A REPORT ON CLOZAPINE AND FELODIPINE INDUCED ADVERSE EFFECTS IN A PATIENT WITH ERYTHROMYCIN TOXICITY

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ABSTRACT

Objective To report a case of clozapine, felodipine induced adverse effects in a patient with erythromycin toxicity. Case summary A 52 years old, Malaysian male, who is hypertensive, schizophrenic, on regular use of felodipine (5mg), clozapine (300mg), for the past 6 years was presented to the emergency department of a public hospital in Malaysia due to attempted suicide at his home. The day prior to admission, patient allegedly consumed 10 tablets of 500mg erythromycin, 8 tablets of 5mg felodipine. Discussion Upon admission, patient’s vital parameters were abnormal. He also presented with severe ankle edema, dizziness, and hypotension with random blood glucose level of 260mg/dl. Moreover, he had one episode of seizure attack in the emergency department. Conclusion This case represents a good example for erythromycin induced drug interaction leading to side effects produced by two other drugs co-administered. Adverse effects were treated successfully and further monitoring was done by the clinical pharmacist.

KEYWORDS: Therapeutic Drug Monitoring; Postural hypotension; hepatic enzyme CYP3A4; Erythromycin estolate; Schizophrenia.

1. INTRODUCTION

Schizophrenia is a chronic, disabling mental illness characterized by a wide range of symptoms including abnormal thinking, loss of contact with reality, hallucinations.1 It is
strongly linked to an increased risk of suicide attempts and completed suicides.\textsuperscript{[2]} Among people diagnosed with schizophrenia an estimated 20-40\% attempt suicide.\textsuperscript{[3]}

2. ETHICAL APPROVAL
Approval was obtained from Medical Research and Ethics Committee (MREC) of Malaysia and respective hospital.

3. CASE REPORT
A 52 years old Malaysian male with schizophrenia and hypertension been prescribed with clozapine (300mg) and felodipine (5mg) for the past 6 years. Patient also had past history of epilepsy which was not revealed to his psychiatrist previously.

Patient was under the care of his caregiver at home. However, he was rushed to the emergency department of a public hospital in Malaysia due to an attempted suicide by consuming 10 tablets of 500mg erythromycin, 8 tablets of 5mg felodipine at his home a day prior.

He presented to the hospital with severe ankle edema, headache, dizziness, and syncope due to severe hypotension. Symptomatic treatment was administered and hypotensive condition was managed by administering fludrocortisone (0.1mg/day) along with fluid infusion. As his blood glucose elevated to 260mg/dl he was started with the administration of regular insulin (0.6 units/kg). Also, in the emergency department, patient developed one episode of seizure attack and was prescribed with carbamazepine suspension 100mg 4 times daily.

Upon stabilization of vital parameters, patient was transferred to medical ward and he had 3 episodes of vomiting with continues nauseated feeling. His blood test later demonstrated a low neutrophil count of 26\% (normal value: 40-74\%) even a profound increase in liver enzymes (AST, ALT) was seen. On the fourth day of admission, the blood glucose level, blood pressure, and neutrophil count returned normal. However, severe agitation was noted and he was administered with parenteral haloperidol.

A table with all the laboratory parameters of the patient is placed in appendices.

As the patient was prescribed with carbamzepine which is a narrow therapeutic index agent and already the patient was on erythromycin toxicity, we the clinical pharmacist of the hospital monitored the serum levels of drugs and other parameters.
Appendices

The following table gives the measures of all the laboratory parameters in this patient:

<table>
<thead>
<tr>
<th>NO</th>
<th>PARAMETERS</th>
<th>NORMAL RANGE</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>DAY 4</th>
<th>DAY 5</th>
<th>DAY 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BLOOD PRESSURE</td>
<td>120/80 mmHg</td>
<td>82/50</td>
<td>100/62</td>
<td>110/70</td>
<td>132/76</td>
<td>130/75</td>
<td>130/78</td>
</tr>
<tr>
<td>2</td>
<td>HEART RATE</td>
<td>70-90 beats/min</td>
<td>104</td>
<td>96</td>
<td>96</td>
<td>90</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>BLOOD GLUCOSE</td>
<td>5.6-6.9 mmol/L</td>
<td>14.4</td>
<td>11.9</td>
<td>7.2</td>
<td>7.8</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>4</td>
<td>NEUTROPHIL</td>
<td>40-74%</td>
<td>26%</td>
<td>29%</td>
<td>31%</td>
<td>57%</td>
<td>54%</td>
<td>61%</td>
</tr>
<tr>
<td>5</td>
<td>TOTAL BILIRUBIN</td>
<td>3-21μmol/L</td>
<td>47</td>
<td>26</td>
<td>12</td>
<td>19</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>ALT</td>
<td>0-0.58 μKat/L</td>
<td>2.1</td>
<td>1.7</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>AST</td>
<td>0-0.58 μKat/L</td>
<td>1.0</td>
<td>0.9</td>
<td>0.3</td>
<td>0.3</td>
<td>0.28</td>
<td>0.28</td>
</tr>
</tbody>
</table>

ALT= Alanine Amino Transferase, AST=Aspartate Amino Transferase.

4. DISCUSSION

Ankle edema, dizziness, profound syncope, observed in this patient was due erythromycin consumption causing inhibition of felodipine metabolism, thereby leads to an increased felodipine plasma concentration, moderate interaction between erythromycin and felodipine.\(^4\) Initial management comprised of fluid resuscitation, ankle edema was treated with slight elevation of his limbs, and hypotension was corrected by administering fludrocortisone 0.2mg/day with adequate fluid.\(^5\) As erythromycin has large volume of distribution, no hemodialysis or peritoneal dialysis was indicated.

The second issue in this patient was hyperglycemia with leukopenia. Both are major side effects of clozapine therapy.\(^6,7\) These effects were prominent in this patient due to erythromycin consumption. As CYP3A4 is one of the main isoenzymes for clozapine metabolism, erythromycin causes enzyme inhibition leading to toxicity.\(^8,9\) As a result, clozapine was withheld in this patient for few days.

Clozapine has been reported to cause 3-5% of seizure in post marketing surveillance.\(^10,11\) However, in this patient, he was seizure free for 2years despite his daily 300mg clozapine therapy. As a consequence of erythromycin induced enzyme inhibition, patient had recurrent attack of seizure in ward. Carbamzepine which is the drug of choice for partial seizure was given to this patient with Therapeutic Drug Monitoring (TDM).

5. CONCLUSION

This case represents a drug-drug interaction between erythromycin and other drugs which was treated successfully and further monitoring was done by the hospital clinical pharmacist.
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CONFLICT OF INTEREST: None declared.

REFERENCES