

Case report

Cross hepatotoxicity between tricyclic antidepressants

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SUMMARY Cross hepatotoxicity between drugs is very uncommon. We report the case of a patient in whom acute hepatitis was induced by a tricyclic antidepressant, amineptine, and recurred early after administration of another tricyclic antidepressant, clomipramine. This observation suggests that the tricyclic ring is involved in the mechanism of the deleterious effect of both drugs to the liver.

Cross hepatotoxicity is very uncommon: it has been well documented only between derivatives of erythromycin,^{1,2} between haloalkane anaesthetics,^{3,4} between phenothiazines,⁵ and between mianserine and nomifensine,⁶ two new antidepressants not belonging to monoamine oxidase inhibitors or tricyclic family. In this report, we describe the case of a patient in whom acute hepatitis was induced by a tricyclic antidepressant, amineptine, and recurred after administration of another tricyclic antidepressant, clomipramine.

Case report

A 39 year old woman was admitted on 2 August 1984 for anicteric acute hepatitis. She had no history of previous disease of the liver or biliary tract. She had not received blood transfusion or blood products. From 17 July, 1984, she was given amineptine, 300 mg daily, for depression. On 30 July, she complained of nausea, abdominal pain, and chills. On 31 July, she noticed dark urine. Her body temperature was 40°C. On admission, the liver measured 12 cm on the right midclavicular line and was tender; clinical examination was otherwise normal. White blood cell count was 4800/mm³, with 6% eosinophils; serum bilirubin, 20 µmol/l; serum alanine aminotransferase (ALT), 1360 U (normal, 5-40); serum aspartate aminotransferase (AST), 560 U (normal, 5-30); serum gamma-glutamyltransferase (GGT), 205 U (normal, 10-40); serum

alkaline phosphatase (AP), 5.5 U (normal, 2-5); HBsAg, anti-HBs, anti-HBc, and anti-HAV IgM, absent; tests for antibodies to mitochondria, smooth muscle, nuclei, and DNA, negative. The liver and biliary tract were normal at ultrasonography. Administration of amineptine was interrupted on the day of admission. On 8 August, clinical manifestations had disappeared and liver function tests had improved: serum bilirubin, 7 µmol/l; ALT, 426 U; AST, 120 U; GGT, 152 U; AP, 3.5 U.

From 10 August, another tricyclic antidepressant, clomipramine, 100 mg daily, was given to our patient. On 17 August, the patient complained of abdominal pain and marked abnormalities of liver function tests recurred: ALT, 1050 U; AST, 985 U; GGT, 279 U; AP, 7 U. The drug was then discontinued. Abdominal pain disappeared and liver function tests returned quickly to normal. The time relationship of three serum enzymes and administration of amineptine and clomipramine is shown in the Figure.

Discussion

The hepatic injury in our patient can be reasonably ascribed to the antidepressants. There was no other cause of liver disease. The first episode of hepatitis occurred 15 days after the onset of amineptine administration, and the patient improved rapidly after its cessation. Several cases of amineptine-induced hepatitis have been reported, with features similar to those observed in our patient, in particular abdominal pain and fever.⁷ At therapeutic dose, amineptine hepatotoxicity is likely to be immuno-

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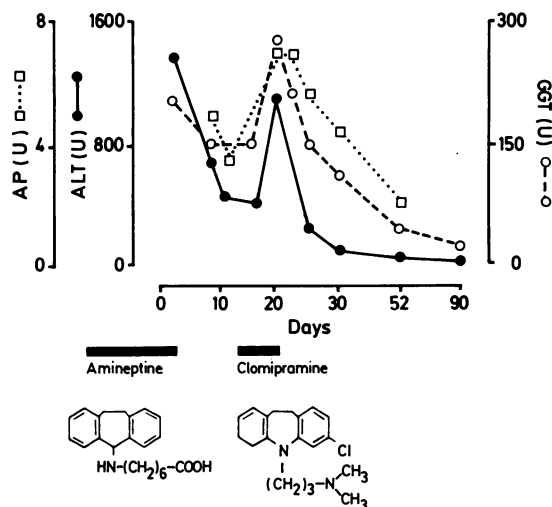


Figure Time course of serum alkaline phosphatase (AP), serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) in relation to administration of amineptine and clomipramine.

logically mediated: (a) amineptine hepatitis is associated with hypersensitivity manifestations⁷; (b) hepatitis recurs early after readministration of amineptine.⁷ Similarly, in our patient, the first episode of hepatitis, caused by amineptine, was associated with hypersensitivity manifestations, and the second episode of hepatitis took place early after administration of clomipramine.

Amineptine and clomipramine are antidepressants having a common chemical structure consisting of a closely related tricyclic ring and a different side chain (Figure). Amineptine-clomipramine cross hepatotoxicity suggests that the tricyclic ring, rather

than the side chain, is involved in the mechanism of the deleterious effect of both drugs to the liver. This view is at variance with a recent report suggesting that amineptine hepatotoxicity might be related to the presence of an acyl chain and the ensuing inhibition of the β -oxidation of fatty acids.⁸

A practical implication of our observation of cross hepatotoxicity is that, in patients in whom hepatitis has been induced by a tricyclic antidepressant, administration of another tricyclic antidepressant should be avoided or, if decided, carefully monitored by repeated liver tests.

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