Metronidazole-Associated Hepatotoxicity in a Hemodialyzed Patient

D.		Hestin
B.		Hanesse
L.		Frimat
P.		Trechot
P.		Netter
M.		Kessler

Department of Nephrology and Pharmacology University Hospital of Nancy,
Vandœuvre, France

Dr. D. Hestin, Service de Néphrologie, Hôpital de Nancy-Brabois, Rue du Morvan, F-54500 Vandœuvre (France)

Dear Sir,

Metronidazole is a synthetic nitroimida-zole derivative used in the treatment of infection caused by anaerobic bacteria and protozoa. Although animal toxicity tests have revealed histological liver changes in monkeys treated with high doses of metronidazole [1], only 2 cases of hepatitis associated with metronidazole have been published [2, 3].

A 68-year-old woman treated with regular hemodialysis since 1982 was admitted to hospital for a septicemia caused by *Staphylococcus aureus* related to infection of the vascular access.

Treatment consisted of the administration of intravenous vancomycin and netilmicin at the end of each dialysis session (vancomycin 500 mg and netilmicin 100 mg). The fever dropped within 24 h, but on the 5th day, a puncture site abscess appeared, which had to be lanced surgically.

Bacteroides fragilis was isolated from culture of abscess material

and metronidazole 250 mg b.i.d. per os was added to antibiotic therapy, while netilmicin was stopped. The patient then became asymptomatic and was discharged from hospital. Four days after the initiation of metronidazole, she was readmitted for drowsiness, vomiting, nausea and pain in the right upper abdominal quadrant. On physical examination, the liver was moderately enlarged, and laboratory tests detected elevated liver enzymes: aspartate aminotransferase (AST) 1,450 IU/l (normal < 27 IU/l), alanine aminotransferase (ALT) 650 IU/l (normal < 20 IU/l), but there was no evidence of cholestasis. Laboratory tests performed before starting metronidazole were unremarkable (AST 17, ALT 14). There was no history of alcohol abuse, no blood transfusion and the patient had been taking antidepressants for many years. Antibodies against hepatitis C virus were detected 3 years previously, without episodes of cytolysis. Serological tests for viral hepatitis A, B and delta, and HIV were negative. Metronidazole was withdrawn and vancomycin maintained for 1 month. Within 4 days, serum levels of AST and ALT decreased and returned to normal values in 15 days.

This case strongly suggests a drug-induced hepatic disease because of the rapid onset of abnormalities after starting metronidazole and their complete regression when this agent (alone) was withdrawn. Although the half life of the parent drug is not altered in patients with impaired

renal function, the hydroxy metabolite can accumulate [3], as is the case in elderly patients [4]. In our case, we believe that both the age of the patient and the impairment of renal function have led to toxicity.

References

- Nir I: Antiprotozoal drugs; in Dukes MNG (ed): Side Effects of Drugs. Amsterdam, Excerpta Medica, 1988, vol 4, pp 204-207. Appleby DH, Vogtland HD: Suspected metronidazole hepatotoxicity. Clin Pharmacol 1983; 2:273-274.
- Uchihara M, Maeda M, Koyama W, Sakamoto S, Kanayama M: A case of metronidazole-induced liver injury. Acta Hepatol Jpn 1984; 25: 1612-1615.
- Seyffard G (ed): Drug dosage in renal insufficiency. Dordrecht, Kluwer Academic Publishers, 1991, pp 389-390.
- Martindale: The Extra Pharmacopoeia, ed 29. London, Pharmaceutical Press, 1989. pp 666-672.

©1994 S. Karger AG, Basel
0028-2766/94/ 0682-0286\$8.00/0