Cyclopamine: Inhibiting Hedgehog in the Treatment of Psoriasis

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GOAL

To understand cyclopamine in the treatment of psoriasis to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the effect of inhibiting the hedgehog intracellular signaling pathway in the treatment of psoriasis.
2. Describe the mechanism of action of cyclopamine in patients with psoriasis.
3. Recognize the cautions of using cyclopamine in women of childbearing potential.

CME Test on page 183.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: August 2006.

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Drs. Meth and Weinberg report no conflict of interest. The authors discuss off-label use of cyclopamine. Dr. Fisher reports no conflict of interest.

The steroidal alkaloid cyclopamine, a direct inhibitor of the hedgehog (Hh) intracellular signaling pathway, has demonstrated promising initial results in the treatment of psoriasis. Cyclopamine initially was shown to be effective in the induction of the differentiation and apoptosis of basal cell carcinomas (BCCs). This brief review explains both the details of Hh signaling and the role of cyclopamine in interrupting it. Most importantly, this article discusses the implications of recent findings on the treatment of psoriasis. Although considerable research and clinical trials lie ahead, cyclopamine-induced Hh inhibition may represent the latest mechanistic pathway to combat psoriasis.

Cutis. 2006;78:185-188.

Accepted for publication March 22, 2006.

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Psoriasis is a common chronic dermatologic disease that affects approximately 3% of the US population.[1] Research has implicated T-cell mediated immunity as having an increasingly important role in the pathophysiology of this disorder. The pathogenesis of psoriasis now is best linked to the antigen-based activation of Langerhans cells, which subsequently drive a T-cell inflammatory

cascade.[2] Along with this new understanding has come a radical shift in the approach to treating this disease. While the focus of psoriasis treatment was once on excessive keratinocyte proliferation and abnormal differentiation,[3] the new target is the activated T cell. Along with the older immunomodulating agents, newer biologic agents have been designed to interrupt various stages in the inflammatory response.

Despite the influx of treatments for psoriasis, clearance still is not always a realistic expectation[4]; therefore, the search for therapeutic options continues. One of the most promising options is the steroidal alkaloid cyclopamine (Figure), a direct inhibitor of the hedgehog (Hh) intracellular signaling pathway. Building on work demonstrating cyclopamine's success in the induction of the differentiation and apoptosis of basal cell carcinomas (BCCs),[5] investigators have now provided evidence of this compound's use in the treatment of psoriasis.[6]

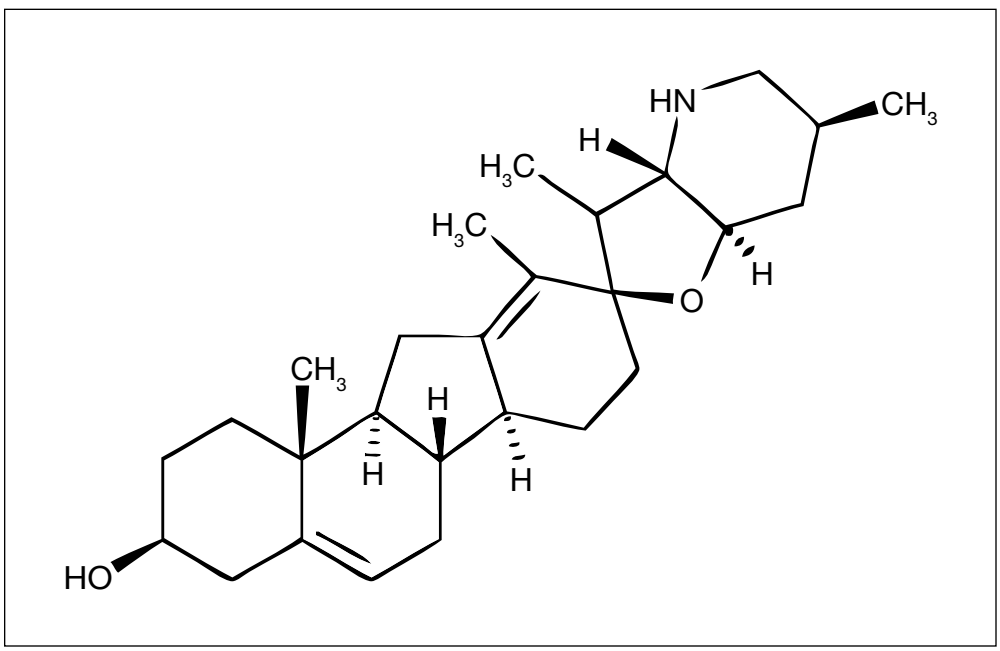
Hh Signaling

The Hh gene was first identified more than 25 years ago in *Drosophila melanogaster* as a critical organizer of cell-fate determination during embryogenesis and development.[7,8] More recently, the Hh signaling pathway has shown saliency in regulating cellular proliferation and differentiation in a wide array of human tissues. Consequently, the pathway has been implicated in aberrant cell survival in numerous human malignancies,[9] ranging from BCCs[5,10] and medulloblastomas[11] to small cell lung,[12] gastrointestinal,[13] breast,[14] and prostate[15] tumors.

