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SCIENTIFIC LITERATURE

Case Report

Case Report: Immune Hemolytic Anemia during Hydralazine and Piperacillin Treatment

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ABSTRACT

We report two cases of patients with heart failure and chronic kidney disease showing signs of immune hemolytic anemia after receiving a combination of hydralazine and piperacillin/tazobactam. Drug induced hemolysis is a rare, but serious, condition. Piperacillin is one of the most common drugs to cause drug induced hemolytic anemia. Hydralazine, which is used for treatment of heart failure, may cause drug induced hemolytic anemia, but the mechanism is not well described. Both patients received piperacillin but direct antiglobulin tests were not positive until hydralazine was added to the treatment. One of the patients was later treated with piperacillin/tazobactam with no significant change in hemoglobin. Based on the two cases, we suggest that the combination of hydralazine and piperacillin/tazobactam may increase the risk of drug induced hemolytic anemia.

INTRODUCTION

Drug induced hemolytic anemia (DIHA) is a rare condition and it is difficult to diagnose. A study from Denmark showed a prevalence of DIHA of 1.5 per 100.000 [1]. During the spring of 2020, two independent cases of immune hemolytic anemia were diagnosed after receiving hydralazine and piperacillin with tazobactam (pip-tazo).

CASE PRESENTATION

Patient A

Patient A (Figure 1) was an 82-year-old Caucasian male with chronic heart failure classified as New York Heart Association (NYHA) stage IIb and Chronic Kidney Disease Stage 5 (CKD5). Besides this, he suffered from well-treated hypercholesterolemia and hypertension. He had never received treatment with neither hydralazine nor pip-tazo.

In May 2020, patient A was admitted with non-ST-elevation myocardial infarction, and acute percutaneous coronary intervention followed by Transcatheter Aortic Valve Implantation (TAVI) were performed. Postoperative Ejection Fraction (EF) was 40%, and he started hydralazine.

After surgery, blood tests showed decreasing hemoglobin and biochemical signs of infection, and pip-tazo treatment was initiated. During the following week, continuous decreasing hemoglobin, increasing Lactate Dehydrogenase (LDH), and moderate reticulocytosis (maximum of 277*109/l) were detected. Haptoglobin levels were immeasurably low and unchanged in repeated measurements. Direct Antiglobulin

Test (DAT) was positive after one week of treatment with hydralazine and pip-tazo. DIHA was considered, and both drugs were discontinued. Three weeks after discontinuation, LDH-levels were decreasing and hemoglobin was slowly increasing. Two DATs were negative six and seven weeks after discontinuation of hydralazine and pip-tazo.

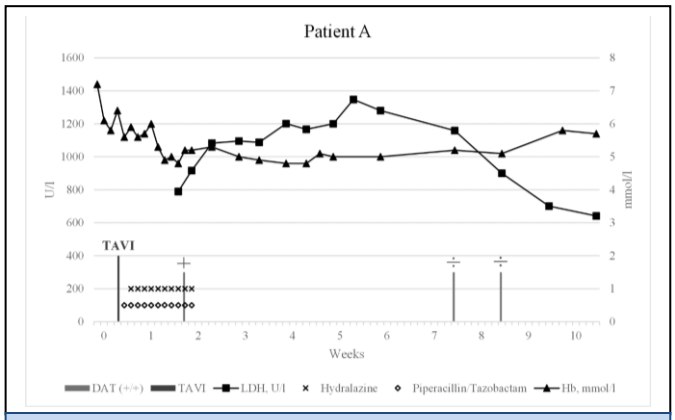

Figure 1: Patient A. Timeline (weeks), comparing piperacillin/tazobactam- and hydralazine treatment, transcatheter aortic valve implantation (TAVI) with direct antiglobulin test (DAT), lactate dehydrogenase (LDH) and hemoglobin (Hb) levels. The vertical line pointing towards "TAVI" illustrates when (weeks) TAVI was performed. The vertical lines pointing towards + or ÷ illustrates when the patient had DAT and whether it was positive (+) or negative (÷).

Patient B

Patient B (Figure 2) was a 52-year-old Caucasian male, who had a history with kidney transplantation in 2013 and continuously decreasing kidney function since then to CKD5. Since April 2020, he had received center hemodialysis three times weekly. He was treated for renal anemia with iron supplementation and erythropoietin (Darbepoetin). In the past seven years, he had been treated with pip-tazo five times with no sign of anemia or hemolysis.

In April 2020, he was admitted due to pneumonia and heart failure. He started pip-tazo. Further blood tests showed increasing LDH, decreasing hemoglobin, and high haptoglobin (2,68 g/l). Moderate reticulocytosis was detected and DAT was negative. One week after admission, he had TAVI-surgery, and after three weeks infections was well-treated and pip-tazo was discontinued. Hydralazine treatment was initiated due to heart failure with an EF of 35%. Again, infection parameters were increasing and pip-tazo treatment was resumed. After one and a half week of hydralazine and six days of pip-tazo, haptoglobin levels were immeasurably low, and DAT was positive. Both drugs were discontinued followed by an increase in hemoglobin and haptoglobin and a decrease in LDH. Four weeks after discontinuation of the drugs, the patient was treated with pip-tazo for one week. This time, it was followed by a small increase in LDH and no significant change in hemoglobin. DAT was not performed and haptoglobin levels were not measured.

