Acute Hepatitis Associated with Barakol

MONGKON HONGSIRINIRACHORN, MD*,
SOMBAT THREEPRASERTSUK, MD**,
ANUCHIT CHUTAPUTTI, MD*

Abstract

Barakol is a natural anxiolytic extracted from *Cassia siamea*, known as *"Khi-lek"* in Thailand. The authors studied the adverse effects of Barakol in 12 healthy Thai patients, aged 29-81 years (mean 52.5) who took Barakol 3-180 days (mean 76.9). Eight of them were admitted with the first episode of anorexia and jaundice for 4-60 days (mean 14.3) after taking 20-40 mg/day (2-4 tablets) of Barakol. There was no relationship between degree of symptom and dosage/duration of Barakol intake. Three asymptomatic cases were detected with increased aminotransferase from a routine check-up, including an 81 year old female who took half of the dosage for 120 days. The last one was a male patient who presented with low-grade fever and nausea and vomiting. All patients had neither a history of chronic liver disease nor known hepatotoxic substance ingestion. On admission, the mean total bilirubin was 5.7 mg/dl and liver function test (LFT) revealed moderate to severe hepatitis (Aspatate amino transferase (AST) range 111-1,473 U/L: mean = 692). None of them had detected viral markers. Liver biopsy was done in 3 cases and the histopathological findings were compatible with interface hepatitis. Two non-biopsy cases developed recurrent transaminitis after one-week re-challenging without informing the physician. Their symptoms and LFT completely improved within 2-20 weeks (mean 5.9) after Barakol abstinence.

Key word : Barakol, Hepatitis

**HONGSIRINIRACHORN M,
THREEPRASERTSUK S, CHUTAPUTTI A
J Med Assoc Thai 2003; 86 (Suppl 2): S484-S489**

* Section of Digestive and Liver Diseases, Department of Medicine, Phramongkutklao College of Medicine, Bangkok 10400,

** Division of Digestive System, Department of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand.

At present, complementary and alternative medicine such as herbal medicine, Thai massage, healthy food and group therapy are becoming popular. In the United States there was an increasing use of alternative medicine from 33.8 per cent to 42.1 per cent during 1990-1997. Most conditions were chronic diseases such as stress condition, chronic headache, back pain and insomnia[1]. 42 per cent of these are used for treatment and 58 per cent for prevention. After the economic crisis, more people became interested in alternative medicine. However, there should be concern about the alternative medicine that may give benefit or risk, especially herbal medicine. Therefore, it is necessary to consider the quality and safety of herbal medicine by doing research and following it up after it has been launched. All products should give general information in terms of indication and adverse side effects[2].

Barakol, a natural anxiolytic extracted from *Cassia siamea* Lamk or *Siamese senna* or Cassod tree, known as *"Khi-lek"* in Thailand[3]. It is classified as Phylum *Leguminosae* and was first extracted from leaves[4] in 1969 by Hassanali W, Nottingham University[5]. Ten grams of dry leaves could extract 80 mg of Barakol (0.8%) by using 15 per cent ethanol 100 ml in 2 h[6]. In animal models, Barakol is not only a dopamine agonist (diazepam like effect) but also a serotonin antagonist[7,8]. The lethal dosage is 300 mg per kilogram BW[9]. Besides Barakol, the authors also extracted anthraquinones from *Cassia siamia* [10]. Hyperbilirubinemia results from Barakol and should be avoided.[11] This herbal medicine was launched in August 1997 after the economic crisis in Thailand. Barakol was prepared in tablet form, containing 10 mg per tablet, anybody can buy it at over the counter drugstores. The authors expect that more than a thousand people have used this drug for treatment of anxiety or insomnia.

The aim of this paper was to report and study the clinical, biochemical and pathological findings related to the adverse effects of Barakol in healthy Thai patients.

MATERIAL AND METHOD

During 1999-2000, there were 12 patients who attended the Liver Clinic of Phramongkutklao Hospital and King Chulalongkorn Hospital, Bangkok, Thailand, with acute hepatitis. They used Barakol tablets because of insomnia. All cases had no chronic liver diseases. 11 patients were females, aged 29 to 81 yrs (mean 52.5 years). All of the patients had negative virological markers for hepatitis A, B, C; and there were no other causes such as autoimmune-hepatitis, hemochromatosis, Wilson's disease and alcoholic liver disease.

The Drug Induced Liver Injury (DILI) scale [12] was used to assess each patient's condition. It was validated, that the authors have used in clinical practice for precise and early diagnosis that's usually based on circumstantial evidence such as detailed pharmacological history, exclusion of alternative causes, extrahepatic manifestation, re-exposure of drugs and previous reports in the literature (Table 1).

