Efficiency of rifampicin in emergency treatment of severe hyperbilirubinemia : report of two cases and review of literature

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Abstract

We showed in this study that rifampicin therapy is more effective than plasmapheresis and steroid treatment in diseases associated with severe hyperbilirubinemia. In our opinion, rifampicin treatment may suitable especially for patients with persistent hyperbilirubinemia, and it would be appropriate to use rifampicin as a challenge therapy to patients with severe hyperbilirubinemia, but liver function tests in these patients must be monitored closely. (Acta gastroenterol. belg., **2015**, 78, **256-258**).

Key words : rifampicin, hyperbilirubinemia, and intrahepatic cholestasis.

Introduction

Bilirubin is the catabolic product of heme metabolism, which is formed by the breakdown of heme, most of which is present in hemoglobin and myoglobin. Elevation of bilirubin concentrations can be due to overproduction, impaired uptake conjugation, or excretion and backward leak of bilirubin from damaged hepatocytes or bile ducts. Long-term exposure to severe hyperbilirubinemia has been shown to cause brain damage and mortality in infants (1). Although therapy for hyperbilirubinemia per se is generally not necessary in adults, some of them need therapy due to the neurotoxicity of bilirubin, which is confined to extreme elevation of unconjugated bilirubin (2). Thus, early intervention needs to be performed in severe hyperbilirubinemia. The emergency treatment of severe hyperbilirubinemia consists of plasmapheresis and phototherapy to prevent neurological damage (3), but these therapies have been shown to be ineffective in the prevention of mortality and morbidity. Thus, new therapeutic approaches are required in the treatment of severe hyperbilirubinemia.

Rifampicin, an antibiotic drug of the rifamycin group, inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase (4). Rifampicin can be used in the treatment of pruritus due to chronic cholestasis (5) In addition to these beneficial effects of rifampicin, we present here two cases of severe hyperbilirubinemia successfully treated with rifampicin.

Case 1

A 22-year-old male patient admitted to our hospital with jaundice and generalized pruritus for one month. He had no known disease or drug use. At admission time, the laboratory tests revealed high levels of serum total bilirubin (40.5 mg/dl) and conjugated bilirubin (20.4 mg/dl) and normal levels of aspartate aminotransferase (AST), alanine

aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). Direct and indirect Coombs tests were negative. Red blood cells were normal on peripheral smear examination. Serologic tests for viral and autoimmune etiology were all negative. The liver and bile duct imaging with computed tomography and magnetic resonance cholangiopancreatography (MRCP) were all normal. Perivenular canalicular cholestasis was detected on liver biopsy, which was performed for assessing the diagnosis. We started ursodeoxycholic acid at a dose of 1000 mg per day for cholestatic pruritus. Pruritus complaint decreased, but biochemical abnormalities did not change. To decrease serum bilirubin levels, a plasmapheresis was performed twice per week. Bilirubin level decreased effectively, but 1 week after cessation, it increased again. For decreasing inflammation and excluding autoimmune disorders, prednisolone was used at a dose of 20 mg per day for 2 weeks, but this therapy did not affect the outcome. After administration of phototherapy 3 times for conjugation of unconjugated bilirubin, the total bilirubin level decreased slightly, but not significantly. Thus, we looked for new therapeutic approaches for hyperbilirubinemia in the current literature. Consistent with previous studies, we considered using rifampicin with a dose of 600 mg/day. After starting the medication, serum total bilirubin reduced to 16.41 mg/dl 1 week later and to 3.01 mg/dl 5 weeks later and remained within a range of 1 and 3 mg/dl for 4 months until the last visit. Rifampicin-related side effects were not observed (table 1).

Case 2

A 60-year-old man was admitted to our hospital with 2-week history of jaundice and pruritus. One week before

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Table 1. — **The course of two patient's liver function tests**

Parameters	Before admission	At admission	After PMP	After steroid	Before rifampicin	1 wk after rifampicin	5 wk after rifampicin
Case 1							
AST (U/l)	22	18	20	21	21	23	22
ALT (U/l)	24	21	22	23	25	26	28
ALP (U/l)	108	103	101	96	102	105	102
GGT (U/l)	35	34	36	32	31	34	33
T. Bil (mg/dl)	37.2	40.5	20.2	38.3	35.2	16.41	3.01
I. Bil (mg/dl)	18.1	20.4	10.3	18.1	17.1	8.6	1.4
Case 2							
AST (U/l)	702	42	40	33	34	31	28
ALT (U/l)	956	74	70	67	59	46	32
ALP (U/l)	451	257	254	221	203	154	78
GGT (U/l)	398	122	134	97	81	52	33
T. Bil (mg/dl)	20.1	28.42	18.3	42.1	43.1	15.2	1.5
I. Bil (mg/dl)	11.2	15.3	10.1	20.2	21.5	7.3	1.1

