Bahrain Medical Bulletin Vol. 27, No. 4, December 2005

Family Physician Corner

Case Study: Which is to be incriminated?

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Background: Drug-induced liver injury is increasing. This has multifactorial origin. Diabetic patients are more prone to such adverse effects since their multiple drugs are increasing in size and diversity. Several drugs used in diabetics are known to be hepatotoxic. In this case study, this issue is highlighted with special emphasis on presentation, diagnosis, management and prevention.

Presentation: Fifty-one year old diabetic Arab male presented to the clinic with few days history of nausea, few episodes of vomiting and metallic taste. He had no history of abdominal pain, urinary symptoms or change in stool consistency, no history of reported allergies.

The patient is a known case of myasthenia gravis of 12 years duration and type 2 diabetes of 13 years duration. He underwent thymomectomy as a treatment for his myasthenia gravis. The patient's father is type 2 diabetic and his son is type 1 diabetic. He smokes few cigarettes per day and does not consume alcohol. The patient was on the following medications: Avandia 4mg since 18 months, Zocor 10mg since five years, Imuran (50-100mg per day) and Prednisone (10-40mg per day) because of myasthenia gravis, Glucovance 5/500 mg twice a day for five months. The Zocor dose was increased to 20mg per day two weeks before presentation.

On presentation the patient was afebrile, had a blood pressure of 120/80 and BMI of 29. He was alert, conscious and oriented. The patient was not jaundiced or dehydrated. No tremors were observed and abdominal examination was normal.

The patient's serum test results were as follows: glucose, 10.7 mmol/L; sodium 141mmol/L; potassium, 3.97 mmol/L; creatinine, 85 µmol/L; ketones, negative; and hemoglobin A1c 8.0%. His liver enzymes were deranged: Alanine Aminotransferance (ALT) 429 U/L, Aspartate Aminotransferance (AST) 727 U/L, Alkaline Phosphatase (ALP) 120 U/L, Bilirubin was normal and gamma Glutamyltransferase (GGT) 385 U/L.

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Question

1. At this stage, what are the provisional diagnoses and the line of laboratory workup?

Answer

This patient had 20-fold increase in liver enzymes, though presented with mild symptoms only. His Bilirubin level was normal; therefore this is non-cholestatic reason. No clinical or biochemical reason for admission was observed at this stage.

The common causes of acute liver enzymes elevation are acute hepatitis, alcoholic liver disease, biliary tract disease and drug-induced hepatic injury[1]. Hepatitis profile was negative in this patient and he is not known alcohol consumer; therefore the first two common causes are excluded. Ultrasonic examination of the abdomen revealed fatty infiltration of the liver with no other gross injuries or evidence of biliary tract disease.

Drug-induced liver disease is a circumstantial diagnosis that comes only after thorough exclusion of other common causes and with the presence of a likely causative drug. There are more than 800 drugs implicated as causative agents in liver disease[1]. It seems, thus, unavoidable to use one of these drugs in our daily clinical practice. Nevertheless, it is very uncommon to encounter such complication with even the most widely known drug to inflict liver disease[1]. In this case a diagnosis of drug-induced liver injury was suspected.

Question

2. Assuming the previous patient had drug-induced liver injury, which of the following drugs to be implicated as the incriminating agent, Zocor, Avandia or Imuran?

Answer

Some of the medications the patient is taking are hepatotoxic like Avandia, Zocor and Imuran.

Avandia (rosiglitizone) belongs to the Thiazolidinedione group. This is an antidiabetic insulin sensitizer group. Another drug related to Avandia, troglitisone, was implicated in causing liver failure and death and was drawn from the market[2]. In the pre-approval controlled trials, both Avandia and placebo groups had 0.2% incidence of elevated ALT (more than three times the upper limit of normal) compared to 0.5% on active comparators[2].

After marketing Avandia, there were few reported cases of ALT elevations. There were no reported cases of acute liver failure however[2]. Avandia mechanism of liver injury is thought to be idiosyncratic. That means it is not dose-related, unpredictable and not immune mediated[3].

Zocor, simvastatin, belongs to the statin class which is lipid a lowering class. Statins were thoroughly tested in wide range of patients in clinical trials[4]. Patients with liver disease were excluded from clinical trials[4]. Statin-induced liver affliction was defined as ALT or AST elevation of more than three times above baseline on more than two occasions. There was inter-class variation in liver affliction. Zocor has a reported incidence of 1.8% of liver enzyme elevation[4]. Statin-induced liver injury is dose-related and most likely to occur in the first few weeks after its administration[4].

Based on the above arguments of statistical and pathophysiological processes and based on the fact that Imuran (an immunosuppressive agent) is more likely to cause acute liver failure in transplanted patients rather than simple ALT or AST elevation, Zocor was the most likely inflicting drug and hence was discontinued in this patient[5]. One week after Zocor discontinuation, liver enzymes were the same and the patient was still symptomatic. At this point, Avandia was discontinued. Few days later, the patient's symptoms and the liver enzymes dramatically improved. Figure one depicts the course of drug administration and discontinuation in correlation to the ALT level. Both Zocor and Avandia are thus incriminated in the development of drug-induced liver injury in this patient.

