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Acute pancreatitis due to Danazol in a patient of paroxysmal nocturnal haemoglobinuria

Case Report

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ABSTRACT

Background: *An exhaustive list of the drugs causing the acute pancreatitis did not include danazol as one of the drugs. Moreover, the standard textbook of pharmacology did not include acute pancreatitis as one of the side effects of danazol. We report a patient of danazol induced acute pancreatitis.*

Case presentation: *A 41-year-old gentleman had been diagnosed with paroxysmal nocturnal haemoglobinuria (PNH). The patient had been started on Tab. Prednisolone-1 mg/kg/day and Tab. Danazol-200 mg/bd. After a month, the patient presented with acute abdomen with pain in the epigastrium radiating to the back. Investigations confirmed acute pancreatitis and acute kidney injury. We have diagnosed acute pancreatitis due to Danazol. The patient improved with the stoppage of danazol and support of dialysis.*

Discussion: *Even though eculizumab and ravulizumab are currently the preferred treatments for PNH, government-run facilities continue to employ steroids and danazol. Therefore, it is crucial to be aware of this side effect.*

Conclusion: *We reported acute pancreatitis caused by danazol in a patient of PNH. We did not attempt to re-challenge our patient with the danazol for the evident reason that the underlying PNH could become life-threatening.*

Keywords: *acute pancreatitis, danazol, paroxysmal nocturnal haemoglobinuria*

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INTRODUCTION

Saini and others[1] proposed drugs implicated as causing acute pancreatitis into four groups based on the quality of evidence. Randomized controlled trials (RCTs) have the most evidence (class 1), while case-control and pharmacoepidemiologic studies are given class 2. Case reports of high-quality were then divided into 2 classes. Class 3 included high-quality case reports that had a rechallenge and/or a consistent latency. The class 3 is again divided into three sub-classes, class 3a: case reports showing "rechallenge and consistent latency", class 3b: case report showing rechallenge only and class 3c: case report showing consistent latency only.

Latencies were defined as early (less than 24 hours), intermediate (1–30 days), and long (more than 30 days). Class 4 consists of drug with high-quality case reports but no case report had a rechallenge nor a consistent latency.

Acute pancreatitis has been linked to the following medications: statins, azathioprine, thiazides, sulfonamides, furosemide, estrogens, tetracycline, chlorthalidone, corticosteroids, ethacrynic acid, phenformin & procainamide.[1] The list includes all of the drugs used in clinical practice, albeit it is not all-inclusive. We report a patient of danazol induced acute pancreatitis.

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Case Report:

A 41-year-old gentlemen non-diabetic and non hypertensive has presented with yellow discolouration of sclera and body, abdominal distension, reduced urine output and breathlessness of four days duration.

About two months before his presentation patient had been diagnosed paroxysmal nocturnal haemoglobinuria. The flow cytometry had shown significant paroxysmal nocturnal hemoglobinuria (PNH) clones were detected on the erythrocytes and granulocytes

The patient had been started on Tab. Prednisolone - 1mg/kg/day and Tab.Danazol-200 mg bd. After a month, patient presented with acute abdomen with pain in epigastrium radiating to the back and extending to right and left hypochondrium, nausea, vomiting of two days duration. Within next 48 hours, he developed jaundice, oliguria, swelling of feet and face. The investigations are given in the table 1.

Table 1: Investigations

Parameter	Result At diagnosis	Result Current presentation
Haemoglobin (g/dL)	2.9	4.4
Total Leucocyte count (/mm^3)	2500	1700
Platelet count (/mm^3)	84000	37000
Total bilirubin (mg/dL)	6.06	25.8
Direct Bilirubin (mg/dL)	3.07	19.0
Serum glutamic-oxaloacetic transaminase (IU/L)	850	100
Serum glutamic pyruvic transaminase (IU/L)	568	60
Serum alkaline phospatase (IU/L)	54	75
Serum lactate dehydrogenase (IU/L)	1935	1935
Serum haptoglobin (mg/dL)		< 10
Direct & indirect Comb's test	Negative	Negative
Serum amylase (IU/L)	-	1364 (reference range: 30 to 110)
Serum lipase (IU/L)	-	4010 (reference range: 0 to 160)
HbsAg/ Anti HCV antibody / HIV	Negative	Negative
Igm Leptospira antibody	-	Negative
IgM Dengue antibody and NS-1 antigen	-	Negative
IgM scrub typhus antibody	-	Negative
Quantitative buffy coat for malaria parasite	-	negative
Blood and urine cultures	-	Sterile
Bone marrow biopsy	Subcortical cellular marrow with increase in erythroid precursors, shift to left in myeloid maturation and adequate megakaryocytes	-
Flow cytometry	Significant PNH clones were detected on the erythrocytes and granulocytes	-
Ultrasound	-	Bulky head of pancreas, bulky kidneys and splenomegaly without evidence of hepatic or portal vein thrombosis.
CT scan abdomen	-	Right kidney: 11.0 x 5.9 cm Left kidney: 11.8x 5.8 cm Acute pancreatitis, hepatosplenomegaly

We have diagnosed acute pancreatitis due to Danazol. We stopped danazol. The patient received nine sessions of haemodialysis along with six units of blood transfusions. We started the patient on tablet prednisolone 1 mg/kg/day.

In the next three weeks, the urine output improved to 2.5 litre per day, bilirubin and serum creatinine reduced to normal values, and haemoglobin stabilized at 10.4 g/dL with no further requirement of blood transfusions. The serum amylase and lipase also declined to 24 IU/L and 16 IU/L, respectively.

DISCUSSION

The literature on acute pancreatitis due to danazol is scarce. The standard textbook of pharmacology mentioned hirsutism and elevation of hepatic transaminases as significant adverse effects.[2] Though the treatment of PNH has now been advanced to eculizumab (approved in 2007) and ravulizumab (approved in 2018), both monoclonal antibodies designed to target the complement protein C5, thereby preventing its cleavage and the formation of the terminal attack complex.[3,4] Nevertheless, danazol and steroids are still being used at government-run institutes. We did not attempt to re-challenge our patient with the danazol for the evident reason that the underlying PNH could become life-threatening.

The previously published articles on acute pancreatitis following the use of danazol are given in table 2.

Table 2: Published articles on acute pancreatitis following the use of danazol.[6]

Ref.	Age/ gender	Primary diagnosis	Interval between the start of the danazol and symptoms
5	34 years/ female	Endometriosis	4 days
6	33 years/ female	Systemic lupus erythematosis	3 weeks
7	Mid-40s /male	Telomere biology disorders	3 years

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