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First Case of Methimazole-Induced Cholestatic Jaundice in An Elderly Man with Hyperthyroidism by RUCAM Scale.

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ABSTRACT

Methimazole is an anti-thyroid drug that acts mainly via inhibits the enzyme thyroperoxidase. It has been reported that methimazole is widely used and generally well tolerable in patients with hyperthyroidism. In recent years more and more reports were involved in the methimazole caused people's liver damage and most of these literatures were inappropriate disgnosed by Naranjo scale or not quantitative assessment for disgnosis. We describe a case of patient with hyperthyroidism, gastritis and epilepsy who had developed hepatic damage after multiple drugs administration. After a series of examinations, diseases such as hepatitis, infectious mononucleosis et.al were excluded. Because of the diagnostic challenge and Naranjo scale is less sensitivity for rare reaction in liver injury, Feng Yue and Xiaohua Zhou contributed equally to this work methimazole induced cholestatic jaundice hepatitis was first made by the RUCAM scale. After methimazole was discontinued, her liver enzyme results began to improve. Along with a literature review, we find RUCAM scale not Naranjo scale is important to quantitative assessment drug-induced liver injury include methimazole-induced cholestatic jaundice.

Key words: methimazole - cholestatic jaundice - hyperthyroidism- RUCAM scale

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INTRODUCTION

Methimazole is widely prescribed for thyrotoxic and most common adverse effects such as rash, indigestion and vomit are generally well tolerated[1]. Methimazole-induced cholestatic hepatitis is a rare but serious adverse reaction which may be misdiagnosed by Naranjo scale[2] or be short of quantitative assessment in most published literatures[3-6], furthermore properly assessment is very important to patients when two or more drugs have potential liver toxicity were given simultaneously.

We describe a rare case of 69-year-old yellow man with hyperthyroidism who developed cholestatic liver injury by RUCAM scale instead of Naranjo scale for appraisal of drug-induced hepatotoxicity.

Case report

A 69-year-old yellow man was admitted to the affiliated Yancheng hospital of southeast university medical college for complaints of pruritus and lack of appetite, jaundice that had appeared 1 week earlier. The patient had no history of liver disease and denied drug allergies, alcohol use, smoking or any illicit drug misuse. Her medical history was remarkable for epilepsy and astroesophageal reflux. **A**

Her drug therapy consisted of carbamazepine(CBZ) 200 mg/bid and omeprazole 20 mg/qd. He had been taking CBZ for more than 10 years, the concentration of CBZ in plasma and liver function were normal which were monitored every month and omeprazole drug had been taking for more than 3 months without any obvious adverse effects. The patient's surgical history included radical surgery for esophageal carcinoma performed 5 years earlier. Hyperthyroidism was diagnosed four weeks before this admission, started with methimazole 10 mg/ tid(Table 1).

Table 1: The laboratory values of the patient 4 weeks ago

Laboratory Variable	Value	Normal range
CBZ(mg/L)	8.81	4.0～12.0
T3 (mgl/L)	2.99	0.66～1.61
FT3 (pmol/L)	8.57	3.28～6.47
T4 (ng/L)	167.95	54.4～118.5
FT4 (pmol/L)	16.77	7.64～16.03
TSH (uIU/mL)	0.01	0.49～4.91
TB (μmol/L)	8.13	5.10～19.00
ALP (U/L)	78.1	0～125
GGT (U/L)	34.3	5～60
AST (U/L)	18.6	5～40
ALT (U/L)	30.9	5～50

CBZ: carbamazepine, FT4: free thyroxine, FT3: free triiodothyronine, TSH: thyroid stimulating hormone, TB: Total bilirubin, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Physical examination on admission indicated that the patient was thin, awake, alert, no fevers and severe icterus of the sclerae, blood pressure was 133/81 mmHg, respiratory rate 19 breaths/minute and heart rate 71 beats/minute. No abnormal was found after the patient's abdomen, heart, hepatic and splenic examination.

Liver function tests revealed slightly increased levels of AST 88.2 U/L and ALT 59.2 U/L respectively, but levels of ALP 631 U/L and TB 370.3 μmol/L were remarkable highly, direct bilirubin and indirect bilirubin levels were 295.6 μmol/L (0 ~ 5μmol/L) and 74.7.0 μmol/L (0–19μmol/L), respectively.

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Serologic tests for infectious mononucleosis and acute viral hepatitis A, B and C were negative. Results for antinuclear antibody titer, antismooth muscle antibody, ceruloplasmin, alpha fetoprotein, carcinoembryonic antigen and tumor marker 125,199 were normal as well.