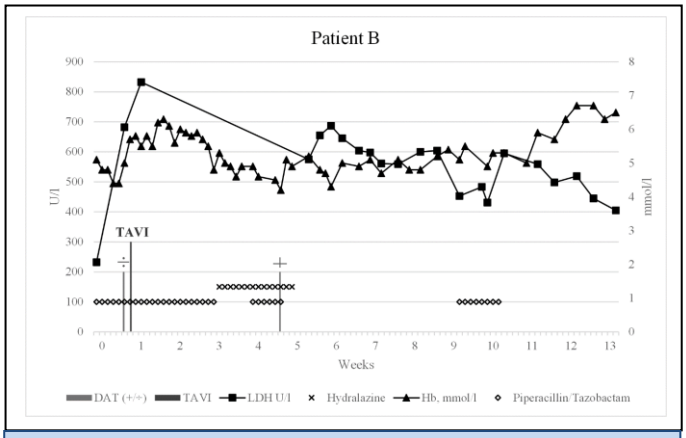

Figure 2: Patient B. Timeline (weeks), comparing piperacillin/tazobactam- and hydralazine treatment, transcatheter aortic valve implantation (TAVI) with direct antiglobulin test (DAT), lactate dehydrogenase (LDH) and hemoglobin (Hb) levels. The vertical line pointing towards "TAVI" illustrates when (weeks) TAVI was performed. The vertical lines pointing towards + or ÷ illustrates when the patient had DAT and whether it was positive (+) or negative (÷).

DISCUSSIONS

Hemolytic anemia is a rare condition characterized by a destruction of erythrocytes resulting in anemia. In DIHA, drug administration results in immunization against the drug and/or red blood cells. The erythrocytes are destructed through antibody-mediated complement-activation or antibody-mediated phagocytosis [2]. DAT detects antibodies bound directly to the patient's erythrocytes and is used to distinguish immune mediated hemolysis from non-immune hemolysis. DIHA is always immune mediated and if DAT is negative, DIHA is unlikely [3].

Pip-tazo is commonly prescribed for patients admitted in the hospital with severe infections and is one of the most common drugs to cause DIHA [4]. A suggested mechanism for the reaction behind piperacillin-induced DIHA is that drug interaction with the erythrocyte membrane results in neoantigens consisting of erythrocyte membrane proteins and drug epitopes. This mechanism can activate complement cascade leading to hemolysis [3,5].

Hydralazine is used to treat arterial hypertension and treatment-resistant heart failure. Due to many adverse side effects it is not commonly prescribed in Denmark. Hydralazine-induced hemolysis was first described in 1977 [6], but the specific mechanism of the reaction is still unknown [7].

In spring 2020, two patients with chronic kidney disease and heart failure presented with signs of hemolysis during treatment with pip-tazo and hydralazine. None of the patients received other drugs known to cause DIHA. One to two weeks after starting treatment with hydralazine and pip-tazo, both patients showed signs of hemolytic anemia with positive DATs. This leads to the question whether the combination of the two drugs could trigger an autoimmune response causing DIHA.

Patient B had decreasing hemoglobin and increasing LDH before treatment with hydralazine. At this time, however, DAT was negative and haptoglobin was high. These biochemical findings are most likely explained by infection or surgery. DAT was found positive after one and a half weeks treatment with hydralazine suggesting that hydralazine may have been involved in triggering the autoimmune reaction. The patient was later treated with piperacillin without evidence of DIHA. Separately, hydralazine and piperacillin may be incomplete antigens, but the combination may develop a complete antigen on the surface of erythrocytes leading to activation of the immune system. Another hypothesis could be that hydralazine alters the immune system in a way that increases the risk of developing autoantibodies. Hence, data from patient B suggests that the combination of hydralazine and piperacillin may increase the probability of an autoimmune response resulting in direct antiglobulins and DIHA.

Patient A started receiving the two drugs simultaneously making it difficult to distinguish whether one or both drugs triggered the hemolysis. In the present cases, DATs were not positive until the patients had received both pip-tazo and hydralazine, suggesting that hydralazine could activate the autoimmune reaction triggered by piperacillin treatment.

Reticulocytosis is a strong indicator of hemolytic anemia and expected to be strongly elevated. However, the present cases include patients with CKD5, in which reticulocytosis might be compromised by decreased amount of erythropoietin. Hence, interpretation of reticulocyte count should not be decisive for the diagnosis.

Both cases in this case report had CKD5 and therefore reduced renal elimination of pip-tazo. The doses of pip-tazo were adjusted relative to the patients' kidney function, but serum concentrations of the drug had not been measured. High plasma concentration might increase the risk of developing DIHA. In our search, we did not find evidence that patients with CKD5 have an increased risk of DIHA. Both patients had undergone TAVI-surgery leading to the question whether this might trigger hemolysis, but biological valves do not seem to increase the risk of hemolysis[8]. Adding to this fact, both patients had positive DATs suggesting an autoimmune and not a mechanical hemolysis which makes the TAVI-surgery an unlikely cause of hemolysis.

CONCLUSION

DIHA is a rare but serious condition. Hydralazine has been described as a possible cause of DIHA, but the mechanism is largely unknown. In a short period of time, two patients admitted with heart failure and CKD showed signs of DIHA. Both were treated with pip-tazo and hydralazine, and DATs were only positive after administration of both drugs. Therefore, clinicians may need to be aware of the risk of DIHA when adding hydralazine to the heart failure treatment in patients who are also on pip-tazo due to infection.

LEARNING OBJECTIVE

Case: two patients with heart failure and chronic kidney disease developing direct antiglobulin positive drug induced hemolytic anemia after receiving hydralazine and piperacillin. Clinicians should consider that a combination of hydralazine and piperacillin may trigger an autoimmune response that increases the risk of drug induced hemolytic anemia.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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