UNIVERSITI PUTRA MALAYSIA

TOXICITY OF ANTIFUNGAL DRUGS ITRACONAZOLE AND FLUCONAZOLE IN RATS

NOR SHAHIDA ABDUL RAHMAN

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TOXICITY OF ANTIFUNGAL DRUGS ITRACONAZOLE AND FLUCONAZOLE IN RATS

By

NOR SHAHIDA ABDUL RAHMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfilment of the Requirements for the Degree of Master of Science

March 2004
DEDICATION

“Dedicated especially to my parents Abdul Rahman Mat and Tuan Zaharah Tuan Yusoff, sisters, brothers and all those individuals behind the scenes who make me possible to complete my study successfully.”
Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Master of Science

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Chairman: Associate Professor Muhammad Nazrul Hakim Abdullah, Ph.D.

Faculty: Medicine and Health Sciences

Itraconazole and Fluconazole are the newer antifungal drugs that have been used for several years. Both these drugs have a broad-spectrum antifungal activity and currently are used to treat infections caused by Candida albicans, Aspergillus spp., Paracoccidioides brasiliensis, Sporothrix schenckii, Histoplasma capsulatum, Cryptococcus neoformans and many others. The objective of this study is to investigate the in vitro and in vivo cytotoxicity of these two antifungal drugs. The in vitro and in vivo cytotoxicity of fluconazole and itraconazole were studied in thirty eight male Sprague Dawley rats. Freshly isolated rat hepatocytes were obtained for the in vitro treatment of fluconazole and itraconazole using a liver perfusion technique. The cell viability test was done by trypan blue exclusion. As a result, both fluconazole and itraconazole cause a reduction in cell viability of hepatocytes. However, itraconazole exerted its cytotoxicity more than fluconazole in both time- and dose-dependent manner. Meanwhile, cytotoxicity of itraconazole was reduced significantly by Phenobarbital pretreatment. Phenobarbital did not have any effect on the
cytotoxicity induced by fluconazole. *In vivo* studies revealed that rat's liver and
kidney treated with repeated-doses of itraconazole showed a significantly higher in
total protein in liver and kidney and significant increase in serum ALP and ALT
activity. This is in agreement with histological findings that the rat treated with
repeated-doses of itraconazole showed severe histological features compared to
fluconazole. Morphological changes such as inflammation and fibrosis of liver were
frequently seen in repeated-doses of itraconazole. This present study suggests that
Phenobarbital plays a role in the cytoprotection of hepatocytes to itraconazole-induced
but not fluconazole-induced cytotoxicity *in vitro*. 
Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KETOKSIKAN DADAH ANTI-KULAT ITRACONAZOLE DAN FLUCONAZOLE DALAM TIKUS

Oleh

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Mac 2004

Pengerusi: Professor Madya Muhammad Nazrul Hakim Abdullah, Ph.D.

Fakulti: Perubatan dan Sains Kesihatan

Sementara itu, ketoksikan yang disebabkan oleh dadah anti-kulat itraconazole dapat dikurangkan dengan menggunakan Phenobarbital. Phenobarbital tidak mempengaruhi ketoksikan yang disebabkan oleh fluconazole. Kajian *in vivo* juga menunjukkan terdapat peningkatan dalam jumlah protein dan aktiviti serum ALP dan ALT di dalam hati dan buah pinggang tikus yang diberi suntikan itraconazole secara berulang-kali. Secara histologinya, tikus yang diberi suntikan itraconazole secara berulang-kali menunjukkan kesan ketoksikan yang ketara terhadap hati dan buah pinggang tikus jika dibandingkan dengan tikus yang diberi suntikan fluconazole secara berulang-kali. Perubahan morfologi seperti keradangan dan fibrosis pada hati telah dilihat dengan kerap dalam suntikan itraconazole secara berulang-kali. Dengan itu, kajian ini telah menunjukkan bahawa phenobarbital memainkan peranan dalam mengurangkan ketoksikan yang dihasilkan oleh itraconazole tetapi tidak mempengaruhi ketoksikan yang disebabkan oleh fluconazole secara *in vitro*. 
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I certify that an Examination Committee met on 5th March 2004 to conduct the final examination of Nor Shahida Abdul Rahman on her Master of Science thesis entitled “Toxicity of Antifungal Drugs Itraconazole and Fluconazole in Rats” in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the relevant degree. Members of the Examination Committee are as follows:

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Date: 17 MAY 2004
DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at UPM or other institutions.

NOR SHAHIDA ABDUL RAHMAN

Date: 13 APR 2004
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6.28 The mean plasma ALT levels of post-treated rats with repeated-doses of fluconazole and itraconazole

6.29 The mean plasma ALP levels of pre-treated rats with repeated-doses of fluconazole and itraconazole

6.30 The mean plasma ALP levels of post-treated rats with repeated-doses of fluconazole and itraconazole

6.31 Light micrograph of liver from normal non-treated rat

6.32 Light micrograph of rat’s liver treated with repeated high dose of 100mg/kg fluconazole

6.33 Light micrograph of rat’s liver treated with repeated high dose of 100mg/kg fluconazole