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Ofloxacin-induced fulminant hepatitis: a case report

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INTRODUCTION

Fluoroquinolones (FLQ) are synthetic antibiotics widely used for treatment of bacterial infections in elderly patients. The profile of adverse effects consists of headache, dizziness, seizures, confusion, diplopia, peripheral neuropathy, photosensibility, tendinopathy, kidney failure, pseudomembranous colitis, psychiatric effects. FLQ are also known to cause liver enzymes increase. Indeed, the FLQ may be responsible for liver disorders ranging from asymptomatic elevated liver enzymes to fulminant hepatitis responsible for death. This hepatotoxicity is considered as a class effect of FLQ. Fulminant hepatitis is a side effect reported in the summary of products characteristics of some FLQ,

In European database of suspected adverse drug reactions reports (Eudravigilance), 67 cases of fulminant hepatitis are reported with FLQ: 8 fatal cases with ofloxacin, 12 cases with ciprofloxacin (including 9 deaths), 32 cases with levofloxacin (including 19 deaths) and 15 cases with moxifloxacin (including 12 deaths).

We report a fatal case of a patient treated with ofloxacin who developed fulminant hepatitis.

OBSERVATION

84 year-old female patient

Medical history:

- High blood pressure
- Breast cancer
- Varicose ulcer
- Hypothyroidism
- Chronic alcoholism

Médical treatment:

- Amiodarone
- Bisoprolol
- Acetylsalicylic acid
- Levothyroxine
- Zopiclone
- Cholecalciferol
- Glycerol/vaseline/paraffine

Disease history

July 2014

- Treatment with ofloxacin for urinary tract infection
- Liver function test normal except a small increase of alkaline phosphatase

22/09/2014

- Treatment with ofloxacin for 3 days for cystitis
- Liver function test normal (15 days previously)

25/09/2014

- Fulminant hepatitis
- ALAT : 1484 UI/L
- ASAT : 5206 UI/L
- Gamma-GT : 155
- PAL : 1962

Simultaneously

- Hypoglycémia (0.2 g/L)
- Hypotension (60/40 mmHg)
- Bradycardia (50 beats/min)
- Desaturation (82%)

26 – 28/09/2014

- The condition of the patient is not improving despite rehydratation and glucose injection.
- Death of the patient on the 28th of september 2014

DISCUSSION - CONCLUSION

The overall incidence of acute liver injury with FLQ is estimated, according to some authors, from less than 1 to 6 cases per 100 000 treated patients (1).

Orman et al (2), in a prospective study with a record of drug hepatotoxicity, identified 12 cases of liver damage with FLQ (6 with ciprofloxacin, 4 with moxifloxacin, 1 with levofloxacin and 1 with gatifloxacin) between September 2004 and January 2010. The time of onset of disorders following the introduction of the drug was short (1-39 days, average of 4 days). In some cases, symptoms occurred in the days following discontinuation of the drug. Liver damage were describd in cytolytic categories, cholestatic or mixed. The cytolysis was characterized by a shorter time of appearance. The disease required hospitalization in 8 cases, led to organ failure in 3 cases, liver transplantation in one case (chronic cholestatic disorder with ductopenia with moxifloxacin) and death in one case (acute liver failure with ciprofloxacin) .

The FLQ hepatotoxic mechanism is not completely understood. Trovafloxacin, marketed in 1997, was removed from the European market two years later because of hepatotoxicity. The etiology of hepatotoxicity may be formation of reactive oxygen species during metabolism, which could be toxic for liver mitochondria (3). According to some authors, the formation of these metabolites is associated with certain parts of the structure of trovafloxacin: difluoro-aniline group (4) and / or the cyclopropylamine group (5). Levofloxacin has no such groups. Moxifloxacin has no difluoro-aniline group; cyclopropylamine is used to synthesize moxifloxacin. Cyclopropylamine is part of the moxifloxacin in a way that the synthese of free radicals is not possible. Moreover, the rapid onset of delay, the reappearance of a more serious disorder if rechallenge, and the lack of common metabolites between different molecules seems to be more in favor of an immuno-allergic mechanism.

The risk of cross-reactions between different FLQ is not clearly demonstrated as regards liver damage. However, according Orman et al (2), it may be suspected because of the similarities between the different cases (symptoms and onset time). The authors report also the case of a patient who presented a mixed hepatitis with ciprofloxacin and subsequently developed cytolysis with levofloxacin.

Few publications compare the risk of liver damage between different FLQ. In a recent case-control study of 2014 (1) evaluating the risk of hepatotoxicity of FLQ, Alshammari et al compared the risk of developing severe liver disease in veterans exposed to ciprofloxacin, levofloxacin or moxifloxacin *versus* unexposed subjects. The FLQ were associated with an increased risk of hepatotoxicity (20%) compared to patients unexposed to FLQ (OR 1.2, 95% CI 1.04-1.38). Regarding the risk associated with each FLQ individually, significant risk of liver damage was observed for ciprofloxacin (OR 1.29, 95% CI 1.05-1.58), but there was no significantly increased risk of liver damage with levofloxacin or moxifloxacin compared to the control group. Chronic alcoholic patients had a 8 times higher risk of liver damage with FLQ compared to non-alcoholic patients. Kidney disease and gallbladder emerged as predictors of liver damage with the FLQ.

The various Summaries of Product Characteristics of the 8 molecules marketed in France shows a disparity in serious or fatal hepatitis evocation with the FLQ. Harmonization is required with this class effect and a research concerning factors of potential risk to better target high-risk populations. Both physicians and patients need to be aware of potential symptoms and take prompt action if signs of hepatotoxicity emerge, especially in elderly fragile patients.

References:

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