Study reveals possible solution to elevated cancer risk from important anti-infection drug

November 5 2019, by Alex Gardner

Credit: CC0 Public Domain

For the last decade, medical experts have known that voriconazole, an effective antifungal medication used to prevent dangerous infections in

patients with compromised immune systems, was linked to the development of particularly aggressive squamous cell carcinoma (SCC) in skin exposed to ultra violet (UV) rays. However, the mechanism of how voriconazole causes SCC was unclear. Now a team of Penn Medicine researchers led by John T. Seykora, MD, Ph.D., an associate professor of Dermatology in the Perelman School of Medicine at the University of Pennsylvania, have now made a promising discovery, showing that voriconazole increases levels of oxidative stress in skin cells called keratinocytes, and that a common antioxidant, acetylcysteine, can mitigate voriconazole's cancer-inducing side-effect in keratinocytes. Their findings were published recently in Experimental Dermatology.

Although SCC only develops in a subset of patients, the consequences can be devastating: tumors can develop and expand rapidly, invade surrounding tissue, and metastasize to lymph nodes. Despite the known risk, the potentially life-saving benefits of voriconazole for patients with suppressed immune systems—such as patients who have received organ transplants—still warrants use of the drug.

The research team, including co-first authors Vivian Lee, MD, an assistant professor of Ophthalmology and Dermatology, and Michael Gober, MD, a former instructor in Dermatology, conducted studies in both cell cultures and animal models to examine the cellular effects of voriconazole in combination with UV exposure. Using a clue from a prior study on goldfish neurons where the compound azole was found to inhibit the anti-oxidative enzyme catalase, the team hypothesized that voriconazole would have the same effect on catalase in the skin because it contains an azole moiety. Inhibition of catalase would then induce higher levels of oxidative stress in skin cells, promoting the formation of SCC. Utilizing various assays and a unique genetic mouse model developed by the Seykora lab, this study proved the researchers' hypothesis to be correct.

The team went on to pretreat human skin cells in culture with N-acetylcysteine, an antioxidant, to help mitigate the effects of increased oxidative stress. The team found that the antioxidant reduced two markers of oxidative stress in mouse skin tissue exposed to UV radiation.

"Once we knew what the relationship between voriconazole and catalase was, we could attempt to interfere with it and diminish the effects," Seykora said.

This finding sets the stage for trials pairing voriconazole with an antioxidant to see if the combination decreases rates of SCC and if it could serve as an effective treatment for those who have to take the anti-fungal drug.

"Conducting human trials to show that the combination of voriconazole and N-acetylcysteine is safe and effective is the next step in this research. Since N-acetylcysteine has existed for years and is a common treatment for other conditions, we anticipate a safe pairing," said Seykora, who hopes to see one of his colleagues begin human clinical trials within the coming years. "People with suppressed immune systems already have other medical concerns to worry about. We don't want them to have to worry about elevated skin-cancer risk, too."

More information: Vivian Lee et al. Voriconazole enhances UV-induced DNA damage by inhibiting catalase and promoting oxidative stress, *Experimental Dermatology* (2019). DOI: 10.1111/exd.14038

Provided by Perelman School of Medicine at the University of Pennsylvania