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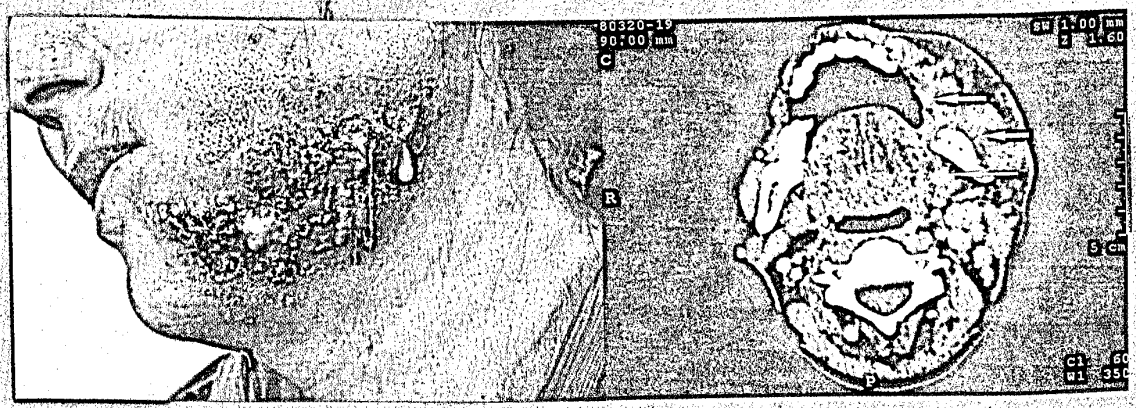

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The Rise and Fall of Oral Ketoconazole

Aditya K. Gupta[1,2] and Danika C.A. Lyons[2]

Abstract

Background: Ketoconazole was the first broad-spectrum oral antifungal agent available to treat systemic and superficial mycoses. Evidence of hepatotoxicity associated with its use emerged within the first few years of its approval. Growing evidence of serious side effects including endocrine dysregulation, several drug interactions, and death led to the review of oral ketoconazole in 2011.

Objective: This article chronicles the use of oral ketoconazole from its introduction to its near replacement in medicine.

Conclusion: Due to its hepatotoxic side effects, oral ketoconazole was withdrawn from the European and Australian markets in 2013. The United States imposed strict relabeling requirements and restrictions for prescription, with Canada issuing a risk communication echoing these concerns. Today, oral ketoconazole is only indicated for endemic mycoses, where alternatives are not available or feasible. Meanwhile, topical ketoconazole is effective, safe, and widely prescribed for superficial mycoses, particularly as the first-line treatment for tinea versicolor.

Résumé

Contexte : Le kétoconazole a été le premier antifongique oral à large spectre servant à traiter les mycoses systémique ou superficielles. Des preuves de son hépatoxicité ont émergé dès les premières années ayant suivi son approbation. L'accumulation de données probantes sur ses effets secondaires graves, entre autres des troubles endocriniens, plusieurs interactions médicamenteuses et le décès, a mené à une revue de ce médicament en 2011.

Objectif : Le présent article présente les usages du kétoconazole oral, depuis son arrivée en médecine jusqu'à son remplacement presque total.

Conclusion : En raison de ses effets secondaires hépatotoxiques, le kétoconazole oral a été retiré du marché en Europe et en Australie en 2013. Les États-Unis ont imposé des conditions strictes relativement au nouveau libellé des indications approuvées et des restrictions à la prescription de ce médicament, tandis que le Canada a diffusé des communiqués sur les risques et les préoccupations soulevées par ce médicament. À l'heure actuelle, le kétoconazole oral n'est indiqué que pour traiter les mycoses endémiques, lorsqu'il n'existe aucune autre solution. Il reste que le kétoconazole oral est efficace, sûr et largement utilisé pour traiter les mycoses superficielles, notamment en traitement de premier recours du pityriasis versicolor.

Keywords

ketoconazole, azole antifungal, history, hepatotoxic, indication

Introduction

The development of the first broad-spectrum oral antifungal, ketoconazole (Nizoral), in 1977 by Janssen Pharmaceutica represented an exciting new advancement in the field of medical mycology.[1] Ketoconazole received United States (US) Food and Drug Administration (FDA) clearance for use in systemic fungal infections in July 1981.[2,3] It remained the only oral antifungal available for the treatment of systemic fungal infections for nearly a decade thereafter.[3] Until recently, oral ketoconazole has been a mainstay of treatment for a plethora of superficial and systemic fungal infections. However, the drug was taken off the market in Europe and Australia in 2013 as a result of the risk of serious hepatic side effects.[4-6] Similarly, strict restrictions and cautionary advisements were added to oral ketoconazole labelling in the US and Canada in 2013. Today, oral ketoconazole is recommended in these countries only in the event of severe or life-threatening systemic infections when alternatives are unavailable.[7,8]

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