

Possible olanzapine-induced hepatotoxicity in a young Chinese patient

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We present a case of a 17-year-old man with first-episode schizophrenia who developed olanzapine-induced hepatitis, cholestasis, and splenomegaly, all of which were reversed after ceasing olanzapine. Clinicians prescribing olanzapine should be aware of this possible hepatotoxicity. Patient education, vigilance from clinicians, and careful clinical examination can help detect this complication early.

Introduction

Hepatitis and cholestatic jaundice are common complications of the use of conventional antipsychotics, particularly chlorpromazine.^{1,2} Olanzapine is a second-generation antipsychotic (SGA) medication almost devoid of extra-pyramidal side-effects and hyperprolactinaemia. Nevertheless, there are reports of transient liver biochemistry abnormalities associated with olanzapine³ but the mechanism underlying this complication is not known. We report a case of a young man who developed transient severely abnormal liver biochemistry with hepatosplenomegaly and cholestatic jaundice, after receiving olanzapine.

Case report

A 17-year-old Chinese boy had a first episode of schizophrenia in early 2008 and was assessed by us on 14 July 2008. He had no family or personal history of liver disease, or abnormal liver biochemistry and gave no history of alcohol or substance abuse. His liver biochemistry analysis, performed on 16 July 2008 (before the commencement of risperidone and olanzapine) was normal. He was admitted to Castle Peak Hospital from 14 July to 18 August 2008 for management of his schizophrenia. He was initially treated with haloperidol, 3 mg per day, on 15 July 2008. Twenty-two days after commencing haloperidol (7 August 2008), he was found to have prominent Parkinsonism features, extra-pyramidal side-effects of haloperidol. His treatment was changed to risperidone on 7 August 2008 and he remained on risperidone after being discharged from Castle Peak Hospital. The risperidone dosage was gradually adjusted to 4 mg per day. He attended psychiatric follow-up on 1 September, 3 September, 8 September and 17 September 2008, and we found no evidence of hepatotoxicity. As he remained physically asymptomatic, his liver biochemistry was not tested during the period he was given risperidone. About 6 weeks after receiving risperidone (17 September 2008), he developed akathisia—a feeling of internal restlessness that is a known extra-pyramidal side-effect. He was taken off risperidone and commenced on olanzapine, 10 mg daily (without tapering) on 19 September 2008. On day 1 and day 4 after commencing olanzapine, he reported no adverse effects but on day 8, he passed tea-coloured urine and developed diarrhoea. On day 10, he attended our psychiatric clinic and was found to have clinical jaundice. He had no recent history of eating uncooked seafood or Chinese herbal medicine, and had not travelled. His body mass index was 15.9 kg/m². A physical examination revealed that he was afebrile but had hepatomegaly, 2 cm below the costal margin, and a palpable spleen tip. He was admitted to the paediatric ward for further assessment.

Key words

Antipsychotic agents; Hepatitis, toxic; Jaundice; Schizophrenia; Splenomegaly

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His liver biochemistry tests showed an elevated alkaline phosphatase 241 U/L (reference range, 50-120 U/L), alanine aminotransferase 120 U/L (10-40 U/L), and total bilirubin 124 µmol/L (5-21 µmol/L). The liver biochemistry tests performed before commencement of olanzapine (16 July 2008) were normal, ie alkaline phosphatase 117 U/L, alanine aminotransferase 13 U/L, and total bilirubin 21 µmol/L. Figure 1 shows the time course of the change in liver chemistry after receiving olanzapine. His haemoglobin level and white blood cell count were normal, he had no eosinophilia and his clotting profile was normal. The tests for hepatitis A immunoglobulin M, hepatitis B antigen and antibodies, and hepatitis C antibodies were negative. The serum copper and caeruloplasmin were normal. The Widal test was negative. The tests for complement 3 and 4, and the autoimmune markers,

anti-nuclear antibodies and rheumatoid factor, were all normal. His serum amylase was elevated (155 U/L), as was his gamma glutamyltransferase (481 U/L; reference range, 0-30 U/L). A urine toxicology screen yielded metabolites of olanzapine. No illicit substance was found in the urine. Ultrasonography of his hepatobiliary system showed splenomegaly (14 cm) and hepatomegaly, no gallstones, a normal-sized common bile and intrahepatic ducts.

