the context of the polymedication-carcinogenesis axis, including reports linking it to basal cell carcinoma [6].

Ranitidine, another drug used for gastric acid reduction, was found to be contaminated with NDMA, which led to various gastrointestinal cancers [66]. Higher risk for ranitidine compared with proton pump inhibitors (PPIs) and other H2 antagonists (PRR 3.66, 95% CI 3.19–4.20) was found [66]. Elevated and significant proportional reporting ratios (PRRs) were observed for pharyngeal (PRR 9.24), esophageal (PRR 3.56), stomach (PRR 1.48), colorectal (PRR 16.31), liver (PRR 2.64), and pancreatic (PRR 2.18) cancers [65]. Increased PRRs were also reported for anal (PRR 4.62) and gallbladder (PRR 4.62) cancer [66].

At present, there are no definitive data clarifying whether such tumors, when observed, are related to the metabolic products of esomeprazole or to a possible unmetabolized nitroso derivative.

Alpha-hydroxylation of nitrosamines in the liver represents the primary metabolic activation pathway [67]. This cytochrome P450-dependent reaction is a crucial step in nitrosamine-induced carcinogenesis [67,68]. Cytochrome P450 enzymes catalyze the oxidation of the carbon atom adjacent to the nitroso group, producing chemically unstable agent, which spontaneously decomposes, generating a highly reactive carbenium ion [68-70]. These ions act as

potent agents, forming DNA adducts that can initiate mutagenesis and tumor formation (68-70).

A study by Li et al [71] using NDMA indicatesthat approximately 67% of the compound is metabolically converted via alpha-hydroxylation. The resulting intermediates are sufficiently stable to exert toxic effects, making it a key mechanism of nitrosamine-mediated toxicity.

While alpha-hydroxylation leads to metabolic activation and formation of DNA-reactive species, cytochrome P450 enzymes can also catalyze denitrosation [71]. This alternative pathway serves as a detoxification mechanism, reducing sometimes the carcinogenicity [71].

In the liver, nitrosamines undergo metabolic activation and can then also probably/ hypothetically subsequently be deposited in the skin.

Upon exposure to UV radiation, these compounds undergo photodecomposition (before metabolic activation in the liver), generating nitric oxide [6,7].

This mechanism could be seen as relevant for both keratinocyte and melanocyte tumors, indirectly supporting - alongside the international data discussed previously - the latest data on the genotoxicity and phototoxicity of nitrosamines.

Conclusion

The overlap between the medications (ramipril / amlodipine, moxonidine, febuxostat,esomeprazole) and the subsequent development of not one, but two distinct cutaneous tumors - basal cell carcinoma and melanoma - located in proximity, raises several important considerations:

1. Polymedication may result in competitive inhibition of shared metabolic pathways, potentially leading to increased plasma concentrations of certain drugs and, consequently, a higher cumulative mutagenic burden.
2. Each medication may possess a different carcinogenic or photocarcinogenic potential, thereby contributing to different pathogenic pathways and the possible emergence of multiple tumor types in the same patient under long-term combined exposure.

Although some medications have already been identified by regulatory authorities as being at risk for nitrosamine contamination, others have not yet been listed. Nevertheless, when considering their pharmacokinetic and pharmacodynamic properties - particularly the presence of nitrosatable functional groups and systemic tissue distribution - the potential for nitrosamine impurity formation appears less theoretical and more like a reality [72].

We conclude that several mechanisms of nitrosopharmacogenesis may be considered:

1. Exogenous nitrosogenesis/nitrosocontamination, based on the external synthesis or presence of nitrosamines, including:

1.1. Drug-specific nitroso derivates such as nitroso-ramipril, nitroso-amlodipine, etc

1.2. External contamination with small-molecule nitrosamines (e.g., NDEA, NDMA), which enter the body in preformed form, are absorbed, and subsequently found in the blood and skin.

2. *Endogenous Nitrosogenesis*, which does not require preformed exogenous nitroso compounds that, under gastric conditions and in the presence of certain dietary components, may undergo nitrosation and form N-nitrosamines in vivo. But this requires a specific drug structure: drug structure, containing secondary and tertiary amino groups.

These represent the fundamental principles of Drug-related Nitrosogenesis/ Photo Nitrosocarcinogenesis.

Before metabolic activation, nitroso compounds may distribute systemically and deposit in peripheral tissues, including the skin, regardless of their origin or intrinsic carcinogenic potency. Following ultraviolet exposure, photodecomposition may occur, accompanied by nitric oxide release, interaction with reactive oxygen species (ROS), and molecular events that can contribute to carcinogenesis, including melanoma and non-melanoma skin cancer.

Such complex processes may precede, or occur independently from, hepatic metabolic activation, which itself can generate reactive carcinogenic intermediates.

Models of Nitroso-photocarcinogenicity are additionally influenced by dietary Nitrosogenesis, further integrating exogenous intake, endogenous formation, pharmacokinetics, and environmental exposure into a multifactorial process.

Given the continuously rising global incidence of cancer, and skin cancer in particular, stricter regulatory surveillance and more comprehensive evaluation appear warranted.

Conflict of Interests

The authors declare no conflict of interest.

Ethical Statement

Ethics approval statement is not required.

Informed Consent Statement

Written informed consent for publication of their details was obtained from the patient.

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