Drug Induced Coagulopathy with Non-Alcoholic Steatohepatitis: A Case Report

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ABSTRACT

This case report presents de-challenge of acenocoumarol after abnormal increase of International Normalized Ratio and re-challenge of drug after stabilizing the abnormal values. A 66-year-old female came with the complaints of abdominal distension and bilateral lower limb swelling to a tertiary care hospital’s General Medicine OPD. She had a history of double valve replacement twelve years ago and open-heart surgery for ischemic heart disease four months back. She was on acenocoumarol since four months which is certain cause of drug induced coagulopathy according to World Health Organization causality assessment scale. Acenocoumarol was withheld and low dose of Vitamin K was administered. After the international normalized ratio was below 2, acenocoumarol was re-administered with dose of 0.5 mg, followed by 1 mg for two days and 2 mg for the next day. Obeticholic acid is initiated to prevent further fibrosis of liver. Acenocoumarol induced coagulopathy is a common complication seen with the use as it has varied pharmacokinetics and pharmacodynamics and hence patient should be counseled well about monitoring parameters of anticoagulants. It is required that specific dosing algorithms to be developed for Indians considering the demographics, clinical variables and genetic profile which paves path to the individualized treatment.

Keywords: Acenocoumarol, Adverse Drug Reaction, Causality assessment, Coagulopathy, Dosing algorithm.

INTRODUCTION

Acenocoumarol is coumarin derivative oral anticoagulant which is also known as Vitamin K Antagonist (VKA).1 Other coumarin derivatives are warfarin and phenprocoumon.2 VKA’s are highly effective in the treatment of Deep Vein Thrombosis (DVT), Pulmonary Thromboembolism (PTE), Atrial Fibrillation (AF) and Heart Valve Replacement.1,3,4 But these drugs have narrow therapeutic index and depict huge degree of inter-individual variability in its pharmacokinetics and pharmacodynamics.1 Various factors associated with dosing requirements of acenocoumarol are age, body weight, dietary vitamin K, comorbid diseases, concomitant medications and genetics.2,4 More than 30 different genes have been identified which are involved in the metabolism of Coumarinic Oral Anticoagulants (COAs) and inter-individual variability is seen because of varied sensitivity that can be identified by the genetic polymorphism.5 Acenocoumarol have short half-life of 18 to 24 hr and hence from theoretical point of view the difference in the doses of acenocoumarol administered can show varied anticoagulation effect.5

Cumarin induced coagulopathy are based on elevated levels of Prothrombin Time (PT) which is usually expressed as International Normalized Ratio (INR).6 INR variability is a measure of INR deviated from intended range over time with respect to several factors. The risk of bleeding can be identified by monitoring the INR variability.7 Time in Therapeutic Range (TTR) is used to assess quality of anticoagulation which again differs according to race.8

There are two approaches for drug induced coagulopathy, one approach is by...
withholding acenocoumarol and allowing the INR level to come back to normal level and second approach is by withholding acenocoumarol and administering Vitamin K. Another option is withholding acenocoumarol, and administering Vitamin K and fresh frozen plasma. This case presents acenocoumarol induced coagulopathy which is corrected by withholding acenocoumarol, administering low doses of Vitamin K and re-administering acenocoumarol.

CASE DESCRIPTION

A 66-year-old female patient came with the complaints of abdominal distension since two months, swelling in bilateral lower limb since 3 days with a history of passage of stools after every 2 to 3 days and decreased urine output in a tertiary care teaching hospital. Her medical history includes double valve replacement 12 years ago, open heart surgery for Ischemic Heart Disease (IHD) 4 months back following which she was on acenocoumarol 2 mg once daily (OD) [Tuesday and Sunday] and rest of days 1 mg OD. One month back she was newly diagnosed with type 2 diabetes mellitus. On examination, her weight was 55.84 Kg; pulse was 82 beats per minute, blood pressure of 120/80 mm Hg and respiratory rate of 22 cycles per minute. On systemic examination, her heart’s S1 and S2 were heard along with metallic click, she was conscious and oriented with bilateral air entry positive whereas her abdomen was distended. On laboratory investigation, hemoglobin was 8.9 g/dL, total leucocyte count was 3170 cells/cumm, red blood cells were 2.8 million cells/cumm, platelet count 0.80 lakhs/cumm, hematocrit was 26.5%, and random blood sugar was 152 mg/dL (reference range < 140 mg/dL) with normal urea, creatinine and electrolytes. The PT, INR, Activated Partial Thromboplastin Clotting Time (APTT) are shown in Table 1. An Ultrasonogram (USG) of abdomen and pelvis showed shrunken liver with altered echotexture and surface nodularity, mild spleenomegaly, moderate ascites suggesting chronic liver parenchymal changes with anterior wall intramural fibroid. Hence it was confirmed as Non-alcoholic Steato Hepatitis (NASH).