The probability of the diagnosis of DILI was expressed as a final score that could vary from -6 to 20. The five degrees of adverse drug reactions was established, according to the observed score: definite (score > 17), probable (score 14-17), possible (score 10-13), unlikely (score 6-9), and excluded (score < 6).

RESULTS

Duration of Barakol intake was 3-180 days (average 77). The degree of hepatitis varied from asymptomatic to fatigability, nausea, vomiting, anorexia and jaundice. 8 patients developed nausea, vomiting and icteric sclera in 4-60 days (mean 14.3) after taking 10-40 mg/day of Barakol without significance of duration or dosage. One male patient presented with fever, nausea-vomiting without jaundice. 3 cases were asymptomatic but only transaminitis was detected and recurrent transaminitis developed in 1 week after they re-used this drug by themselves without informing the doctor. The liver function test showed abnormal values of total bilirubin range 0.6-12.5 mg/dl: (mean = 5.76 mg/dl) and AST range 111-1,473 U/L (mean = 692 U/L). Ultrasonography of the upper abdomen was done in all cases and revealed liver parenchymal disease. Liver biopsy was done in 3 cases was consented and these results were compatible with drug induced hepatitis including a mild degree of piecemeal necrosis at the portal triads with a cholestasis picture in canaliculi and the liver lobules revealed focal hydropic change, scattered necrosis with acidophilic bodies. By using the DILI scale (Fig. 3)[12], Barakol probably induces hepatotoxicity. These symptoms and biochemical values completely improved after discontinuation of Barakol within 2-23 weeks (mean 5.4) without dose-related Barakol or duration of intake (Table 2).

Table 1. Drug-induced Liver Injury Diagnostic (DILI) s cale.

	Score
I Temporal relationship between drug intake and the onset of clinical picture	
A. Time from drug intake until the onset of first clinical or laboratory manifestations	
- 4 days to 8 weeks (or less than 4 weeks in the case of re-exposure)	3
- Less than 4 days or more than 8 weeks	1
B. Time from withdrawal of drug until the onset of first clinical manifestations	
- 0-7 days	3
- 8-15 days	0
- More than 15 days	-3
C. Time from withdrawal of drug until normalization of laboratory values	
- Less than 6 months in cholestatic pattern or 2 months in hepatocellular pattern	3
- More than 6 months (cholestatic) or 2 months (hepatocellular)	0
II Exclusion of alternative causes	
Viral hepatitis, alcoholic liver disease, biliary tree obstruction, preexisting liver disease, hypotension, pregnancy	
Complete exclusion	3
Partial exclusion	0
Possible alternative cause detected	-1
Probable alternative cause detected	-3
III Extrahepatic manifestations	
Rash, fever, arthralgia, eosinophilia (>6%), cytopenia	
4 or more	3
2 or 3	2
1	1
None	0
IV Intentional or accidental re-exposure to the drug	
Positive rechallenge test	3
Negative or absent rechallenge test	0
V Previous report in the literature of cases of DILI associated with the drug	
Yes	2
No (drugs marketed for up to five years)	0
No (drugs marketed for more than five years)	-3
Total score	20

DISCUSSION

In general[13], 5 per cent of jaundice and 10 per cent of acute hepatitis are caused by drugs which are probably under diagnosed because of a low level of physician awareness. After the DILI scale[12] (Drug induced liver injury scale) was validated, the authors used it in clinical practice for precise and early diagnosis that's usually based on circumstantial evidence such as detailed pharmacological history, exclusion of alternative causes, extrahepatic manifestation, re-exposure of drugs and previous reports in the literature.

The authors diagnosed Hepatitis associated with Barakol by using the DILI scale. All of the patients probably had a degree of adverse drug reactions (Table 3).

In the present study there was no co-relation between the duration and dosage of Barakol in 8 symptomatic cases. Only one male patient presented with different symptoms than the female patients. 3 cases developed recurrent transaminitis 1 week after they re-used this drug without informing the doctor. These indicated positive findings of drug induced hepatitis including the DILI scale. All symptoms and biochemical values completely improved after discontinuation of Barakol without dose-related Barakol or duration of intake. Finally, the authors could not

Table 2. Information of 12 patients with hepatitis associated with Barakol in 1999-2000.

Case	Age	Sex	Day of exposure	Dosage mg/day	Symptoms	ALT U/L	TB/DB mg/dl	Symptom & biochemical value improved within (week)
1	60	F	60	20	Yes	1,146	15/12	23
2	61	M	21	20	Yes	1,076	1.8/1.3	4
3*	81	F	150	10	No	127	0.8/0.4	4
4*	30	F	30	20	No	643	0.6/0.3	4
5	49	F	3	20	Yes	432	7.8/4.6	4
6	63	F	90	20	Yes	740	3.9/3.0	6
7	29	F	120	20	Yes	934	7.0/6.1	3
8	55	F	30	20	Yes	779	7.5/5.5	6
9*	50	F	180	20	No	413	1.0/0.7	2
10	58	F	60	20	Yes	399	8.0/4.1	6
11	41	F	90	40	Yes	1,100	12/7.2	2
12	54	F	90	20	Yes	1,168	7.4/3.6	4

* = Positive re-challenge, ALT = Alanine transminase, TB = Total bilirubin, DB = Direct bilirubin.

