

Ceftriaxone and hepatitis

Introduction

Ceftriaxone (Rocephin®) has been registered since June 1984. It is indicated for *the treatment of severe bacterial infections, that are most likely caused by ceftriaxone sensitive microorganisms, and when parenteral therapy is required.* Examples of registered indications are bacterial meningitis, infections of bones or joints and severe infections of the skin or soft tissues. Ceftriaxone is a member of the cephalosporin group and is active in both Gram-positive and Gram-negative bacteria [1-5].

The current observation describes the possible association between ceftriaxone and hepatitis.

Drug induced hepatitis can be due to cholestatic liver injury, hepatocellular injury or a combination of both. In order to classify the type of liver injury in a drug-related event, the Benichou criteria can be used. The Benichou classification is based on the ALAT:AP ratio, where a ratio of 5 or higher indicates hepatocellular damage, a ratio of 2 or lower indicates cholestatic injury, and ratios between 2 and 5 indicate a mix of both [6]. It should be noted that the Benichou classification is a biochemical indicator, and its results do not always correspond with the pathophysiological findings.

Reports

On November 5th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of hepatitis associated with the use of ceftriaxone.

Case A (report number 24654) This serious (life-threatening) spontaneous report from a general practitioner concerned a female aged 71 years and older, who was initially treated with nitroglycerin sublingual spray for acute dyspnea and chest pain. Within two hours she developed fever (39°C), cyanotic lips and fingers, increased blood pressure (150/80mm Hg), increased heart rate (88 bpm) with extrasystoles. Ceftriaxone treatment (1000 mg daily) was started to avoid hospitalisation and two days later, the patient developed cholestatic jaundice. Hepatic parameters three days after start of ceftriaxone were: ALAT 196 U/l [5-40]; ASAT 102 U/l [5-40]; AF 309 U/l [45-125]; bilirubin direct 7 µmol [<5]; GGT 454 U/l [<40]. According to the Benichou criteria, this indicated cholestatic liver injury. Ceftriaxone was withdrawn two days after start and the outcome was unknown.

Case B (report number 119188)

This serious spontaneous report from an doctor on internal medicine concerns a female aged 61-70 years, with a history of multiple sclerosis since 2007, epilepsy, and a neurogenic bladder disorder for which she had a suprapubic bladder catheterisation. The patient experienced hepatitis following intravenous administration of ceftriaxone 2000 mg daily for suspicion of a urinary tract infection (after switching of suprapubic catheter) with a latency of several hours after start. The drug ceftriaxone was withdrawn after 5 days and ciprofloxacin was started. The patient was recovering without additional treatment. Hepatic parameters two days after start of ceftriaxone were: ALAT 162 U/l [0-45]; ASAT 166 U/l [0-40]; AF

217 U/l [0-120]; bilirubin total 8 µmol/l [0-17]; GGT 663 U/l [<35]. According to the Benichou criteria, this indicated cholestatic liver injury.

Concomitant medications were clonazepam, diazepam, levothyroxine, metoclopramide, valproic acid, nadroparine, docusate containing laxative, plantago ovata laxative, temazepam, carbamazepine, macrogol containing laxative, paracetamol suppositories, levetiracetam, cetirizine, ciprofloxacin, tramadol, and fluticasone nasal preparation.

Case C (report number 129317)

This serious (life-threatening) spontaneous report from a specialist doctor (intensive care) concerns a female aged 51-60 years, with immune haemolytic anaemia and hepatitis following administration of ceftriaxone for Lyme borreliosis with a latency of 6 days after start. An ultrasound showed abnormalities of the liver, however, serology was negative. Laboratory results for hepatic parameters were not reported. The patient developed an acute respiratory distress syndrome (ARDS) and was admitted to the intensive care. The drug ceftriaxone was withdrawn and the patient was treated with kidney replacement therapy for renal insufficiency and with a blood transfusion. At the time of reporting, approximately one month after the complaints started, she was recovering from hepatitis and recovered with sequel form the haemolytic anemia.

According to the reporter, lyme borreliosis could be a confounding factor.

Other sources of information

SPC

Although 'increased liver enzymes', 'reversible cholelithiasis' and 'symptomatic calcium-ceftriaxone precipitates in the gallbladder' are mentioned in the SmPC's of ceftriaxone containing products, hepatitis is not described as an ADR in this document [1-5].

Literature

A Medline search revealed two case report regarding ceftriaxone associated hepatitis.

In 2011, Kaur et al. [7] published a case report concerning a 24-year-old female with cholelithiasis who was admitted in the hospital for planned cholecystectomy. Postoperatively ceftriaxone, piroxicam, and ranitidine were administered. On the third day, a yellowish discoloration of the skin over the abdomen was observed. The patient had received four doses of 1 g ceftriaxone, 20 mg of piroxicam, and 150 mg of ranitidine when the diagnosis of jaundice was made. Ceftriaxone and piroxicam were withdrawn and ranitidine was continued. Liver function tests were performed and showed a total serum bilirubin of 6.5 mg/dl, both direct and indirect were raised with values 4.2 and 2.3 mg/dl, respectively; ASAT 148 IU/L, ALAT 164 IU/L, and alkaline phosphatase was 580 IU/L. Ultrasonography did not reveal any obstruction or pressure on the biliary tree. Liver function tests after 48 h showed decrease in the levels of serum bilirubin (2.5 mg/dl) without significant decrease in ASAT, ALAT, and alkaline phosphatase levels. Ranitidine 150 mg was orally continued and laboratory tests were repeated after 3 weeks. All readings were within the range, without any residual effect of the drug .

