

## Case report

## Prolonged benign intrahepatic cholestatic syndrome due to administration of fucidic acid with ticarcillin-clavulanic acid

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### SUMMARY

We present the case of a 64-years-old man who was admitted because of 15 days jaundice, white stools, coloured urine, weakness and upper abdominal pain. He had a history of Billroth II operation 35 years ago and before 1 month he was admitted in the Department of Ophthalmology because of a trauma in his eye.

The laboratory exams revealed mixed hyperbilirubinemia with transaminasemia and elevation of  $\gamma$ GT and alkaline phosphatase. Because the imagine techniques including ERCP were implying the possibility of a bile duct malignancy a laparotomy was performed which proved negative for malignancy. The Liver biopsy revealed a cholestatic protype with no findings for neoplasia, cirrhosis or other kind of inflammation and the final diagnosis was prolonged de-lated benign intrahepatic cholestatic syndrome due to the possible synergic action of fucidic acid with ticarcillin-clavulanic acid. These drugs were administered 1 month before during his admission at he Department of Ophthalmology. The biochemical profile became normal 2 months later and the patient lives in excellent health.

**Key words:** jaundice, bilirubin, cholestasis, fucidic acid, ticarcillin-clavulanic acid

### INTRODUCTION

Fucidic acid is an antibiotic produced from the fermentation broth of fucidium coccineum and has been known for many years (Godtfredsen, Toholt and Tybring, 1962).<sup>1</sup> Its importance in the treatment of staphylococcal infections including those which are resistant to penicillin and other antibiotics is well recognized. The usefulness of this drug is increased by its ready penetration into many tissues and its toxicity to several Gram positive and negative microorganisms. The equation which describes the serum fucidate concentration/ time data is  $C_p = 5.9 e^{-1.82t} + 4.3e^{-0.13t}$ .

The half life value of the drug is about 5.5 h (5+1 h) and after a single dose of 500 mg it is reported a mean peak serum concentration of 28 mg/l which occurred 1-2 h after the dose.<sup>2</sup> Fucidic acid mainly route of excretion is bile. Thin-layer and paper chromatography of an ethyl-acetate extract of bile from patients receiving fucidic acid shows that only a small amount of the antibiotic is excreted unchanged. Of the seven metabolites which were detected by thin-layer chromatography of the extract, the three most abundant (G, C and E) have been isolated and characterized (the dicarboxylic metabolite, a hydroxy derivative and a glycoroconjugate). Remaining metabolites A, B, D and F are present in small amounths only and have not been obtained in a pure state. Only very small amounts of fucidic acid and 3-Ketofucidic acid were found in urine.<sup>3</sup>

Fucidic acid interacts with other drugs such as lincomycin, rifabacin and hydrocortisone due to its bile excretion. Its side effects are thromboflebitis, dyspepsia, nausea and reversible jaundice. The jaundice results when the drug is administered intravenously in high doses and in a short time administration. However, after drug is interrupted the bilirubin levels turn to normal limits with-

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in 4-24 hours.

Ticarcillin-clavulanic acid is a relatively new drug used for infections of Gram positive and negative microorganisms as well as several anaerobic.

Ticarcillin (TCA) and clavulanic acid (CA) distribute in lymph, bile, peritoneum and other fluids and body tissues. The mean peak concentration after single I.V. injection was 2-4 h in experimental animals and in healthy volunteers.<sup>4</sup> The mean biliary peak was after 1 h for TCA and CA and it is well established that they are submitted hepatic biotransformation. In healthy subjects after duodenal fluid aspiration 0.07% of TCA and 0.01% of CA initial dose concentrations were detected and recovered during the next 4 hours. The biliary pharmacokinetics determined in humans makes it possible to consider favorably the prophylactic use of TCA and CA in surgery of the biliary tree and the treatment of biliary tract infection.<sup>3</sup> The drug mainly excretion is from the urinary tract but one must be aware that the drug can elevate transaminases, alkaline phosphatase, LDH, bilirubin, creatinine; all of them remain only during or shortly after drug administration.<sup>4</sup>

## CASE REPORT

We present a 64-years-old man who was admitted to our hospital because of a 15 dys jaundice, white stools, coloured urine, weakness and an upper abdominal pain with no experience of fever or weight loss.

He had a history of a Billroth type II operation 35 years ago due to duodenal ulcer and pyloric stenosis and a recent administration, one month ago, to the Department of Ophthalmology because of a trauma in his eye. The patient was a heavy smoker and alcohol user for the last 40 years and he was taking no drugs at all. The physical examination revealed a thin person with jaundice. The upper abdomen was painful with Murphy's sign.

Laboratory tests of the peripheral blood revealed anemia with Ht 28%, AST 103 UI/ml, ALT 249 UI/ml,  $\gamma$ -GT 256 UI/ml, alkaline phosphatase 1038 U/L and total bilirubin 15.8 mg/dl with direct bilirubin 7.78 mg/dl.