Table 3. Patients' score by using the DILI scale.

	DILI scale					
Case	Relationship	Exclusion	Extrahepatic	Positive rechallenge	Previous Report*	Total
1	9	3	1	0	2	15
2	9	3	2	0	2	16
3	6	3	1	3	2	15
4	6	3	1	3	2	15
5	9	3	1	0	2	15
6	9	3	1	0	2	15
7	9	3	2	0	2	16
8	9	3	1	0	2	15
9	6	3	1	3	2	15
10	9	3	1	0	2	15
11	9	3	1	0	2	15
12	9	3	1	0	2	15

* Local report of cases of DILI Associated With Barakol[21,22]

conclude the relationship between dosage/duration of Barakol intake and degree of symptoms/timing of recovery

From the pathological finding, 3 patients had a mild degree of piecemeal necrosis at the portal triads (interface hepatitis) with cholestasis picture in canaliculi and the liver lobules revealed focal hydropic change, scattered necrosis with acidophilic bodies. These are the characteristics of drug induced hepatitis which indicate that the mechanism of Barakol induced liver injury should appear from hepatotoxic effect more than hypersensitivity.

SUMMARY

Barakol probably acts as drug induced liver injury, but we could not conclude that hepatitis developed from direct effect or from another additive. So, caution should be taken with the rational use of drugs in clinical practice until the exact mechanism has been elucidated.

(Received for publication on April 6, 2003)

REFERENCES

1. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. JAMA 1998; 280: 1569-75.
2. Jonas WB. Alternative medicine-learning from the past, examining the present, advancing to the future (editorials). JAMA 1998; 280: 1616-7.
3. Khi-lek: Thai herbal medicine. Hhao-Sod Newspaper. March 30, 2000: 28.
4. Themsiriroukula R, King TJ, Wallwork SC, et al. Thai herbal medicine. Bangkok: Siambook and Publication, 1999: 90-1.
5. Hassanali-Walji, Barakol, a novel dioxaphenalene derivative from Cassia siamia. J Chem Soc Chem Commun 1969; 12: 678.
6. Tangsrisamruang P. The Preliminary Extraction of Barakol from Cassia siamea and concentration by pervaporation. A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Engineering in Chemical Engineering, Department of Chemical Engineering, Bangkok: Chulalongkorn University 1997.
7. Thongsaad W, Deachapunya C, Pongsakorn S, Boyd EA, Bennett GW, Marsden CA. Role of Barakol as a natural anxiolytic. Phar Biochem Behav 1996; 53: 753-8.
8. Thongsaad W, Pongsakorn S, Sudsuang R, Bennett GW, Kendall DA, Marsden CA. Barakol, a natural anxiolytic, inhibits striatal dopamine release but not uptake *in vitro*. Eu J Pharmacol 1997; 319: 157-64.
9. Fiorino DF, Treit D, menard J, Lermer L Phillips AG. Is Barakol anxiolytic? Behav Pharmacol 1998; 9: 375-8.
10. Chantarayodha P. The CNS Effect of Barakol. PhD research, Department of Physiology, Bangkok: Faculty of Pharmacy, Chulalongkorn University 1988.
11. Koff RS, Gardner R, Harinasuata U, et al. Profile of hyperbilirubinemia in three hospital-populations, Clin Res 1970; 18: 680.
12. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997; 26: 664-9.
13. Lewis JH, Zimmerman HJ, Drug-induced liver disease. Med Clin North Am 1989; 73: 775-92.
14. Zimmerman. HJ, Ishak KG. General aspects of drug-induced liver disease. Gastroenterol Clin North Am 1995; 24: 739-58.
15. Zimmerman HJ, Maddrey WC. Toxic and drug-induced hepatitis. In Schiff L, Schiff ER (eds) : Disease of the Liver, ed 5. Philadelphia: JB Lippincott; 1993: 707-83.
16. Nathan MB. Drug-induced liver disease. In James HG, Kenneth RM, Scott LF (eds) Current Diagnosis and Treatment in Gastroenterology, 1st ed, 1996: 571-6.
17. Nathan MB, Robert KO. Drug-induced liver disease. In Zakim D, Boyer TD (eds) Hepatology: A Textbook of Liver Disease, 3rd ed Philadelphia, W.B. Saunders Company 1996: 962-71.
18. William ML. Drug-induced hepatotoxicity. N Engl J Med 1995; 333: 1118-27.
19. Gary LD. Chronic hepatitis. In Kaplowitz N (ed.) Liver and Biliary Diseases, 2nd ed. Pennsylvania, W.B. Saunders Company 1996: 334-5.
20. Fugh-Berman A. Herb-drug interactions. Lancet 2000; 355: 134-8.
21. Hongsirinirachorn M, Chutaputti A. Hepatitis associated with Anhydrobarakol. Annual meeting of The Royal College of Physician of Thailand 2000: 132.
22. Threeprasertsuk S, Hongsirinirachorn M, Chutaputti A. Hepatitis associated with Barakol. Thai Clinic 2000; 16: 385-90.