On 1 October 2008 (day 13), the olanzapine was discontinued. Amisulpride, another SGA, was commenced on 8 October 2008. The patient's liver function tests gradually returned to normal within a period of 2 months. Shortly after switching from olanzapine to amisulpride, the patient developed a mild relapse of schizophrenia with exacerbated persecutory and referential delusions, which were managed by adjusting the dosage of amisulpride. He has not reported any side-effects from amisulpride.

Discussion

Our patient fulfils the criteria for drug-induced hepatotoxicity: the absence of serological evidence of viral hepatitis, absence of chronic liver disease, absence of drug and alcohol misuse, and a temporal relation to the antipsychotic medication therapy. The question of which of the two drugs (risperidone or olanzapine) caused the adverse drug reaction is more difficult to resolve because no liver biochemistry tests were performed while he was on risperidone therapy. Figure 2 shows the commencement, duration, and discontinuation of the antipsychotic medications. We applied Naranjo ADR probability scales⁴ and found a score of 3 for both olanzapine and risperidone, indicating a possible adverse drug reaction to either. As our patient was never given both SGAs at the same time, the adverse drug reaction could have been caused by olanzapine alone, or the sequential use of risperidone followed by olanzapine.

The clinical evidence of hepatotoxicity was first noted during olanzapine therapy and the elevated alkaline phosphatase peaked about 2 weeks after discontinuation of olanzapine. An extrapolation curve for alkaline phosphatase (Fig 1) suggests that it is likely that the level was normal before the commencement of olanzapine therapy. In contrast, the clinical symptoms of hepatotoxicity only started after the risperidone had been discontinued for more than 1 week, and this was followed by a rise in alkaline phosphatase over the next 3 weeks. In the literature, most reports describe risperidone-induced hepatotoxicity remitting within a week after discontinuation of the drug,^{5,6} while olanzapine-induced hepatotoxicity takes longer to remit—up to 3 weeks.⁷ We believe that it is reasonable to conclude that our patient suffered probable olanzapine-

一名年青病人服用olanzapine (奧氮平) 引致肝中毒的懷疑個案

本文報告一名患有首發精神病的17歲男性，因服用奧氮平引致肝炎、膽汁阻塞，以及巨脾；上述症狀在病人停止服用奧氮平後消失。醫生應注意為病人處方奧氮平後可能引致的肝中毒。病人教育、醫生提高警覺及仔細為病人進行身檢，都可及早監察這種併發症的出現。

