UNIVERSITI PUTRA MALAYSIA

TOXICITY OF ANTIFUNGAL DRUGS ITRAConAZOLE AND FLUCONAZOLE IN RATS

NOR SHAHIDA ABDUL RAHMAN

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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

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