The Hh pathway has 3 main components: (1) the Hh ligand, a transmembrane receptor circuit composed of the negative regulator Patched (Ptc); (2) the activator Smoothened (Smo); and (3) a cytoplasmic complex that regulates the Gli family of transcription factors. In the normal resting state, the 7-transmembrane protein Smo's activity is suppressed by the 12-transmembrane protein Ptc. It is only with Hh ligand stimulation of the Ptc receptor that this inhibition is released, leading to Smo activation of the Gli transcriptional response.[16-20] Consistent with this model, autonomous Hh signaling may result from either inactivating mutations (eg, loss of heterozygosity or truncating mutations) in the gene *Ptc* or activating mutations in the gene *Smo*.[21] Abnormal activation of the Hh pathway is responsible for the pathway's tumorigenic properties, subsequently defining Ptc and Smo as a tumor suppressor and proto-oncogene, respectively.[16] Characteristic of their newly discovered roles, Ptc and Smo are 2 of the newest targets in oncology.

Cyclopamine and Hh

Even before the Hh pathway was understood, Binns et al[22] reported an epidemic of cyclopia (complex birth defect characterized by the absence of median facial structure and an undivided forebrain—ie, holoprosencephaly) in sheep herds of the western United States. The etiology of this birth defect ultimately proved to be ingestion of a lily, *Veratrum californicum*, during gestation. The lily is common in the subalpine meadows from which the steroidal alkaloid cyclopamine was extracted.[23,24] It took almost 40 years,



Structure of steroidal alkaloid cyclopamine.

though, to prove that cyclopamine's teratogenic effects were related to the gene family *Hh*.

Cyclopamine's involvement in the Sonic Hh pathway was first shown in studies with chick embryos.[25,26] Incardona et al[25] noted that Sonic Hh pathway–dependent patterning of the ventral tube is interrupted in cyclopamine-treated embryos, yielding offspring with facial malformations similar to the cyclopic sheep discovered almost 40 years prior. Although the researchers were unable to locate the exact mechanism of action, the findings suggested cyclopamine's role as a direct antagonist of Hh signal transduction. More recently, Chen et al[27] used photoaffinity and fluorescent derivatives to prove that this inhibitory effect is mediated by the direct binding of cyclopamine to the heptahelical bundle of Smo. When properly understood, cyclopamine inhibits Hh signaling by antagonizing Smo, thereby interrupting the Gli-mediated transcriptional pathway.

With this discovery and the knowledge that Hh overactivation is implicated in numerous human malignancies, cyclopamine has become one of the more popular compounds in recent oncology trials. Within the past 2 years, cyclopamine and the Hh signaling pathway have become new therapeutic targets for patients with breast,[14] brain,[28] colorectal,[13] and prostate[15] tumors. Cyclopamine's interruption of the Hh pathway has shown promise in the treatment of BCCs. Because most BCCs manifest loss-of-function mutations in Ptc[29] (leading to unrestrained Smo and, therefore, Gli activity), Smo antagonism seems a natural vehicle to target treatment. Recently, Athar et al[30] proved that cyclopamine could be used in mice to prevent UVB-induced BCCs. Athar and colleagues[30] showed that Hh inhibition induced high levels of the gene *Fas*, which augmented tumor apoptosis. Tas and Avci[5] also have recently shown cyclopamine to be effective in the treatment of human BCCs. Using histologic and immunohistochemical markers, the researchers were able to demonstrate inhibition of the proliferation and highly efficient induction of the differentiation and apoptosis of tumor cells. Because apoptotic tumor cells actually had reduced levels of p53 expression, Tas and Avci[5] also concluded that cyclopamine performed its function in a nongenotoxic manner, a positive finding considering the substance's potential teratogenic side effects.

Cyclopamine and Psoriasis

Building on their success inducing epidermal differentiation in BCCs, Tas and Avci[6] hypothesized that cyclopamine may have a mechanistic role in the treatment of psoriasis. In a preliminary proof-of-concept study, they treated a total of 31 psoriatic lesions in 7 patients (all with an established diagnosis of plaque or guttate psoriasis) with a cream containing cyclopamine. At least one lesion (similar in size to a cyclopamine-treated lesion) was treated with base cream alone in each patient. The researchers also conducted an assay comparing cyclopamine with a potent topical steroid, clobetasol-17-propionate. The results were extremely impressive, with clinical and histologic clearance as early as 2 days and frequency of applications ranging from 6 to 8 times per day. Although clobetasol-17-propionate added to cyclopamine's performance, the Smo antagonist was superior to the steroid alone. Histologic and immunohistochemical analysis showed signs of rapid induction of epidermal cell differentiation because there was a vigorous reappearance of the epidermal granular layer, a marked decrease in epidermal hyperplasia, return of the elongated and thickened rete ridges towards normalcy, and normalization of the thinning of the suprapapillary epidermis.[6] The reappearance of granular cells in response to cyclopamine is evidence of the terminal differentiation of spinous cells, a marker associated with the cessation of proliferation. Inhibition of Hh signaling by cyclopamine, therefore, opens new doors in the treatment of psoriasis, moving the concentration away from immunomodulation and bringing the role of keratinocytes back into focus.

Conclusion

The recent study by Tas and Avci[6] opens a new field for therapeutic development in psoriasis, but considerable research lies ahead before cyclopamine becomes a mainstream treatment. Most importantly, little is known about the human toxicity of cyclopamine and its metabolism into the skin. No adverse effects were seen in either of Tas and Avci's[5,6] clinical studies of cyclopamine, yet the drug's role in stem cell development[31] and its teratogenicity[32] cautions its use in women of childbearing potential until sufficient relevant data are available. Additionally, large, prospective, randomized, controlled trials are needed to confirm cyclopamine's effectiveness. If successful, these studies will provide the optimal concentration, frequency, and mode of administration of treatment. Because the importance of Hh in epidermal hyperproliferation and development has been demonstrated, a field recently focused on immunology must once again look at the keratinocyte as a fundamental target in the pathophysiology of psoriasis.

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