PMP plasmapheresis, WK week, AST aspartat aminotransferase, ALT alanin aminotransferase, ALP alkaline phosphatase, GGT gamma-glutamyl transferase, T Bil total bilirubin, I Bil indirect bilirubin.

the onset of symptoms, he had been given a drug including pseudoephedrine, paracetamol, chlorpheniramine maleate and oxolamine citrate for the common cold. Abnormal laboratory tests were revealed as AST 42 U/l, ALT 74 U/l, GGT 122 U/l, ALP 257 U/l, and total bilirubin 28.42 mg/dl. The serologic tests (anti-HCV, HbsAg, anti-nuclear antibodies, anti-smooth muscle antibodies, etc.) were all negative, and the laboratory tests for determining the etiology were normal (ferritin, ceruloplasmin, thyroid stimulating hormone). After gall bladder stone detection in ultrasonography, MRCP was performed because of suspicion of choledecholithiasis. The biliary tract was normal in MRCP. The histological findings, including perivenular necrosis, marked canalicular cholestasis and the bridging necrosis consistent of polymorphonuclear leukocytes were consistent with drug induced liver injury in liver biopsy. Despite removal of the initiating cause of hepatitis, the patient remained severely jaundiced (total bilirubin : 40.5 mg/dl). The plasmapheresis was performed to decrease the bilirubin levels (total bilirubin : 45.2 mg/dl) every other day for 3 times. The bilirubin level decreased to 18.3 mg/dl, but it was increased again to 42.1 mg/dl on the fifth day after discontinuation of therapy. Prednisolone (60 mg per day) and ursodeoxycholic acid (1250 mg per day) was started, but bilirubin levels did not change at the end of the tenth day. Therefore, rifampicin (600 mg per day) was started, and the dose of prednisolone was progressively reduced. Two months later, liver tests and the level of bilirubin were normal (table 1).

Discussion

To prevent life-threatening complications of exposure to severe hyperbilirubinemia, safe and effective therapies are required for persistent hyperbilirubinemia. Recently, van Dijk et al described a new term : persistent hepatocellular secretory failure (PHSF) as serum bilirubin > 15 mg/dl, persistence of elevated bilirubin levels more than 1 week, exclusion of obstructive cholestasis, and no evidence of chronic liver disease before the initiating event (6). Both of our patients were consistent with this definition.

Rifampicin is also a potent activator of the pregnant X receptor (PXR), and with this activation, rifampicin affects key detoxification enzymes and exporters, including CYP3A4, UGT1A1, and MRP2 in human liver cells (6). Consistently, Ellis et al reported that rifampicin reduces bilirubin levels by increasing mRNA levels of UGT1A1 and CYP3A4 in vitro (7). Rifampicin has been shown to treat PHSF patients effectively at a dose of 300 mg/day (6). In our study, we treated our patients with rifampicin effectively at a dose of 600 mg/day. However, long term use of rifampicin may cause allergic reactions and drug-induced hepatitis. The risk of rifampicin-related hepatotoxicity increases significantly when taken together with other hepatotoxic drugs and with long-term use. In fact, most of the liver-related side effects occurred in patients who were treated for tuberculosis using a combination of drugs, especially isoniazid. Prolonged treatment with rifampicin is associated with

hepatotoxicity under cholestatic conditions in up to 12%. Instead, short-term periods (< 2 weeks) seem to be safe in patients with chronic cholestasis (8). Both Ellis *et al*. and van Dijk *et al*. did not observe rifampicin-related hepatotoxicity in their studies (6,7). Consistent with previous studies, we did not observe hepatotoxic adverse effect with the use of rifampicin.

In conclusion, we showed in this study that rifampicin therapy is more effective than plasmapheresis and steroid treatment in diseases associated with severe hyperbilirubinemia. In our opinion, rifampicin treatment may be suitable especially for patients with persistent hyperbilirubinemia, and it would be appropriate to use rifampicin as a challenge therapy to patients with severe hyperbilirubinemia, but liver function tests in these patients must be monitored closely. Further prospective and controlled studies are needed to show the beneficial effect of rifampicin in patients with severe hyperbilirubinemia.

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