CASE REPORT

Acute hepatitis after starting pinaverium bromide in a patient taking mirtazapine

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SUMMARY

A 56-year-old man presented with chronic abdominal pain. He had been evaluated extensively in the recent past undergoing upper gastrointestinal endoscopy, colonoscopy and CT scan of the abdomen with normal results. The provisional diagnosis of irritable bowel syndrome was performed and pinaverium bromide was started. The patient had pre-existing hypertension, a major depressive disorder and gastro-oesophageal reflux disease. He had been taking nebivolol and pantoprazole for several years and mirtazapine for the last 1 year. The patient developed nausea, vomiting and anorexia after 5 days of starting pinaverium bromide. Investigations revealed marked elevation of liver enzymes and bilirubin. He was negative for HIV, HBsAg, anti-hepatitis C virus, IgM for hepatitis A virus, hepatitis E virus, antinuclear antibody and antimitochondrial antibody. An ultrasound showed mild hepatomegaly with hypoechoic echo texture; the rest of scan was normal. Pinaverium and mirtazapine were stopped immediately. The patient was treated symptomatically and his liver profile returned to normal after 4 weeks.

BACKGROUND

Drug-related hepatic injury is not uncommon. In fact, it is one of the most common reasons for regulatory action by the Food and Drug Administration (FDA).¹ Diagnosis of drug-related hepatic injury is circumstantial and diagnosis by exclusion with positive rechallenges is the only process that definitely implicates a particular drug. Mirtazapine is the first of a new class of noradrenergic and specific serotonergic antidepressants (NaSSA). Asymptomatic mild elevation of liver enzyme is seen in 2% of mirtazapine-treated patients.² There are few reported cases of mirtazapine-induced hepatotoxicity.^{3–4} In vitro studies suggest that mirtazapine is unlikely to cause clinically significant drug–drug interactions.⁵ Pinaverium bromide is a quaternary ammonium compound with a calcium-channel blocking property and is used for symptomatic relief in patients with irritable bowel syndrome (IBS). There is no reported case of pinaverium-induced hepatotoxicity in the literature and no reported significant drug–drug interaction.^{6–7} As IBS is often associated with depression, coprescription of mirtazapine and pinaverium is not uncommon.

We present a case of acute hepatitis developing after introduction of pinaverium bromide in a patient taking mirtazapine for 1 year.

CASE PRESENTATION

A 56-year-old man presented with abdominal pain of 6 months' duration. The pain was a dull ache, worse in the lower abdomen and relieved by taking antispasmodics. It was associated with two to three bowel motions per day with a feeling of incomplete evacuation. He had been evaluated extensively in the recent past (including upper gastrointestinal endoscopy, colonoscopy and CT scan of the abdomen) and no obvious organic aetiology could be found. Provisional diagnosis of IBS was performed.

He had pre-existing essential hypertension (HT), a major depressive disorder and gastro-oesophageal reflux disease. He was taking nebivolol and pantoprazole for several years and mirtazapine for the last 1 year.

The patient was a non-smoker and had no history of alcohol or substance abuse. There was no history suggestive of hepatitis, jaundice or gallstones. Family history and social history were not significant.

He was started on pinaverium bromide. After 5 days of starting pinaverium, the patient developed anorexia, nausea and vomiting. On examination the pulse rate was 92/min, blood pressure was 136/86 and he was icteric with tender hepatomegaly. His weight was 70 kg and BMI was 19.8. The rest of the examination was unremarkable.

INVESTIGATIONS

Investigation revealed normal blood count, erythrocytes sedimentation rate and renal function. However, his liver profile was abnormal (table 1). He was negative for HIV, HBsAg, anti-hepatitis C virus, IgM for hepatitis A virus, hepatitis E virus, antinuclear antibody (ANA) and antimitochondrial antibody (AMA). Lipid profile was normal. Ultrasound of the abdomen showed mild hepatomegaly with hypoechoic echo texture suggestive of acute hepatitis; the rest of the scan including biliary tree, pancreas and vascular structures was normal.

Further investigations including liver biopsy and MR cholangiopancreatography were planned but the patient did not consent as he was satisfied with rapid recovery after stopping mirtazapine and pinaverium.

DIFFERENTIAL DIAGNOSIS

Acute infective hepatitis (hepatitis E/hepatitis A) was the first diagnosis for our patient as it is common in India; however, the patient tested negative. Autoimmune hepatitis was another possibility but the screening test for it (ANA, AMA) was

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Table 1 Liver profile trend

	Day 0	Day 7	Day 14	Day 30
Total bilirubin (mg/dL)	6.8	7.2	3.1	1.1
Direct bilirubin (mg/dL)	2.2	3.1	1.8	0.8
Indirect bilirubin(mg/dL)	4.6	4.1	1.3	0.3
SGOT/AST (u/L)	1050	850	222	36
SGPT/ALT (u/L)	1190	566	263	48
Alkaline phosphatase (u/L)	240	258	212	181
γ-Glutamyltransferase (IU/L)	195	190	141	146
Total protein (g/dL)	7.6	7.2	7.3	7.5
Albumin (g/dL)	3.9	3.4	3.3	3.6
Globulin (g/dL)	3.7	3.8	4.0	2.9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

negative. Normal ultrasound of biliary tree made the possibility of cholelithiasis highly improbable. Rarely, complicated malaria or leptospirosis may present with hepatitis; however, the patient had no fever so these possibilities were not considered. As the patient did not have significant hypotension or hypoxia, hypoxic liver injury was not considered.