For treatment, acenocoumarol was withheld for 4 days with 1 ampoule vitamin K stat dose on 3rd and 4th day and acenocoumarol was restarted with 0.5 mg, 1 mg, 2 mg following days. Detailed treatment is shown in Table 2. On 8th day she was discharged with the following advice of tablet acenocoumarol with the dose of 2 mg and 1 mg on alternative days along with hepatoprotectants, anti-diabetic and diuretics.

Causality Assessment

To evaluate the relationship between the drug and adverse reaction, causality assessment was done using World Health Organization-Uppsala Monitoring Center

Table 1: PT, INR and aPTT of a patient.

<table>
<thead>
<tr>
<th>Parameters (seconds)</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (test/control)</td>
<td>55.3/10.6</td>
<td>44/10.6</td>
<td>19.8/10.6</td>
<td>17.9/10.6</td>
<td>22.6/10.6</td>
</tr>
<tr>
<td>INR</td>
<td>4.8</td>
<td>3.8</td>
<td>1.7</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>APTT (test/control)</td>
<td>45.3/30.6</td>
<td>43.2/30.6</td>
<td>32.2/30.6</td>
<td>30.5/30.6</td>
<td>32.1/30.6</td>
</tr>
</tbody>
</table>

Table 2: Treatment chart.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Dose</th>
<th>Frequency</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
<th>D8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tab ALDARTONE</td>
<td>Spironolactone</td>
<td>25 mg</td>
<td>1-1-0</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Tab UDILIV</td>
<td>Urodeoxycholic acid</td>
<td>150 mg</td>
<td>1-0-1</td>
<td>✔</td>
<td>✔</td>
<td>stop</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tab GLYCOMET - 3 TRIO FORTE</td>
<td>Glimpiride + Metformin + Voglibose</td>
<td>3mg+1000mg+0.2 mg</td>
<td>1-0-0</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Inj LASIX</td>
<td>Furosemide</td>
<td>40 mg</td>
<td>1-1-0</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Inj VITAMIN K</td>
<td>Vitamin K</td>
<td>1 amp</td>
<td>Stat</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Tab EVION</td>
<td>Vitamin E</td>
<td>400 mg</td>
<td>1-0-0</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Tab OCABLE</td>
<td>Obeticholic acid</td>
<td>5 mg</td>
<td>1-0-0</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Tab ACITROM</td>
<td>Acenocoumarol</td>
<td>1 mg</td>
<td>0-0-1/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>0-0-1</td>
<td>✔</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td>Tab DOLO</td>
<td>Paracetamol</td>
<td>650 mg</td>
<td>sos</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Inj CEFOJAT SB</td>
<td>Ceftriaxone + Salbactum</td>
<td>1.5 g</td>
<td>1-0-1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>

agents have a narrow therapeutic index and may be associated with bleeding, hence proper drug therapeutic monitoring is required which can be done by monitoring INR, PT, APTT and liver function tests. Coagulopathy is a known complication associated with VKAs and must be suspected in patients taking VKAs and may require additional INR monitoring. The coumarin derivatives work by preventing platelets from sticking to each other to form blood clots. In this case, patient had a history of acenocoumarol use which led to coagulopathy. Proper counseling should be given about monitoring parameters including regular check-up of INR, APTT and PT of blood in patients taking anticoagulants. Treatment was given by withholding acenocoumarol for a specific period of time and administering low dose vitamin K with INR, PT and APTT being monitored. Dosing algorithm can be useful tool in individualizing the dose for anticoagulants.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Declaration of Patient Consent

The authors declare that patient consent was taken for the publication.

ABBREVIATIONS

REFERENCES


