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Long term carbamazepine induced acquired aplastic anaemia at rims hospital, Kadapa: Prescription event monitoring case report

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Abstract
Carbamazepine has broad spectrum anti-seizure activity. It is effective in the treatment of psychomotor (partial seizures), grand mal (generalises tonic-clonic) seizures and mixed seizure patterns. Carbamazepine has a number of effects on hematologic system, but the rare and serious adverse effect is aplastic anaemia. A 50 years old female patient was admitted in female medical ward with chief complaints of fever since 3 days which is insidious in onset & gradually progressive, pedal oedema and breathlessness. Past medical history includes patient was a known epileptic since 20 years and is on medication with Tab. Carbamazepine. In order to prevent serious adverse drug reactions of drugs, close monitoring during treatment course, creating awareness, recognition of the patient and careful management of all patients is essential. Physicians should be alert to the possibility of anti-epileptics ADRs, especially carbamazepine associated aplastic anaemia.

Keywords: carbamazepine, aplastic anaemia, epilepsy, seizures, pedal oedema

Introduction

Carbamazepine is a carboxamide derivative through broad spectrum anti-seizure activity. It is effective in the treatment of psychomotor (partial seizures), grand mal (generalises tonic-clonic) seizures and mixed seizure patterns. Carbamazepine acts by reducing poly synaptic responses and blocks the post-tetanic potentiation i.e., it is a sodium channel blocker. It binds preferentially to voltage-gated sodium channels in their inactive confirmation which prevents repetitive and sustained firing of action potential. Carbamazepine is completely absorbed from gastro intestinal tract, highly bound to plasma proteins, metabolized by liver and excreted through urine. Carbamazepine has a number of effects on hematologic system. It mainly causes aplastic anaemia, agranulocytosis, eosinophilia, leucocytosis and thrombocytopenia. It also causes hypertension, pulmonary hypersensitivity, Steven Johnson syndrome, erythema multiforme, excessive diaphoresis stomatitis, glossitis and dry mouth. One of the rare and serious complication of carbamazepine is the occurrence aplastic anaemia [1].

Approximately 126 cases of aplastic anaemia were reported. More than 100 cases of aplastic anaemia due to Carbamazepine have been published and a characteristic clinical pattern of decreased reticulocyte count has been described. The estimated frequency is 2 patients per 1 million populations per year for aplastic anaemia. The serum enzyme elevations can also lead to the bone marrow depression, although mixed metabolic diseased patterns are probably experienced. Drugs, toxins, viruses and mixed situations such as autoimmune disorders and chemotherapy are the main causes of aplastic anaemia[2]. Bone marrow transplantation is more progressively used to recover patients with aplastic anaemia even though medical supervision has enhanced. The risk of bone marrow depression correlates with the presence of HLA-B*1502. Carbamazepine affects the immune system by impairing humoral and cellular immunity. The risk of the aplastic anaemia may be reduced by the haematological monitoring and physical examination of patients in the first 4-6 weeks.

Aplastic anaemia is pancytopenia with bone marrow hypo-cellularity. Acquired aplastic anaemia is distinguished from iatrogenic marrow aplasia. It is the common occurrence of marrow hypo-cellularity after intensive cytotoxic chemotherapy. Aplastic anaemia is constitutional. Genetic diseases like Fanconi's anaemia and Dyskeratosis congenital are frequently associated with typical physical anomalies and the development of pancytopenia early in life. This disease can also be characterized as marrow failure in normal-appearing adults. The incidence of acquired aplastic anaemia in Europe and Israel is 2 cases per million persons annually, while in Thailand and China, 5 to 7 cases per million have been established. In general, men and women are affected with equal frequency, but there is a biphasic age distribution, with the major peak in the teens and twenties, second rise is seen in the elderly [2].