ภาวะตับอักเสบจากยาสมุนไพรขี้เหล็กเม็ด

มงคล หงษ์ศิรินิรชร, พบ,*
*สมบัติ ตรีประเสริฐสุข, พบ**, อนุชิต จูฑะพุทธิ, พบ**

ยาสมุนไพรขี้เหล็กเม็ด (Barakol) เป็นสารสกัดจากใบแก่หรือดอกตูมของต้นขี้เหล็ก (Cassia siamea) ซึ่งออกฤทธิ์เป็นยาคลายกังวลเช่นเดียวกับ Diazepam การศึกษานี้เป็นรายงานผู้ป่วยจำนวน 12 ราย ที่รับประทานยาสมุนไพรขี้เหล็กเม็ด นาน 3–180 วัน (เฉลี่ย 76.9) ทั้งหมดมีอายุระหว่าง 29–81ปี (เฉลี่ย 52.5) มีผู้ป่วย 8 รายมาพบแพทย์ด้วยอาการดีซ่านและเบื่ออาหารเป็นเวลา 4–60 วัน (เฉลี่ย 14.3 วัน) ก่อนมาโรงพยาบาล หลังจากรับประทานยาสมุนไพรขี้เหล็กจำนวน 2–4 เม็ด (20–40 มก) ก่อนนอน โดยไม่พบความสัมพันธ์ระหว่างอาการกับขนาดหรือระยะเวลาที่รับประทานยา ผู้ป่วย 3 ราย ซึ่งไม่มีอาการ แต่พบว่ามีการเพิ่มของ AST และ ALT อย่างชัดเจน ในจำนวนนี้รวมถึงผู้ป่วยสูงอายุ 1 รายซึ่งรับประทานยาในขนาด 1 เม็ดก่อนนอน นาน 4 เดือน รายสุดท้ายเป็นผู้ป่วยชายมาพบแพทย์ด้วยอาการไข้ต่ำ ๆ ร่วมกับอาการคลื่นไส้อาเจียน ผู้ป่วยทุกรายไม่มีประวัติเป็นโรคตับเรื้อรังหรือรับประทานยาที่มีพิษต่อตับมาก่อนหน้านี้ ค่าเฉลี่ยของ Total Bilirubin ที่ตรวจพบคือ 5.76 มก % ภาวะตับอักเสบส่วนใหญ่อยู่ในขั้นปานกลางถึงรุนแรงโดย AST อยู่ระหว่าง 111–1473 U/L เฉลี่ย = 692) ทุกรายไม่พบเชื้อไวรัสตับอักเสบหรือสาเหตุของโรคตับอื่น ๆ แต่อย่างใด ผู้ป่วย 3 รายยินยอมให้ทำการตรวจชิ้นเนื้อจากตับ พบพยาธิสภาพของการอักเสบในเนื้อตับที่เข้าได้กับตับอักเสบจากยา ผู้ป่วย 3 รายเกิดภาวะตับอักเสบซ้ำจากรับประทานยาสมุนไพรขี้เหล็กเม็ดนาน 1 สัปดาห์ เนื่องจากมีอาการนอนไม่หลับ อาการและผลเลือดของผู้ป่วยทุกรายเป็นปกติใน 2–20 (เฉลี่ย 5.6) สัปดาห์หลังงดรับประทานยาสมุนไพรขี้เหล็กเม็ด

คำสำคัญ : ยาสมุนไพรขี้เหล็กเม็ด, ตับอักเสบ

มงคล หงษ์ศิรินิรชร, สมบัติ ตรีประเสริฐสุข, อนุชิต จูฑะพุทธิ
จดหมายเหตุทางแพทย์ ฯ 2546; 86 (ฉบับพิเศษ 2): S484–S489

* แผนกโรคระบบทางเดินอาหารและโรคตับ, ภาควิชาอายุรศาสตร์ วิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า, กรุงเทพ ฯ 10400
** หน่วยโรคระบบทางเดินอาหาร, ภาควิชาอายุรศาสตร์, คณะเวชศาสตร์เขตร้อน มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400