In 2009, Peker et al. [8] reported of a 12-year-old boy was admitted with complaints of weakness and fatigue. His personal history revealed treatment with ceftriaxone 50 mg/kg per day, 6 d previously, for tonsillitis. Laboratory examination revealed: ASAT, 819 IU/L (10-40 IU/L); ALAT, 871 IU/L (13-40 IU/L); GGT, 285 U/L (9-50 IU/L); alkaline phosphatase, 143 IU/L (40-140 IU/L); total bilirubin, 4.2 mg/dL; and direct bilirubin, 2.8 mg/dL. Hepatitis B surface antigen, antihepatitis B core IgM, anti-hepatitis C virus, anti-hepatitis A virus IgM, and anti-hepatitis E virus were negative, whereas anti-HbsAg was positive. Ultrasonography showed minimal enlarged liver size but with normal parenchyma, and gallbladder was normal. The clinical appearance of the patient did not show any signs of cholelithiasis. Ceftriaxone administration was ceased immediately. At week 4, the biochemical data revealed: ALT, 95 IU/L (13-40); and GGT, 164 IU/L (9-50). Total bilirubin, direct bilirubin, total protein, albumin and other parameters were normal.

Databases

On November 5th 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of (cholestatic) hepatitis associated with the use of ceftriaxone, which was reported disproportionally (ROR = 11.4, 95% CI 3.6 – 36.3). On November 5th 2012, the WHO database of the Uppsala Monitoring Centre contained 188 reports of (cholestatic) hepatitis associated with the use of ceftriaxone and this was reported disproportionally (ROR = 1.17, 95% CI 1.01 – 1.35).

On November 5th 2012, the Eudravigilance database contained 163 reports of (cholestatic) hepatitis in association with ceftriaxone, which was not reported disproportionally (ROR = 2.6, 95% CI: 2.2 – 3.0)

Table 1. Reports of (cholestatic) hepatitis with ceftriaxone in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
Ceftriaxone	Lareb: 3	11.4 (3.6 – 36.3)
	WHO: 188	1.2 (1.0 – 1.4)
	EMA: 163	2.6 (2.2 – 3.0)

Prescription data

The number of patients using ceftriaxone in the Netherlands is shown in table 2 [9]. It should be noted however, that the data in the GIP database apply to the extramural use of drugs. Since ceftriaxone is mainly used in the hospital, these data probably underestimate the actual number of patients using the drug.

Table 2. Number of patients using ceftriaxone in the Netherlands between 2007 and 2011 [9].

Drug	2007	2008	2009	2010	2011
Ceftriaxone	1,021	1,430	1,549	1,941	2,755

Mechanism

Drug induced hepatitis can be due to cholestatic liver injury, hepatocellular injury or a combination of both. The Lareb cases contain two reports where the observed hepatitis is most likely cholestatic in origin. In addition, one of the literature reports also mentions cholestatic hepatitis. Ceftriaxone is known to cause calcium-ceftriaxone precipitates in the gallbladder in some patients. Although these precipitates usually disappear after withdrawal of ceftriaxone, it seems plausible

that they can cause several complications due to cholestasis. For example, the SPC of ceftriaxone mentions pancreatitis as an ADR, which could possibly be caused by biliary obstruction [1-5].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of hepatitis associated with the use of ceftriaxone. Since this analysis was triggered by reports of ceftriaxone, and since there is only one report of cholestatic liver injury for all other cephalosporins, it was decided to investigate a possible signal for ceftriaxone only. Since ceftriaxone is generally not considered as first line treatment, it is possible that the patients described in the cases used other antibiotics on previous occasions. However, this information was not reported to Lareb.

For the three ceftriaxone reports, latencies were between several hours and six days. The latency of several hours for case B seems rather short in relation to the development of hepatitis. In two cases a positive dechallenge was reported. In case A, the patient experienced acute dyspnea and chest pain, which could be indicative of decompensated heart failure. This could possibly be a confounding factor. In case C, the indication for treatment with ceftriaxone (Lyme borreliosis) should be considered a possible confounder. The association between ceftriaxone and hepatitis is statistically supported by the database of the Netherlands Pharmacovigilance Centre Lareb, EMA and the WHO.

Based on the literature and the pharmacological profile, it is most likely that ceftriaxone is associated with cholestatic hepatitis.

The described association is a new signal of (cholestatic) hepatitis with the use of ceftriaxone.

- Signal of (cholestatic) hepatitis associated with the use of ceftriaxone
- Further investigation of the information of the marketing authorization holders is advisable

References

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<http://db.cbg-meb.nl/IB-teksten/h09911.pdf>.
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6. Christian Bénichou, editor. Adverse drug reactions: A practical guide to diagnosis and management. John Wiley & Sons; 1994.

7. Kaur I, Singh J. Cholestatic hepatitis with intravenous ceftriaxone. Indian J.Pharmacol. 2011;43(4):474-5.
8. Peker E, Cagan E, Dogan M. Ceftriaxone-induced toxic hepatitis. World J.Gastroenterol. 2009;15(21):2669-71.
9. College voor Zorgverzekeringen. GIP Databank. College voor Zorgverzekeringen. GIP Databank. (version date: 22-3-2011, access date: <http://www.gipdatabank.nl/>).

This signal has been raised on February 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).