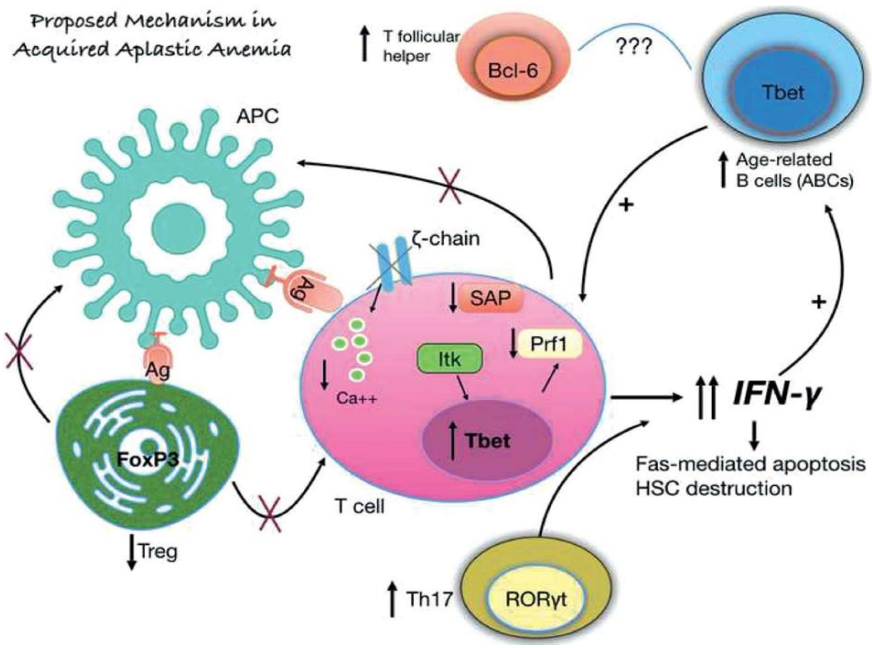

Fig 1: Shows pathophysiology of Aplastic anaemia

Carbamazepine induced aplastic anaemia is the most serious acquired blood dyscrasia because of its associated high mortality which averages about 50%. In drug-induced aplastic anaemia, multipotent hematopoietic stem cells undergo damage before their differentiation to committed stem cells. Therefore, the number of circulating neutrophils, platelets, and erythrocytes is reduced. Previous reports have showed that the incidence of drug-induced aplastic anaemia is 2/million in Europe and North America which is two or three times greater in Asian countries. Symptoms of drug-induced aplastic anaemia are of variable in onset. They may appear from days to months after initiation of the therapy with the causative drug. Symptoms include fatigue, pallor, weakness (signs of anaemia), pharyngitis, fever and chills (signs of neutropenia). Symptoms can also appear as neutropenia followed by thrombocytopenia after the discontinuation of the causative drug, while anaemia develops slowly because of the longer life span of erythrocytes. The pathogenic mechanism of drug-induced aplastic anaemia includes the generation of intermediate metabolites that bind to DNA and proteins to cause bone marrow failure and toxicity on hematopoietic cells. The variability in the presence of these metabolites as a result of genetic variation explains the idiosyncratic nature of drug-induced aplastic anaemia. The idiosyncratic drug-induced aplastic anaemia is characterized by a latent period before the onset of anaemia, continued bone marrow damage after drug discontinuation, and dose independence [3].

