Drug points

Hepatotoxicity associated with zolpidem treatment

David Karsenti, Pascal Blanc, Yannick Bacq, Etienne-Henry Metman, Service d'Hépato-Gastroentérologie, Centre Hospitalier Universitaire Trousseau, and Service de Pharmacologie Clinique, Centre Hospitalier Universitaire Bretonneau, F-37044 Tours Cedex, France

Zolpidem is a hypnotic drug of the imidazopyridine group. Another imidazopyridine, alpidem, has been withdrawn from the market because of its hepatotoxicity.[1 2] Hepatoxicity has been suspected in association with zolpidem, but it has not been clearly established because of concomitant drug treatment.[3 4] We report a case of acute hepatitis mimicking biliary lithiasis after treatment with zolpidem alone at a therapeutic dose, with reappearance of the hepatoxicity after the drug was reintroduced.

A 53 year old woman was admitted in June 1997 for investigation of recurrent abdominal pain. She had no history of recent travel, drug addiction, blood transfusion, or chronic intake of alcohol or toxins. She had first taken zolpidem for insomnia in July 1996. She had had a cholecystectomy for cholangitis in the same month, but we could not clearly establish a chronological link between zolpidem ingestion and this acute episode.

In September 1996 she had again taken zolpidem (20 mg at bed time), and two days later she had developed sudden epigastric pain associated with pale stools, dark urine, but no fever. She had then decided to stop taking zolpidem. The abdominal pain had spontaneously disappeared within 12 hours. Biological investigations performed four days later, when jaundice had been regressing, had shown serum activities of alanine aminotransferase to be 596 IU/l (normal range 5-31), aspartate aminotransferase to be 198 IU/l (8-31), γ-glutamyl transpeptidase to be 242 IU/l (5-35), and alkaline phosphatase to be 134 IU/l (30-104). Total blood bilirubin concentration had been 21.2 µmol/l and the prothrombin time had been normal. Eight days later serum activities of alanine aminotransferase and γ-glutamyl transpeptidase had been 95 IU/l and 115 IU/l respectively. Retrograde endoscopic cholangiography had shown no abnormality.

Six months later, in April 1997, she had had another episode of abdominal pain. Eleven days later alanine aminotransferase and γ-glutamyl transpeptidase activities had been 50 IU/l and 89 IU/l respectively.

In June 1997 ultrasound examination of the biliary tract gave normal results. On questioning she remembered that zolpidem had been reintroduced because her insomnia had recurred (she had taken 20 mg two days before the last acute episode). Viral hepatitis and concurrent infections with Epstein-Barr virus and cytomegalovirus were excluded. No antibodies against smooth muscle, liver and kidney microsomes, or liver cytosol or mitochondria were detected in serum. Five months later the results of liver function tests remained within normal limits and she had no symptoms.

A causal association between zolpidem treatment and liver damage is likely in our case because of the time of onset of the reaction, the clinically significant decrease in serum alanine aminotransferase activity, the exclusion of other causes of hepatitis, the presence of a normal biliary tract on ultrasound and radiological examination, and, above all, the recurrence with zolpidem readministration.[5]

To date, our pharmacovigilance service has not been informed of any other cases of hepatoxicity associated with zolpidem given alone at a therapeutic dose.

1 Ausset P, Malavialle P, Vallet A, Minemont G, Le Bail B, Dumas F, et al. Hépatite subfulminante à l'alpidem traitée par transplantation hépatique. *Gastroentérologie Clinique et Biologique* 1995;19:222-35.
2 Baty V. Hépatite imputable à l'alpidem (Ananxyl), quatre cas dont un mortel. *Gastroentérologie Clinique et Biologique* 1994;18:1129-31.
3 Queneau PE, Koch S, Hrusovsky S, Miguet JP. Zolpidem. Cytolytic hepatitis related to zolpidem. First international symposium on hepatology and clinical pharmacology liver and drugs 1994;38. (abstract). [Available on Medline.]
4 Garnier R. Acute zolpidem poisoning—analysis of 344 cases. *Clin Toxicol* 1994;32:391-404.
5 Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990;11:272-6.

Agranulocytosis associated with lamotrigine

Olaf A Kraus de Camargo, Harald Bode, Sozialpädiatrisches Zentrum, Universität Ulm, Schillerstrasse 15, 89077 Ulm, Germany

To our knowledge, only leucopenia and thrombocytopenia have been described as possible haematological side effects of lamotrigine.[1–3] We report a case of agranulocytosis associated with lamotrigine treatment.

A white girl aged 11 years 10 months who had left renal agenesis, an imperforate anus (corrected postnatally), neuronal heterotopia at the left insula, and seizures had been free of seizures for nearly two years while taking carbamazepine. She had positive serological results for hepatitis B and C. During the anticonvulsive treatment she developed a clinically significant increase in serum transaminase concentrations, raising suspicion of chronic hepatitis C (results of a polymerase chain reaction assay were positive on two occasions and negative on one). As she was clinically well, normally developed, and free of seizures, the anticonvulsive treatment was discontinued, which resulted in serum transaminase concentrations becoming normal.

Twelve months later she was admitted because she had had three focal seizures with secondary generalisation. Anticonvulsive treatment was reinstituted. We opted for lamotrigine treatment alone as this drug does not induce liver enzymes so would not mask the increase in serum transaminase concentrations from progression of hepatitis. Instead of the recommended initial dose of 25 mg/day, she was given 50 mg/day (1.5 mg/kg/day).

Two weeks later her parents observed a cutaneous rash. Lamotrigine was discontinued immediately. After two days she presented to our service still with a maculopapular rash, with confluent papules on the face, slight pruritus, and some abdominal discomfort. A haemogram showed leucopenia (leucocyte count 2.2×10^9/l, proportion of neutrophils 0.34). Liver enzyme activities were slightly raised (alanine aminotransferase 34 U/l (normal range 5-17), aspartate aminotransferase 33 U/l (2-23)). After 3 days she developed agranulocytosis (leucocyte count 3.1×10^9/l, proportion of lymphocytes 0.92 and of monocytes 0.08). She had no clinical problems, and the rash disappeared on the fifth day.

One week after the second haemogram her leucocyte count improved (4.9×10^9/l, proportion of neutrophils 0.56), increasing during the following week (6.5×10^9/l, proportion of neutrophils 0.50). Liver enzyme concentrations remained slightly raised.

1 Nicholson RJ, Kelly KP, Grant IS. Leucopenia associated with lamotrigine. *BMJ* 1995;310:504.
2 Steiner TJ, Findley LJ. Safety data from a placebo-controlled trial of lamotrigine. In: Loiseau P, ed. *Lamotrigine—a brighter future.* London: Royal Society of Medicine Press, 1996:31-5. (International congress and symposium series No 214.)
3 Mackay FJ, Wilton LV, Pearce GL, Freemantle SN, Mann RD. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997;38:881-6.