Abdominal ultrasonography performed on day 2 of hospitalization revealed a thickened gallbladder with a moderate amount of debris, but common bile duct or gallbladder had no stones. Delayed gallbladder visualization consistent with chronic cholecystitis was showed by hepatobiliary iminodiacetic acid scan. A subsequently performed magnetic resonance cholangiopancreaticograms (MRCP) excluded presence of any stone, stricture, or mass in the common bile duct, obstructive jaundice was excluded. The human plasma concentration of CBZ was 13.57 mg/l elevated slightly, then dose of CBZ was adjust to 200mg/100mg/day, therapeutic drug monitoring (TDM) of CBZ was 11.02 mg/l on the third day. Reexamine of Liver enzyme levels little changed . Fig.1 shows the patient's results of TDM throughout her hospitalization (days 1–15).

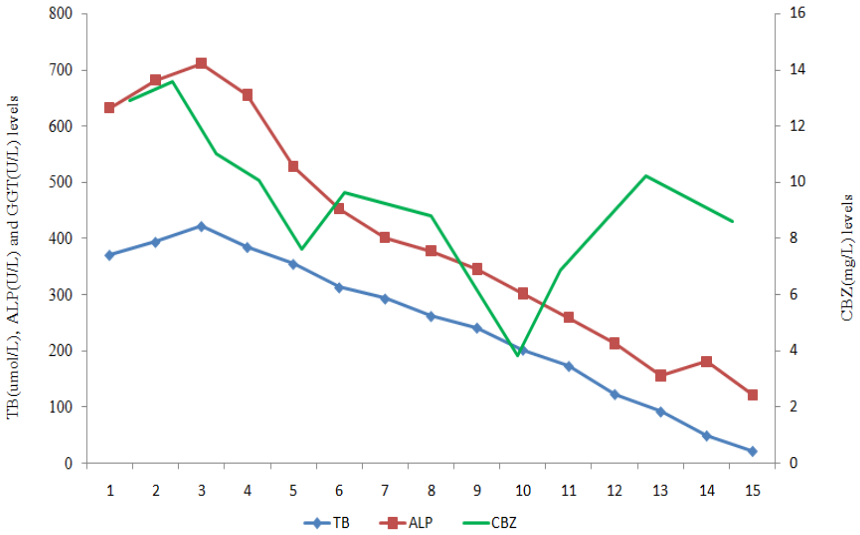

Figure.1. The patient's liver functions and TDM of CBZ over the course of his hospitalization (days 1-15).TB = total bilirubin, ALP = alkaline phosphatase,CBZ = carbamazepine,TDM = therapeutic drug monitoring

Because of presumed diagnosis of drug-induced liver injury, Naranjo scale was introduced for assessment, CBZ and methimazole value were 4 score and 3 score respectively(1 ~ 4 = possible ADR)(Table.2 shows detailed Naranjo scale of methimazole and CBZ). It is difficult to identify which one more possible caused that hepatobiliary, but CBZ and methimazole value were 4 score and 7 score respectively by RUCAM scale(Table.3 shows detailed RUCAM scale of methimazole and CBZ). According the rule of RUCAM methimazole probable induced cholestatic jaundice, CBZ possible induced this reaction. In consideration incidence rate of hepatotoxicity of valproic acid is higher than that of CBZ, further more withdrawal anti-epileptic drug is not allowed to do, CBZ was continued ,only adjusted dose of CBZ by TDM.

Methimazole was discontinued on day 3, Omeprazole and CBZ were continued. Her liver enzyme levels then decreased rapidly, over the next 10 days, her liver enzyme levels trended downward to ALP 122 U/L and TB 21.3µmol/L, AST and ALT levels were within normal limits, Figure 1 shows the patient's liver enzyme levels throughout her hospitalization (days 1–15), CBZ plasma concentration was fluctuations within the allowable range according to the monitoring results. On day 15, the patient was discharged home receiving omeprazole 20 mg/day and CBZ 200mg/bid. For treatment of hyperthyroidism, the patient would be a candidate to receive radioactive iodine ablation of the thyroid gland.