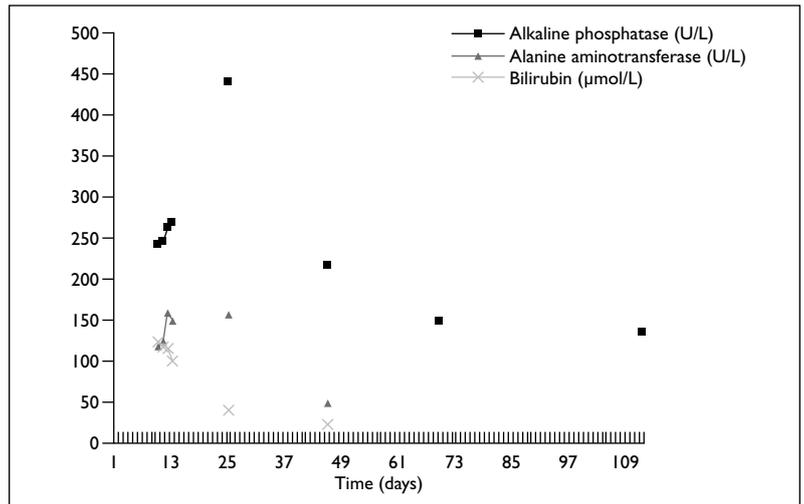


FIG 1. Change in liver biochemistry during olanzapine treatment

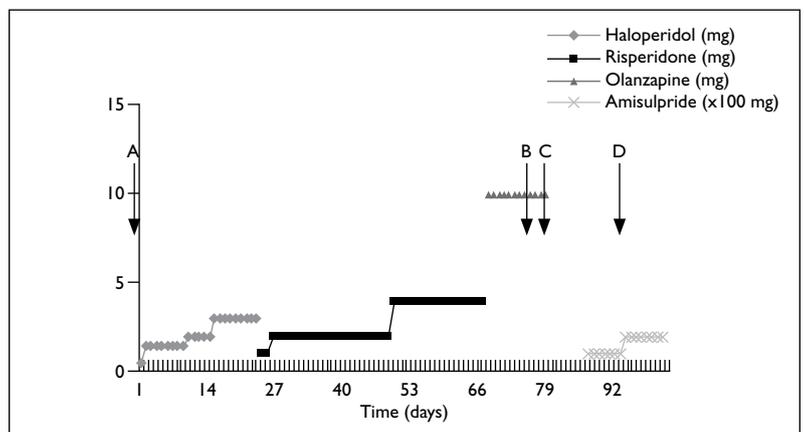


FIG 2. Duration of antipsychotic medications

A: first (normal) liver function tests (LFTs); B: onset of tea-coloured urine; C: onset of clinical jaundice and second (abnormal) LFTs; D: peak of alkaline phosphatase elevation

induced hepatotoxicity.

It is usually very difficult to confirm which drug is the cause of hepatotoxicity when one drug is given straight after another. The lack of objective testing to confirm that our patient's liver biochemistry was normal while receiving risperidone alone is

a limitation in this case report. Psychiatrists do not usually order liver biochemistry tests in a physically asymptomatic patient receiving SGA. When treating a major psychosis such as schizophrenia, it is rare to arrange a drug-free washing-out period between different antipsychotic medications. If the drug is the first to be used, it should be easier to obtain biochemical evidence if hepatotoxicity occurs, because it will not be 'confounded' by the sequential use of other antipsychotics without a time gap. In hospitals run by the Hospital Authority of Hong Kong, olanzapine is regarded as a third-line SGA. Nevertheless, the sequential use of different antipsychotic medications, and the clinical necessity to use second-, third-, or even fourth-line SGAs is common during the treatment of schizophrenia. We speculate that in places where olanzapine is used as a first-line SGA (such as in private practice), the chances of identifying more definitive cases of hepatotoxicity are higher. Nevertheless, we do not advocate universal liver biochemistry tests prior to commencing olanzapine because this adverse drug reaction is rare.

Hepatotoxicity is a known but infrequent complication of conventional antipsychotics as well as SGAs. Among the SGAs, clozapine, risperidone, olanzapine, and quetiapine have been associated with drug-induced hepatotoxicity.⁸⁻¹² The liver complications can be of the hepatocellular type or cholestatic type or both. Infrequently, steatohepatitis

can complicate drug-induced obesity,¹³ which is more problematic in patients receiving olanzapine.¹⁴ Olanzapine-induced hepatitis is believed to be transient, and asymptomatic or sub-clinical.³ There are a few reported cases of clinically severe elevation in liver enzymes induced by olanzapine.^{7,15}

When a patient presents with abnormal liver biochemistry, clinicians should first investigate other causes of hepatitis thoroughly. It should also be remembered that the commonly prescribed drugs, carbamazepine and valproate, can cause hepatotoxicity. If an SGA induces liver damage, it should be discontinued. Amisulpride can be a good alternative antipsychotic. This drug has no known liver side-effects and is excreted entirely by the kidney with no hepatic metabolism. Mental health workers should be aware of olanzapine's potential hepatotoxicity, though cases as severe as this one, ie hepatosplenomegaly with jaundice, are likely to be rare. Olanzapine is a popularly prescribed antipsychotic due to its absence of anti-pyramidal side-effects, lack of induction of hyperprolactinaemia and high tolerability. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study found that olanzapine is the best tolerated of antipsychotics, having the longest 'time-to-discontinuation' period.¹⁴ We expect to see a growing population of psychiatric patients receiving olanzapine. Patients should be educated about its potential adverse effects and complications.

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