There was an iron deficiency but ferritin, B12, folic acid, tumor markers and the rest biochemical profile was within normal limits. The serologic examination was negative for HBV, HCV, HAV, HEV, toxoplasma, and Epstein-Barr virus Monotest. Direct and indirect Coombs were negative, CRP also negative as well as the immunoserologic investigation. The abdominal ultrasound, the CT scan and the MRCP described a slight dilatation of

the common bile duct with a 10mm in diameter and the ERCP was very suspicious for a stenosis in the lower part of the common bile duct. Meanwhile, gastroscopy and coloscopy were negative. The liver biopsy revealed cholestasis with no findings compatible with neoplasia, cirrhosis and inflammation.

As the bilirubin remained stable in the 10th day after the admission a laparotomy was decided which revealed a cholestatic liver with no other special findings. A cholecystectomy was performed and the intraoperative cholangiography was negative for malignancy, lithiasis or other kind of obstruction.

At the 13th day of admission the bilirubin begun to fall dawn at 6.5 mg/dl total - 3.1 mg/dl direct and the patient went home with the diagnosis of iron deficiency anemia and prolonged delayed benign cholestatic syndrome due to Ticarcillin-clavulanic acid and fucidic acid which were administered for 7 days during his admission to the Department of Ophthalmology 1 month before. The patient came 45 days later at the Outpatient Clinica of Internal Medicine in excellent condition with a normal biochemical profile.

## DISCUSSION

There are several previous reports and well documented experiments in animals, in healthy volunteers and in patients with hyperbilirubinemia mentioning the rare potential side-effect of fucidic acid to induce short-time hyperbilirubinemia. It is well known that this hyperbilirubinemia lasts during or shortly after the rapid drug i.v. administration. There are some cases with prolonged hyperbilirubinemia lasting few days but the drug was not interrupted in any of these cases.

On the other hand there are reports of no influence of fucidic acid in Gunn rats or in benign cholestatic patients after surgery because of the coexisting low serum albumin concentration.<sup>5</sup> The hyperbilirubinemia mainly results from the competition of bilirubin with fucidic acid for the limited glucuronidation mechanism, thus compensating for the increased elimination of fucidic acid because of the low serum albumin concentration. These results suggest that fucidic acid can be administered normally even to patients with high bilirubin levels because the post operative serum albumin concentration is usually low.<sup>6</sup> In addition, after several days of fucidic acid administration elevation of serum alkaline phosphatase activity appears in many cases but with no clinical meaning. The mechanism of fucidic acid-associated jaundice may be due to intrahepatic cholestasis because of com-

petition with the excretory pathways of hepatic bile acids related to the steroid like structure of the drug. This cholestatic jaundice is reversible either during therapy or shortly after its interruption.

In postoperative period two situations are likely to occur in patients infected as well as jaundiced. The first is intrahepatic cholestasis accompanied by mild clinical signs of hepatic impairment related to fatty liver and preoperative chronic liver disease and the second is the so-called benign intrahepatic cholestasis in which spontaneous hemolysis plays a major role and in which the main biological sign is an isolated increase in the amount of conjugated bilirubin.

Ticarcillin (TCA) plus clavulanic acid (CA) is submitted to a hepatic biotransformation experimentally and in humans. Samples from serum, choledochal bile, gallbladder bile and gallbladder wall showed that TCA plus CA can produce effective concentrations in the hepatobiliary tract.

Total amount of TCA and CA in cholecystomized patients over 12 h averaged 0.28% (TIC) and 0.05% (CA) of the given dose with a hepatobiliary clearance of 20.5 ml/h (TIC) and 4.4 ml/h (CA).<sup>7</sup> We also know that in patients with normal hepatic function or conjugated hyperbilirubinemia the mean concentrations of TCA in bile from common bile ducts and functioning gall bladders exceeded the mean concentration in plasma and bile from gallbladders with poor or absent function.<sup>7</sup>

To explain what was happened to our patient we first excluded the possibility of hemolysis. Secondly we considered the fact that although we had no laboratory evidence of previous alcohol misuse we strongly believed that the patient was an alcohol overuser with possible microscopic liver deterioration in expectation of a critical strike. This strike may have successfully been offered from the drugs administered for his eye trauma. The mechanism of this prolonged cholestatic syndrome is yet to be clarified; The administered doses of fucidic acid

(500 mg x 4) and TCA plus CA (5.2 g x 3) may be proved exclusively high for this patient. On the other hand, a subclinical jaundice might have presented not followed by drug interruption resulting in drug accumulation in bile. The most believing theory for this prolonged benign intrahepatic cholestatic syndrome is that fucidic acid decreased the hepatobiliary clearance of TCA and CA resulting in the accumulation of the second drug which prolonged the bile excretion of the first drug and secondary lead to liver damage with transaminases elevation.

In conclusion, the hepatobiliary clearance must carefully be considered and monitored when administering drugs with hepatobiliary excretion. The possible synergic action of TCA plus CA and fucidic acid in prolonged benign cholestasis needs, however, more experiments in order to establish a real contra-indication or a simple precaution of the simultaneous use of these very effective drugs in selected groups of patients.

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