DSEN ABSTRACT

Hydrochlorothiazide and the Risk of Skin Cancer

Studies conducted by the Canadian Network for Advanced Interdisciplinary Methods for comparative effectiveness research (CAN-AIM) and the Canadian Network for Observational Drug Effect Studies (CNODES)

Summary

CAN-AIM and CNODES investigated whether hydrochlorothiazide (HCTZ), a commonly prescribed antihypertensive drug, is associated with an increased risk of skin cancer. Overall, CAN-AIM and CNODES found consistent results. In both studies, the use of HCTZ was not associated with increased overall risks of keratinocyte carcinoma or melanoma when compared with angiotensin-converting enzyme inhibitors (ACEIs). However, the CNODES study that had access to longer term follow-up found elevated risks of keratinocyte carcinoma and melanoma with longer durations of use (≥10 years) and higher cumulative doses (≥100,000 mg) of HCTZ, particularly when compared with calcium channel blockers (CCBs).

Key messages

These findings need to be considered in light of previous observational studies which highlighted increased risk of skin cancer; most of these studies were without active comparators, which increases the potential for confounding bias. Given the importance of HCTZ in treating hypertension, physicians, patients, and decision-makers must weigh the benefits and risks of HCTZ compared with other antihypertensive drugs (e.g., ACEIs, CCBs).

CAN-AIM Project Lead & Team

- Sasha Bernatsky, MD PhD
- Team members available here

CNODES Project Lead & Team

- Laurent Azoulay, PhD
- Team members available here

What is the issue? HCTZ, a thiazide diuretic, is among the most prescribed antihypertensive drugs. Some studies have suggested that HCTZ can potentially increase the risk of skin cancer.

What was the aim of the studies? To determine if there is an association between the use of HCTZ and the risk of keratinocyte carcinoma and melanoma compared with ACEIs or CCBs, two other classes of drugs used in the first-line treatment of hypertension.

How was the CAN-AIM study conducted? We evaluated keratinocyte carcinoma and melanoma in new users of HCTZ compared with new users of ACEIs. We studied ~25,000 participants in Canadian Partnership for Tomorrow's Health (CanPath) cohorts (Ontario Health Study; British Columbia's Generation Project; Quebec's CARTaGENE initiative, and Alberta's Tomorrow Project) and ~2 million Americans in MarketScan® Commercial and Medicare databases.

What did the CAN-AIM study find? In CanPath analyses, we did not demonstrate clearly different risks for HCTZ as compared with ACEIs, but confidence intervals were imprecise, such that an increased risk was not ruled out. For certain CanPath analyses, we noted time intervals when keratinocyte carcinoma risk was higher/lower depending on cumulative HCTZ exposure. In MarketScan Commercial subjects, the adjusted hazard ratios (aHRs) were more precise: 0.96 (95% confidence interval [CI] 0.91-1.00) for keratinocyte carcinoma and 1.07 (95% CI 0.95-1.20) for melanoma. In MarketScan Commercial analyses adjusting for smoking, and in Medicare analyses adjusting for race, results were similar to the main analyses. When pooling all CanPath and MarketScan analyses, we did not see clear differences in risk comparing HCTZ with ACEIs either for keratinocyte carcinoma (aHR 0.97, 95% CI 0.92-1.01) or melanoma (aHR 1.03, 95% CI 0.84-1.27). Strengths of CAN-AIM's research include adjustment for factors not normally found in claims data (e.g., smoking, race). However, a limitation was the relatively low number of events, particularly for melanoma.

How was the CNODES study conducted? We conducted a multi-site population-based cohort study using administrative health databases from six Canadian provinces and the United States (US) MarketScan® Commercial and Medicare databases. The study cohorts included patients aged 40 years and older newly treated with HCTZ or a clinically relevant comparator, ACEIs in the primary comparison or CCBs in the secondary comparison, between 1995 and 2018. The risk of keratinocyte carcinoma and melanoma was compared between new users of HCTZ and new users of ACEIs and CCBs separately. Results were combined using a statistical approach called meta-analysis for Canada alone and also including the US data.

What did the CNODES study find? The study cohorts included over one million patients with more than 80,000 keratinocyte carcinoma cases and close to 6,000 melanoma cases. While HCTZ was not associated with an overall increased risk of keratinocyte carcinoma when compared with ACEIs (HR 1.02, 95% CI 0.98-1.07) or CCBs (HR 1.08, 95% CI 0.99-1.17), higher risks were observed with long-term use and higher cumulative doses. For melanoma, there was no clear evidence of an association when compared with ACEIs (HR 1.14, 95% CI 0.99-1.31) or by duration of use or dose. When compared with CCBs, HCTZ was associated with a 32% increase in the risk of melanoma (HR 1.32, 95% CI 1.19-1.46), with higher risks observed with long-term use (≥10 years) and higher cumulative doses (≥100,000 mg). Results were consistent when including the US data. Strengths of the CNODES' study include its large population size and long duration of follow-up. A limitation is the potential for confounding due to unmeasured factors (e.g., sun exposure, race, smoking).

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For more information, please contact: Autumn.Neville@rimuhc.ca (CAN-AIM study) or info@cnodes.ca (CNODES study).