

## **Short Research Article**

### **Dispensing of banned phenolphthalein and ketoconazole: simulated patients method**

#### **Abstract**

Introduction: Banned and harmful medicines can affect patient's health, safety and life. There are two medicines available in Aden community pharmacies (phenolphthalein (PP) and ketoconazole (KZ)) that are globally banned. The objective of this study was to evaluate the availability and dispensing of banned phenolphthalein and ketoconazole by community pharmacists. Methods: A preliminary cross-sectional simulated patients method was carried out. The study gathered data on dispensing behavior. Simulated patients were trained to access the availability of banned drugs existing in the community pharmacies. The availability of these two banned drugs was observed and recorded. The pharmacists were asked about the availability of a PP laxative for treating constipation called in Yemen a khat laxative (Sharbat Alkhat) and KZ for fungal infections in 50 convenient samples of community pharmacies that were selected based on ease of access by the simulated patients. Results: PP was found in 3/50 (6%) pharmacies, while 31/50 (62%) pharmacies kept KZ in the premise. Conclusion: The availability of these drugs in Yemeni pharmacies is worrisome. It can affect the safety of the public.

**Keywords:** banned drugs; medication safety; pharmacy practice; pharmacovigilance

## 1 INTRODUCTION

Harmful medicines are still available in developing countries. Some drugs banned in their country of origin are marketed in developing countries by a few pharmaceutical companies. Due to a lack of legislation and weak legal regulation of drugs in developing countries, these drugs are dispensed to patients without consideration of their potential hazards.

Some international corporations that have established their roots in evolving countries have a goal of attaining the maximum level of income irrespective of humanitarian foresight. However, pharmaceutical and many other companies also use developing countries' markets for selling goods they cannot dispose of elsewhere, such as contaminated food and radioactive waste [1].

There are two drugs available in Aden community pharmacies (phenolphthalein (PP) and ketoconazole (KZ)) that are globally banned. PP was the essential constituent in several over-the-counter laxatives for most of the 20<sup>th</sup> century. The U.S. Food and Drug Administration FDA categorized PP as “safe and effective” in 1975 [2]. However, in 1997, the FDA anticipated that PP should be reclassified as “not commonly documented as safe and effective” [3] after a 2-year feeding study in rodents showed elevated frequencies of neoplasms of the ovary, adrenal gland, kidney, and hematopoietic system [4]. Consequently, the United States voluntarily withdrew most PP, including that contained in laxatives, from the market. Studies indicated the genotoxicity of PP [4] and its ability to cause oxidative damage [5] and bind to estrogen receptors [6]. The individual data on laxative usage and human cancers specified that its use is not associated with an increased risk of large-bowel cancer [7–13].

The United States Food and Drug Administration (FDA) issued a Drug Safety Communication restricted the use of Nizoral (KZ) oral tablets on July 26, 2013 [14]. However, KZ was the only existing systemic remedy for a wide variety of fungal infections. The FDA’s warning emphasized the potential of a possibly fatal drug-induced liver injury (DILI) related to KZ usage, in addition to other risks. The declaration stated that “Nizoral oral tablets should not be a first-line treatment for any fungal infection, [and] Nizoral should be used only when alternative antifungal therapies are not available or tolerated.” At the same time, the European Medicines Agency’s Committee on Medicinal Products for Human Use (EMA-CHMP) [15] has suggested that the selling authorization for oral KZ as an antifungal be postponed.

The CHMP stated that the hepatotoxic risk associated with the usage of KZ overshadows its benefits. Physicians should select an alternative medicine to treat patients with fungal infections. The patients being treated with KZ should consult their physicians. Oral KZ for Cushing's syndrome and topical dosage forms containing KZ are not included in this warning. The FDA Communication [14] states the following: "Serious hepatic injury was identified as the major toxicity for Nizoral tablets and was noted to be unrelated to dose, duration, or indication for treatment. In showing the benefit-risk evaluation, normal side effect shows the DILI, including mortalities and hepatic transplantations, feedback from the FDA Adverse Event Reporting System (AERS) were judged independently by a hepatology expert in FDA. The total hazard for KZ-induced serious liver injury seemed higher than that accompanying other azole antifungal drugs as indicated from pharmacoepidemiologic studies."

