Exploring Hydrochlorothiazide Use and Skin Cancer Risk

A commonly used antihypertensive appears to be linked to an increased risk of SCC. What should dermatologists do?

BY JONATHAN WOLFE, MD

Hydrochlorothiazide is a widely used antihypertensive and one of the most frequently used diuretics worldwide. Around 50 million prescriptions for the drug were filled annually in the US from 2004 to 2015. The drug is a known photosensitizer and has previously been linked to lip cancer. One study found that the risk for lip cancers* (which includes adenocarcinoma, mucoepidemoid carcinoma, Merkel cell carcinoma, basosquamous carcinoma, trichilemmocarcinoma, sclerosing sweat duct carcinoma, epithelial-myoepithelial carcinoma, and hemangiosarcoma) in non-Hispanic white patients increased as the duration of treatment with hydrochlorothiazide and related hypertensives increased.[1] Hydrochlorothiazide has also been linked to increased risk for cutaneous T-cell lymphoma (CTCL).[2,3]

Researchers recently have investigated the potential association of hydrochlorothiazide with risk for non-melanoma skin cancer (NMSC), and the results are concerning.[4]

LATEST EVIDENCE

Using data from the Danish Cancer Registry, researchers identified patients (cases) with NMSC in the period from 2004-2012.[4] Controls were matched 1:20 by age and sex. Cumulative hydrochlorothiazide use from 1995-2012 was assessed. Researchers used conditional logistic regression to calculate odds ratios (ORs) for BCC and SCC associated with hydrochlorothiazide use.

Analysis revealed that high use of hydrochlorothiazide, defined as ≥50,000mg cumulatively, was associated with OR of 1.29 (95% confidence interval [CI]: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. Researchers identified clear dose-response relationships between hydrochlorothiazide use and both BCC and SCC. In fact, in the highest cumulative dose category of ≥200,000mg, use of hydrochlorothiazide was associated with an OR of 1.54 (95% CI: 1.38-1.71) for BCC and 7.38 (95% CI: 6.32-8.60) for SCC. Of note, researchers did not identify a similar association between NMSC and use of other diuretics and antihypertensives.

These results echo earlier findings of an association between a broad grouping of photosensitizing diuretics and risk for skin cancer. That study looked at use of loop diuretics (bumetanide and furosemide), sodium-saving diuretics (spironolactone and amiloride), and thiazides (hydrochlorothiazide, bendroflumethiazide, and indapamide).[5] Researchers identified a total of 8,244 skin cancer cases: 5,964 BCC cases, 1,129 SCC cases, and 1,151 malignant melanoma (MM) cases. A total of 32,412 population controls were selected.

Analysis revealed an increased risk of SCC (IRR of 1.79 [95%; CI: 1.45-2.21]) and MM (IRR of 1.43 [95% CI: 1.09-1.88]) among users of combined amiloride and hydrochl orothiazide therapy. An increased risk of MM (IRR of 3.30 [95% CI: 1.34-8.10]) was found among users of indapamide. There were no strong associations with risk of BCC.

Another study published this spring found an association between photosensitizing antihypertensives and SCC risk, but the risk was "modest."[6] Using electronic pharmacy records, researchers classified patients using antihypertensives according to photosensitizing effect: photosensitizing (alpha-2 receptor agonists and diuretics [loop, potassium-sparing, thiazide, and combination]), non-photosensitizing (alpha-blockers, beta-blockers, central agonists, and angiotensin receptor blockers), or unknown (angiotensin converting enzyme inhibitors, calcium channel blockers, vasodilators, and other combinations). They identified patients who developed a SCC during follow-up (n=3,010) and used Cox modeling to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI).

Risk of SCC was increased in association with any use of photosensitizing antihypertensive drugs (aHR=1.17, 95% CI 1.07-1.28) or antihypertensive drugs of unknown photosen-

PHOTOSENSITIZING DRUGS

FDA identifies the following as photosensitizing drugs. Phototoxicity is more common than photoallergy. *Indicates photoallergic only; All other drugs are phototoxic +/- photoallergic.

- Antibiotics (ciprofloxacin, doxycycline, levofloxacin, ofloxacin, tetracycline, trimethoprim)
- Antifungals (flucytosine, griseofulvin, voricanozole)
- Antihistamines (cetirizine, diphenhydramine, loratadine, promethazine, cyproheptadine)
- Cholesterol lowering drugs (simvastatin, atorvastatin, lovastatin, pravastatin)
- Diuretics (thiazide diuretics: hydrochlorothiazide, chlorthalidone, chlorothiazide.; other diuretics: furosemide and triamterene)
- Non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, celecoxib*, piroxicam, ketoprofen)
- Oral contraceptives and estrogens
- Phenothiazines (tranquilizers, anti-emetics: examples, chlorpromazine, fluphenazine, promethazine, thioridazine, prochloroperazine)
- Psoralens (methoxsalen, trioxsalen)
- Retinoids (acitretin, isotretinoin)
- Sulfonamides (acetazolamide, sulfadiazine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfasalazine, sulfasoxazole)
- Sulfonylureas* for type 2 diabetes (glipizide, glyburide)

sitizing potential (aHR=1.11, 95% CI 1.02-1.20). There was no association with use of non-photosensitizing antihypertensive drugs.

CLINICAL IMPLICATIONS

Use of known photosensitizing drugs, including certain antibiotics, has previously been linked to risk of skin cancer.[7] As dermatologists, we recognize that increased susceptibility to UV damage is likely to confer increased risk for developing UV-mediated skin damage and malignancy. That use of hydrochlorothiazide would be associated with increased skin cancer risk is perhaps not surprising.

The clinical concern is that so many patients use this drug and related compounds, often indefinitely. This underscores the need to take a thorough drug history in patients of all ages.

Among those who are currently being treated with hydrochlorothiazide or related photosensitizing drugs, some patients may be candidates for a therapeutic switch to a non-photosensitizing antihypertensive. A therapeutic switch may be especially worthwhile for patients with a known history of skin cancer or significant risk factors for skin cancer. Additionally, patients who may experience excessive occupational sun exposure or otherwise be subject to substantial UV exposure on a consistent basis may also be candidates for a therapeutic switch. Encourage such patients to discuss a drug switch with the physician managing their hypertension or reach out to the prescriber to discuss.

For those patients who will remain on hydrochlorothiazide or any known photosensitizing drug, it is essential to provide education about proper use of SPF 30 or higher, daily, on all sun exposed skin; additional use of SPF with more prolonged sun exposure; use of UV blocking clothing and umbrellas; and minimizing overall exposure. Such patients, especially if they have a history of skin cancers or are at higher risk, require regular skin exams in the clinic and should be counseled to complete home exams on a regular basis.

By arming patients with information about their increased risk and providing strategies to minimize UV exposure and skin damage, it may be possible to mitigate the risk for developing skin cancers. ■

**Lip cancer includes malignant neoplasms of the vermilion border, commissure, and labial mucosa but does not include cancers originating on the skin of the lip.*

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