TREATMENT

Mirtazapine and pinaverium were stopped.

OUTCOME AND FOLLOW-UP

The patient had symptomatic improvement within 5 days of stopping pinaverium and mirtazapine. Liver enzymes and bilirubin returned to baseline in 1 month.

DISCUSSION

Hepatotoxicity is an injury to the liver that is associated with impaired liver function caused by exposure to a drug or other non-infectious agent.⁸ Drug-related hepatotoxicity is not uncommon. The reported incidence is between 1 in 10000 and 1 in 100 000 patients for many drugs.⁹ However, the actual numbers may be much higher because of under-reporting, difficulties in detection or diagnosis and incomplete observation of persons exposed.⁸ In an effort to improve reporting rates, a group of physicians in France, trained to investigate and report possible causes of hepatic injury from drugs, found a crude incidence rate of about 14/100 000 inhabitants per year, 12% of whom were hospitalised and 6% of whom died.¹⁰ This rate was about 16 times as great as the spontaneously reported rates of adverse hepatic drug reactions in France. This suggests that drugs-related hepatotoxicity is underdiagnosed and under-reported.

Hepatotoxicity may be predictable or unpredictable.¹¹ Predictable reactions typically are dose related and occur after some threshold for toxicity is reached with substances such as acetaminophen, carbon tetrachloride, phosphorus and chloroform. Unpredictable hepatotoxic reactions occur without warning, are unrelated to dose, and have variable latency periods ranging from a few days to months.¹²

Drug-related hepatotoxicity cannot be viewed as a single disease. Many different mechanisms lead to hepatotoxicity, including disruption of the cell membrane and cell death resulting from covalent binding of the drug to cell proteins, which creates new adducts that serve as immune targets, thus inciting an immunological reaction;^{13 14} inhibition of cellular pathways of drug metabolism;^{15 16} abnormal bile flow leading to

cholestasis and jaundice, sometimes with minimal cell injury.¹⁷ Apoptosis occurring through tumour necrosis factor and Fas pathways;^{17 18} and inhibition of mitochondrial function with accumulation of oxygen-free radicals and lipid peroxidation, fat accumulation and cell death.¹⁸

In most cases there is no effective treatment other than stopping the drug and providing general supportive care.

IBS is a common problem with an estimated prevalence of 5–15%.¹⁹ IBS is often associated with depression. A recent study from India indicates (37%) prevalence of depression in patients with IBS.²⁰ As IBS is often associated with depression there are good chances that mirtazapine and pinaverium may be coprescribed.

Mirtazapine is the first NaSSA. It is rapidly and well absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 2 h. Biotransformation is mainly mediated by the CYP2D6 and CYP3A4 isoenzymes. Mirtazapine has few inhibitory effects on CYP isoenzymes and, therefore, the pharmacokinetics of coadministered drugs is hardly affected by it.²¹ Asymptomatic mild elevation of liver enzyme is seen in 2% of mirtazapine-treated patients.² There are three reported cases of mirtazapine-induced hepatotoxicity;^{3 4} in one case the patient developed hepatotoxicity after 3 years of starting mirtazapine. The exact mechanism of hepatic injury with mirtazapine is not known.

Pinaverium bromide is a quaternary ammonium compound with a calcium channel blocking property and is used for symptomatic relief in patients with IBS. Pinaverium has low absorption (8–10%) but is endowed with an excellent hepatobiliary excretion.²² There are no reported cases of pinaverium-induced hepatotoxicity in the literature and it is considered highly safe.^{23 24} There are no reported significant drug–drug interaction with pinaverium.^{6 7} Unfortunately, very limited literature is available on the safety of pinaverium.

Our patient was on mirtazapine for the last 1 year and his routine biochemical evaluations and CT of the abdomen were normal during the follow-up period. He developed hepatitis immediately after being prescribed pinaverium bromide. According to the Roussel Uclaf causality assessment method (RUCAM)²⁵ and Naranjo²⁶ probability scale, causal relationship between mirtazapine treatment and liver injury was highly probable in our patient. For pinaverium, RUCAM²⁵ suggested 'probable', and Naranjo²⁶ probability scale 'possible' in our patient. However, limitations of the above scoring methods are that they do not take into account drug–drug interaction.

Our hypothesis is that the patient developed a delayed idiosyncratic reaction to mirtazapine with addition of pinaverium being incidental. Another possibility is that addition of pinaverium created an immunological target (by combining with mirtazapine or its metabolite) leading to immune-mediated liver injury.

Learning points

- ▶ Known hepatotoxic drugs may produce delayed hepatotoxicity, even after many months.
- ▶ Addition of a new drug may precipitate latent hepatotoxicity.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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