As part of a larger medication safety study among community pharmacists in Yemen, this study was performed to assess the availability of two banned medicines in Yemen i.e. PP and KZ.

## 2 MATERIALS AND METHODS

This preliminary cross-sectional explorative study applied simulated patients to gather data on dispensing behavior. Simulated patients were trained in the accessibility of banned drugs existing in the community pharmacies. The availability of these two banned drugs was observed and recorded. The pharmacists were asked about the availability of a PP laxative for treating constipation called in Yemen a khat laxative (*Sharbat Alkhat*) and KZ for fungal infections in 50 convenient samples of community pharmacies that were selected based on ease of access by the simulated patients.

A small simulated patient case study was carried out to recognize and eradicate the barriers associated with simulated patients and to prepare a training module. The simulated patient visited two randomly chosen community pharmacies in Aden, Yemen. During the visit, the simulated patient requested medications to treat symptoms of constipation and fungal infection. All details and observations of the consultation were documented by the simulated patient. The findings suggested poor professional practices in both pharmacies and paved the way for the study to

compare the dispensing practices of banned drugs and prohibited medicines in community pharmacies in Aden. These two pharmacies were not included in the major study.

A literature review, case study, and training session informed a simulated patient interview method to observe, assess and compare dispensing practices. Twenty students from the Faculty of Pharmacy Aden University were trained to present as simulated patients to determine the availability of banned and prohibited medicines. For standardization and validation of the study, the 20 simulated patients were randomly grouped in ten pairs, and each pair was randomly assigned to visit five pharmacies. Each pair of simulated patients in an interchangeable manner visited two pharmacies. Two encounters with two simulated patients resulting in a total of 100 encounters in pharmacies. The stimulated patient interacted with the staff at the pharmacy and asked questions about the availability of the 2 prohibited medicines PP and KZ in the Yemeni market and recorded the answer of the community pharmacies after each visit to a pharmacy. Descriptive statistics (i.e. frequency and percentage) were used for data analysis.

### **3 RESULTS**

The main intention of the current study was to determine the availability of the banned drugs, which will potentially affect patients' safety in terms of using banned medicines. The dispensing behavior for the two banned drugs (PP and KZ) was observed and recorded in 50 community pharmacies. PP was found in 3/50 (6%) pharmacies, while 31/50 (62%) pharmacies kept KZ in the premise.

### **4 DISCUSSION**

To the authors' best knowledge, the current study is considered the first of its kind in Yemen on the availability of the two banned drugs in the community pharmacies. Likewise, no official document from the High Authority for Medicines was found that prohibited their use in the Yemeni community pharmacies. The PP is dispensed informally in the community pharmacies

under the name of *Sharbat Alkhat*. Although the name is different, the active ingredient is the same. Additionally, KZ is sold in most pharmacies without any restrictions on its use.

The data from one study by Coogan et al. revealed that the infrequent use of PP did not increase the risk of some types of cancers that were identified in animal studies (ovarian cancer, kidney cancer, leukemia, and lymphoma) [16]. However, this study could not verify the risks of using PP on average once a week for no less than two years. Coogan and coworkers thought that level of use could increase the risk of developing some types of cancer [16]. The percentage of community pharmacies dispensing PP is considerable lower than the percentage dispensing KZ.

The data from the present study revealed that the percentage of pharmacies keeping and selling KZ is high (n=31, 62% of community pharmacies sold it) in comparison to PP. KZ was approved in 1981 as an oral antifungal drug and since that time it has been recognized to cause liver damage or impairment. Studies determined that the hepatic injury was the result of direct hepatocellular toxicity rather than immunologically intermediated effects [17]. According to Greenblatt et al., the active metabolite of KZ, N-desacetyl-ketoconazole, may be responsible for the hepatic damage and toxicity as shown in experimental models. However, that toxicity is related to its dosage, concentration and period of application [17]. Nevertheless, information that has been gathered to the present time and published in the biomedical studies shows that KZ is occasionally a quantitatively significant offending medicine that can trigger a process of drug-related liver damage and even liver failure. However, our study only identified the existence of these drugs in the Yemeni pharmaceutical market and availability in community pharmacies. We are not able to clearly associate between the frequency of use and dosage of the two drugs and health risks of the people.

