Letter to the Editor

Hepatotoxicity of amoxycillin-clavulanic acid potassium after fucidic acid use

Dear Sir,

Hepatobiliary complications when using amoxycillin-clavulanic acid potassium (A-CA) are extremely rare. When present they appear to have two patterns; the first is an hepatocellular and the second is a mixed hepatocellular-cholestatic protype.[1] A-CA associated hepatobiliary damage may be delayed, severe and prolonged although complete recovery, even in children, is the rule.[2] Generally this specific drug event has been reported to occur in one case out of 78,209 prescriptions in United Kingdom[3] while it seems that less than 100 similar cases have been well documented and followed up in the literature.

At the moment no attention has been paid to the fact that other drugs with hepatobiliary route of excretion, like fucidic acid, may strengthen this A-CA adverse event and, consequently, result in a more severe outcome.

We report a 57 year-old woman with intrahepatic cholestatic syndrome due to administration of A-CA 10 days after fucidic acid use. Fucidic acid was used for orthopedic purposes (500 mg every six hours for 7 days) while A-CA (625 mg every eight hours for 7 days) was administered one week later for an upper respiratory tract infection. Two weeks later the patient visited the internal medicine emergency unit because of jaundice and upper right quadrant pain. Physical examination and hepatobiliary ultrasonography were not remarkable. Peripheral blood count was within normal limits, prothrombin time (INR) was 1.7 (normal up to 1.2) and liver function tests showed ALT=857 UI/ml, AST=456 UI/ml, γ-GT=256 UI/ml, ALP=313 UI/ml, bilirubin 7mg/ml (direct 5.9 mg/ml). The use of these two drugs (A-CA and fucidic acid) with a short interval time and a similar case[4] with concomitant ticarcillin-clavulanic acid and fucidic acid use prompted us to follow up the patient for the next month when all liver function tests showed normal values.

In a large series of A-CA complicated cases 22 jaundiced patients (10 males, mean age 59 years) were reported.[3] Jaundice appeared approximately 17 days after the use of drug and full recovery in all cases required 29-150 days. No concomitant or previous fucidic acid use was reported in those cases. It has not yet been clarified whether this phenomenon is simply an hypersensitivity reaction or a real genetic predisposition defect in hepatobiliary metabolism. Fourteen out of 20 patients in one study showed DRB1*1501 positivity but this genotype was not sufficiently correlated with the drug adverse event pattern.[3]

Focal destructive cholangiopathy (focal injury to interlobular bile ducts) with peripheral bilirubinostasis, reactive macrophages and portal inflammation may be histological hallmarks. Manifestations from other organs, although rare and not always well documented, have been reported to include acute interstitial nephritis, xerostomia and sialadenitis. Systemic symptoms may include drug-induced fever, peripheral blood eosinophilia, and progression to Stevens-Johnson syndrome or even death in one single case.

When therapy to this adverse event is required, successful use of ursodeoxycholic acid (UDCA) at daily doses of 750mg in two cases of amoxycillin-clavulanic acid potassium (Augmentin)-induced intra-hepatic cholestasis has been

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recently proposed.[5]

In conclusion, the hepatobiliary clearance of several drugs should be carefully monitored and attention should always be paid in cases when possibly hepatotoxic drugs are administered concomitantly or in succession. The question whether these drugs act in a synergic, hypersensitive-like, direct toxic action in possibly genetically predisposed individuals remains, at the moment, the dark side of the moon.

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