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Table2: Naranjo scoring of methimazole and CBZ for causality analysis

No.	Question	Yes	No	Do not know	Methimazole Score	CBZ Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1	+1
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2	+2
3	Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	0	0
4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0	0
6	Did the reaction reappear when a placebo was given?	-1	+1	0	0	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	+1	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0	0
9	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	0	0

Table3: RUCAM scoring of methimazole and CBZ for causality analysis

Items for Cholestatic or Mixed Liver Injury	Score	Methimazole Score	CBZ Score
1. Time to onset from the beginning of the drug/herb			
5–90 days (rechallenge: 1–90 days)	2	2	
<5 or >90 days (rechallenge: >90 days)	1		1
Alternative: Time to onset from cessation of the drug/herb			
(except for slowly metabolized chemicals:≤30 days)	1		
2. Course of ALP after cessation of the drug/herb			
Percentage difference between ALP peak and N			
Decrease ≥ 50% within 180 days	2	2	

Decrease < 50% within 180 days	1		
No information, persistence, increase, or continued drug/herb use	0		0
3. Risk factors			
Alcohol use current drinks/d: >2 for women, >3 for men)	1		
Alcohol use (current drinks/d: ≤2 for women, ≤3 for men)	0		
Pregnancy	1		
Age ≥ 55 years	1	1	
Age < 55 years	0		0
4. Concomitant use of drug(s)/herb(s)			
None or no information	0		
Concomitant drug/herb with incompatible time to onset	0		
Concomitant drug/herb with compatible or suggestive time to onset	−1		-1
Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset	−2	−2	
Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	−3		
5. Search for alternative causes	Tick if negative		
Group I (7 causes)			
HAV:Anti-HAV-IgM	□		
HBV: HBsAg, anti-HBc-IgM, HBV-DNA	□		
HCV:Anti-HCV, HCV-RNA	□		
HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	□		

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Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MRC	□		
Alcoholism (AST/ ALT ≥ 2)	□		
Acute recent hypotension history (particularly if underlying heart disease)	□		
Group II (5 causes)			
Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	□		
Infection suggested by PCR and titer change for			
CMV(anti-CMV-IgM, anti-CMV-IgG)	□		
EBV(anti-EBV-IgM, anti-EBV-IgG)	□		
HSV(anti-HSV-IgM, anti-HSV-IgG)	□		
VZV(anti-VZV-IgM, anti-VZV-IgG)	□		
Evaluation of group I and II			
All causes—groups I and II—reasonably ruled out	2	2	2
The 7 causes of group I ruled out	1		
6 or 5 causes of group I ruled out	0		
Less than 5 causes of group I ruled out	−2		
Alternative cause highly probable	−3		
6. Previous hepatotoxicity of the drug/herb			
Reaction labelled in the product characteristics	2	2	2
Reaction published but unlabelled	1		
Reaction unknown	0		

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7. Response to unintentional reexposure			
Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure	3		
Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction	1		
Increase of ALP but less than N in the same conditions as for the first administration	−2		
Other situations	0	0	0

DISCUSSION

Methimazole is recommended for patients who are thyrotoxic by ATA/AACE guidelines[7].But rare and serious complications hepatotoxicity have been reported now and then in recent years [2,4-6,8,9] and the review of the literature showed more than 30 previous cases of severe hepatotoxicity after use of methimazole, most of the literatures did not quantitative evaluations of methimazole-induced hepatotoxicity for one reason or another[4-6,8,9].

To our knowledge, only one literature reported methimazole induced cholestatic jaundice misestimated by Naranjo scale [2], but it is improper to establish causality in cases of suspected or rare drug-induced liver injury(DILI). Because the items of Naranjo scale include drug concentrations and monitoring, dose relationship including decreasing dose are irrelevant for DILI, they have sensitivity for estimating the probability of adverse drug reactions especially dose-independent toxic reactions. RUCAM scale a liver-specific method is recommend to more accurate causality assessment of DILI than Naranjo scale [10]. In this paper RUCAM scale is introduced to quantitatively assess causality in cases of suspected methimazole induced cholestasis. After the suspected methimazole was discontinued, the reaction was improve. It is unrelated with CBZ which was administrating all the time only the dose was adjusted by TDM. Although excessive concentration of CBZ can lead to hepatotoxicity[11], concentration of CBZ was normal after adjust dose, unfortunately liver enzyme levels still increased rapidly, so time to onset incompatible, high concentrations of CBZ on day1, 2 in hospital may have to do with cholestasis affects the excretion of carbamazepine, but this need more research.

Although assessment of liver pathology through liver biopsy and rechallenge with suspected drug are important components of the RUCAM validated scale, it is unethical and discomfort in this old patient. Further drug-drug interactions were not reported with the patient's concurrent use of methimazole, CBZ and omeprazole.

CONCLUSION

This is first report recognise that RUCAM scale assisted the exclusion of alternative cause such as high human plasma concentration of CBZ has slight potential liver toxicity when old people with hyperthyroidism was on multiple medications onset of hepatotoxicity.

DILI is difficult to assessment when patients receive two or more potential hepatotoxic agent. In virtue of RUCAM provides better definition of the elements to take into consideration and more accuracy in data elements to assist the exclusion of alternative causes than items of Naranjo scale provides, RUCAM scale is required of clinicians in order to diagnose DILI such as methimazole induced hepatotoxicity.

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