The study would like to recommend the following:

1. The health ministry should issue an official document to limit the import of these drugs into the country and prevent their dispensation in the community pharmacies.
2. The Ministry of Health needs to organize a periodic inspection committee to monitor the dispensing of these drugs.
3. The community pharmacists should be made aware of the potential health hazards associated with the long-term use of banned drugs.
4. The list of banned drugs should be periodically renewed and provided to the community pharmacies.
5. The students in the Faculty of Medicine and Health Sciences should be educated about the risk of using the banned medicines.

## **5 CONCLUSION**

The availability of these drugs in Yemeni pharmacies is alarming. The high authority for medicines must put restrictions on their use or provide suitable alternatives for them in the local markets to ensure patient safety.

## **ETHICAL APPROVAL**

The study protocol was endorsed by the Ethics Research Committee of the Faculty of Medicine and Health Sciences, University of Aden. Due to the nature of the study (i.e. to observe the actual practice), the participants were informed about the study after the study has completed. Written informed consent was obtained after the objectives, importance and benefits of the research were mentioned. They were assured that all of the data gathered would be handled with full confidentiality, and it would only be used for research purposes.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## References:

1. Melrose D. Bitter pills: medicines and the third world poor Oxford, United Kingdom Oxfam, 1982.
2. US Food and Drug Administration. Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products. Federal Register, March 21, 1975;40:12,902–10.
3. US Food and Drug Administration. Laxative drug products for over-the-counter human use; proposed amendment to the tentative final monograph. Federal Register, September 2, 1997;62:46,223–7.
4. Dunnick JK, Hailey JR. Phenolphthalein exposure causes multiple carcinogenic effects in experimental model systems. *Cancer Res* 1996;56:4922–6.
5. Sipe HJ Jr, Corbett JT, Mason RP. In vitro free radical metabolism of phenolphthalein by peroxidases. *Drug Metab Dispos* 1997;25: 468–80.
6. Ravdin PM, van Beurden M, Jordan VC. Estrogenic effects of phenolphthalein on human breast cancer cells in vitro. *Breast Cancer Res Treat* 1987;9:151–4
7. Nakamura GJ, Schneiderman LJ, Klauber MR. Colorectal cancer and bowel habits. *Cancer* 1984;54:1475–7.
8. Kune GA, Kune S, Field B, Watson LF. The role of chronic constipation, diarrhea, and laxative use in the etiology of large-bowel cancer. Data from the Melbourne Colorectal Cancer Study. *Dis Colon Rectum* 1988;31:507–12.
9. Kune GA. Laxative use not a risk for colorectal cancer: data from the Melbourne Colorectal Cancer Study. *Z Gastroenterol* 1993;31:140–3.
10. Sonnenberg A, Muller AD. Constipation and cathartics as risk factors of colorectal cancer: a meta-analysis. *Pharmacology* 1993;47 Suppl 1:224–33.

11. Le Marchand L, Wilkens LR, Kolonel LN, Hankin JH, Lyu LC. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res* 1997;57:4787–94.
12. Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. *Epidemiology* 1998;9:385–91.
13. Ghadirian P, Maisonneuve P, Perret C, Lacroix A, Boyle P. Epidemiology of sociodemographic characteristics, lifestyle, medical history, and colon cancer: a case–control study among French Canadians in Montreal. *Cancer Detect Prev* 1998;22:396–404.
14. FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. UCM 362444: 26 July 2013.
15. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. Benefit of oral ketoconazole does not outweigh risk of liver injury in fungal infections. EMA/ 458028/2013. 26 July 2013.
16. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD, Shapiro S. Phenolphthalein laxatives and risk of cancer. *Journal of the National Cancer Institute*, 2000; 92 (23):1943-4. doi: 10.1093/jnci/92.23.1943.
17. Greenblatt HK, David J. Greenblatt. Liver injury associated with ketoconazole: review of the published evidence. *The Journal of Clinical Pharmacology* 2014;54(12):1321–1329. doi: 10.1002/jcph.400.