Risk and Benefit Evaluation of Oral Ketoconazole: A Review from Taiwan Adverse Drug Reaction Reporting System and Health Insurance Database

Yi-Hsuan Chen, Wei-I Huang, Wen-Wen Chen
Taiwan National ADR Reporting Center, Taiwan Drug Relief Foundation, Taipei, Taiwan

Introduction

Oral ketoconazole is indicated for treatment of fungal infections and has also been used in advanced prostate cancer and Cushing's syndrome. In July 2013, EMA suspended this product because the risk of liver injury is greater than the benefit in treating fungal infection[1]. Concurrently, FDA decided to restrict its indication and added several warnings to manage the risk[2].

Aim

To evaluate the risks associated with oral ketoconazole use and to explore the usage patterns of oral ketoconazole in real clinical practice in Taiwan.

Methods

By using Taiwan National ADR Reporting System database, we reviewed all ADR reports related to oral ketoconazole from July 2007 to September 2013. Prescription pattern of oral ketoconazole was evaluated by using a longitudinal cohort dataset with 1 million individuals sampled from the National Health Insurance beneficiaries (LHID).

Results

We identified 58 ADR reports associated with oral ketoconazole in the database, including 40 (69%) females and 18 (31%) males. Among these reports, oral ketoconazole was indicated mainly for minor skin fungal infection or tinea. Hepatobiliary disorders (53%) were most reported, including fatalities and liver transplantations. By using LHID, we identified 24,704 oral ketoconazole prescriptions in 2011, which was 10 times greater than any other antifungal agents. 77% of the prescriptions were prescribed in physician clinics, where regular liver profile monitoring is less likely to put into practice in our society. Besides, since ketoconazole related liver injury may occur early even when commenced with recommended doses, it is not feasible to come up with a risk management plan to adequately reduce the risk. We also observed 6 cushing's syndrome patients and 110 prostate cancer patients treated with oral ketoconazole in LHID.

Table 1. Demographics of reported oral ketoconazole cases

Item	Hepatobiliary disorders	All
No. of cases	31	58
Age（year）		
Mean ±SD	45±15	51±20
Range	16-86	16-94
Gender（N）		
Male	8	18
Female	23	40
Outcome of adverse reaction（N）		
Death	1	2
Life threatening	4	5
Hospitalization	20	25
Non-serious	6	26

Table 2. Prescription pattern of oral ketoconazole in Taiwan in 2011

Medical care institute	No. of prescription（%）
Medical centers	280（1.1%）
Regional hospitals	354（1.4%）
District hospitals	1,103（4.5%）
Primary care clinics	19,103（77.3%）
Pharmacy	3,864（15.6%）
Total	24,704（100.0%）

Conclusions

In consideration of current clinical practice in Taiwan, along with the seriousness of the hepatic risk associated with oral ketoconazole use and the substitutability of oral ketoconazole in treating fungal infections, we believe the benefits of oral ketoconazole use did not outweigh the risks. Therefore, a recommendation of suspending the marketing authorizations of oral ketoconazole is preferred. For cushing's syndrome and prostate cancer patients, authorities should ensure oral ketoconazole availability in controlled conditions.

Reference

1. European Medicines Agency. (7/26/2013). *European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole*; Retrieved october 18, 2013, from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Ketoconazole-containing_medicines/WC500146616.pdf
2. Food and Drug Administration. (7/26/2013). *FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets dueto potentially fatal liver injury and risk of drug interactions and adrenal gland problems*; Retrieved october 18, 2013, from http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362444.pdf