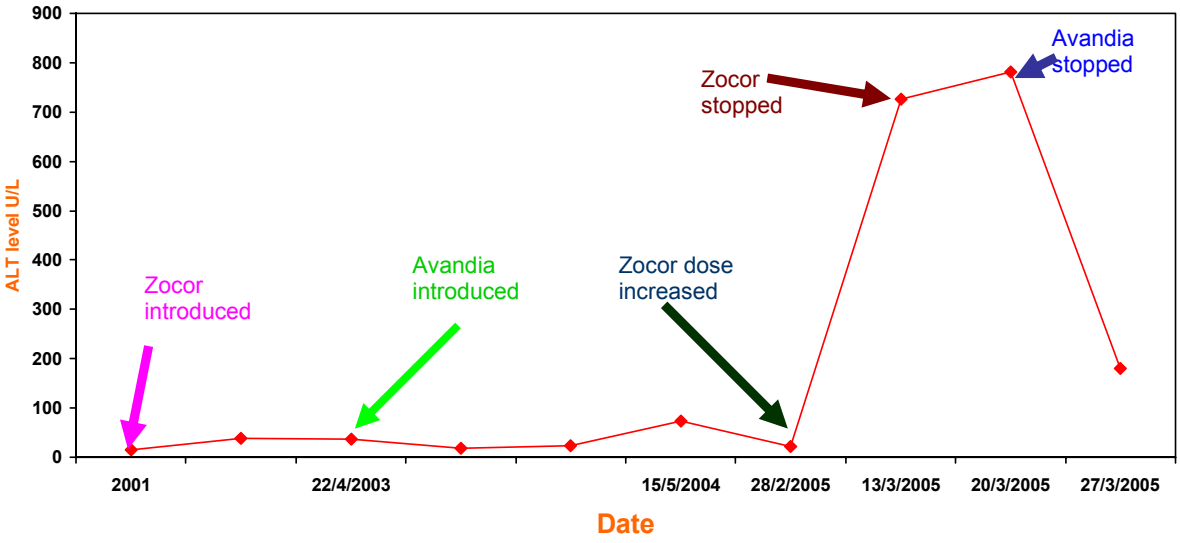

Figure 1: The time course of Zocor and Avandia introduction and discontinuation against the ALT level.

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Questions

3. How can we monitor hepatotoxic drugs like Zocor and Avandia to avoid liver injury?
4. Is it safe to combine more than one hepatotoxic drug?
5. Can we use hepatotoxic drugs in patients with chronic liver disease?

Answers

The FDA recommendations of liver function monitoring in patients using Zocor and Avandia are shown in table 1[6].

Table 1

Since more than 800 drugs are implicated as hepatotoxic, it is inevitable that clinicians are inclined to combine more than one hepatotoxic drug[7]. Same can be said about using hepatotoxic drugs in patients with chronic liver disease[7]. Chronic liver disease is quite common in USA[7]. More than 1.8% of the US population are infected with hepatitis C. Moreover, one fifth of the US population has elevated liver enzymes for one reason or another[7]. Since this patient is on two hepatotoxic agents, caution should be exercised when increasing the dose of any of them. It is believed that the increase in the Zocor dose has triggered this elevation in liver enzymes.

Liver enzyme monitoring in these cases is more meticulous and cautious. Close monitoring of liver enzymes every two weeks are recommended especially if you are increasing the hepatotoxic drug dose or adding another one[6]. This applies also to patients with chronic liver disease. These recommendations are not evidence-based[6].

Question

6. Can we reintroduce the supposedly incriminating agent?

Answer

Drug-induced liver injury tends to be of two distinct types:

1. Hypersensitivity reactions which occur through immune mediation and show signs and symptoms of allergic reaction like fever, rash, eosinophilia and cholestatic-like picture. This tends to occur in the first four to six weeks of drug initiation.

2. Metabolicidiosyncratic reaction that occurs anytime during the first year of initiation. This has hepatitis-like picture[8].

Drugs that cause liver injury through immune-mediated mechanism should not be reintroduced, though this may be the most definite way of confirming the diagnosis[9]. On the other hand, idiosyncratic-mode of action drugs can be safely reintroduced, if they did not cause liver failure, starting with small doses and going up[10]. This can be accomplished after the subsidence of the acute event. LFTs should be monitored weekly[10].

In summary, the great advent in drug technology has provided the clinician with alternatives in prescription. This; however, brought about the issues of drug side-effects

and drug-drug interaction. Drug-induced liver disease is an example of such notion. It is important for clinicians to comply with the drug monitoring recommendations, to be aware of the different drug-drug interaction and the mechanism of drug-induced injury in order to avoid the predictable side effects.

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Table 1: FDA Recommendations for liver enzymes monitoring when using Zocor and Avandia (Chalasani et al).[6]

Name	**Liver Function Test**	**Time frame for monitroing**	**Comments**
Zocor	AST or ALT	LFT prior to initiation. LFT repeated semiannually during the first year or until 1year after the last dose increase.	Patients taking 80 mg daily, LFTs should also be checked after the first 3 months. If LFTs are increased, a second test should be obtained. LFTs should be repeated weekly until they return to normal. If ALT still more than 3 times the upper limit of normal (ULN), the drug should be stopped.
Avandia	AST or ALT	LFT prior to initiation and then monthly for the first year and periodically thereafter.	If LFTs are increased, a second test should be obtained. LFTs should be repeated weekly until they return to normal. If ALT is still more than 3 times the upper limit of normal (ULN), the drug should be stopped.