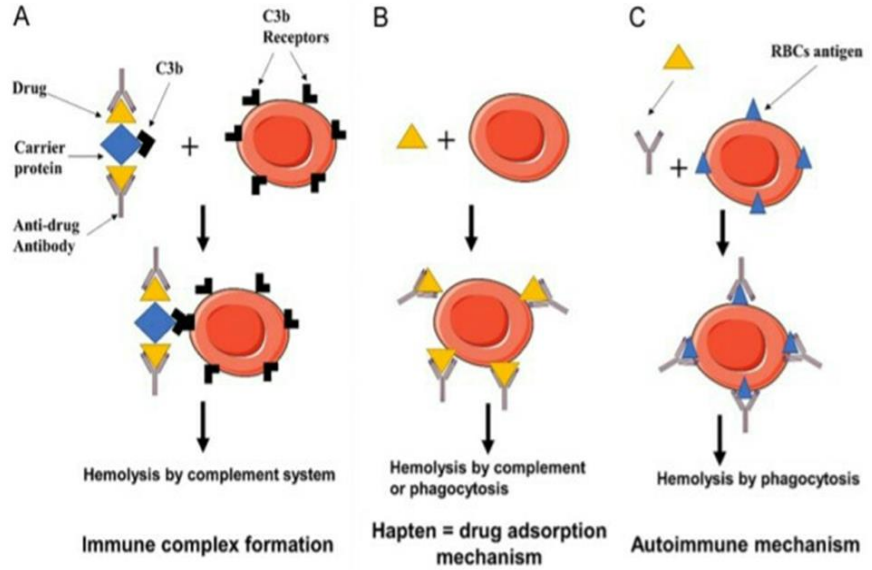

Fig 2: Shows mechanism of Carbamazepine Induced Acquired Aplastic Anaemia

Management of Aplastic anaemia can be categorized depending on the blood counts into: moderate (neutrophils < 1,500 cells/mm3, platelets < 50,000 cells/ mm3 and haemoglobin < 10 g/dL), severe (neutrophils < 500 cells/mm3, platelets < 20,000 cells/mm3 and reticulocytes < 1%) and very severe aplastic anaemia (neutrophils < 500 cells/mm3, platelets < 20,000 cells/mm3, reticulocytes < 1% and neutrophils < 200 cells/mm3). For accurate diagnosis of aplastic anaemia and to exclude other causes of pancytopenia, a bone marrow aspirate and biopsy is a necessity. Treatment of aplastic anaemia aims to limit the requirement for transfusions, improve peripheral blood counts, and minimize the risk for infections, and should be based on severity of the disease. Because of the high mortality associated with drug-induced aplastic anaemia, treatment should be initiated immediately after the anaemia be diagnosed [4]. Removal or withdrawal of the causative agent of aplastic anaemia is the first step in the treatment and may help in the disease reversal. Treatment of moderate disease cases should be based on the degree of cytopenia and usually ranges from no clinical intervention to immunosuppressive therapy. Basically, allogeneic hematopoietic stem cell transplantation and immunosuppressive therapy are the two major options for patients with carbamazepine-induced aplastic anaemia. The therapy of choice depends on several factors, including disease severity, age and availability of a human leukocyte antigen-matched donor. Immunosuppressive therapy is the preferred first-line therapy for patients who are not candidates for allogeneic HSCT and for those older than 40 years [5]. Currently, the standard immunosuppressive therapy for aplastic anaemia is a combination of cyclosporine and anti-thymocyte globulin. Cyclosporine inhibits activation of resting T cells via suppression of interleukin (IL)-2 production and release [6]. Addition of cyclosporine to anti-thymocyte globulin improved failure-free survival, reduced the number of required immunosuppressive courses, and increased the response rate. This immunosuppressive regimen has been demonstrated to achieve 5-year survival rates, with a lower response in older patients.

Case report

A 50 years old female patient weighing 49 kilograms was admitted in female medical ward with chief complaints of fever since 3 days which is insidious in onset & gradually progressive, pedal oedema and breathlessness. Past medical history includes patient was a known epileptic since 20 years and is on medication with Tab. Carbamazepine. Patient personal history includes, she was taking mixed diet, her sleep was disturbed, bowel and bladder habits includes constipation. On general examination, the patient was conscious and coherent. On physical examination, her vitals were found to be BP-90/80 mm Hg, PR-72 bpm, RR-26 cpm. On systemic examination P/A: Splenomegaly, RS: Wheeze+ breathlessness of grade-IV. Patient laboratory parameters as follows Haemoglobin: 2.5 gm/dl, Reticulocyte count: 0.5, MRI: Chronic lacunar infarct in bilateral capsule-ganglionic regions. Based on the subjective & objective evaluation, the patient was diagnosed with seizures with aplastic anaemia. The treatment was given as follows: On day 1: Injection Pantop in a dose of 40mg once in a day, Injection Ceftriaxone in a dose of 1gm twice in a day, Tablet B-complex in a dose of 67mg once in a day, Tablet Iron folic acid in a dose of 335.5mg once in a day, O_2 inhalation & 1⊙whole blood transfusion was done. On day 2: Injection Augmentin in a dose of 1.2gm thrice in a day, Tablet Doxycycline in a dose of 100mg twice in day, Injection Methyl cobalamin in a dose of 1000mcg once in a day, Injection Pantop in a dose of 40mg once in day and Nebulisation with Asthalin was given for every 6 hrs. On day 3: same medication was continued & advised to take Tablet Valproate in a dose 200mg. On day 4: same medication was continued, Injection Iron sucrose 2amp in 100ml NS was advised to give on alternate days along with Tablet Vitamin C in a dose of 500mg was added once in a day. On day 5 & 6: same medication was continued. On day 7: The patient was discharged with the following medications: Tablet Iron folic acid in a dose of 335.5mg once in a day, Tablet Vitamin C in a dose of 500mg once in a day, Tablet B-complex in a dose of 67mg once in a day, Tablet Calcium in a dose of 500mg once in a day, Tablet Valproate in a dose of 200mg *(Carbamazepine is replaced with Valproate).* Based on the above information, hereby we have suspected that this patient suffering from aplastic anaemia, which is adverse drug reaction of Tablet Carbamazepine.

Causality assessment: To evaluate the relationship between the drug and reaction, we have performed causality assessment by using scales like WHO causality assessment scale, Naranjo's scale, Karch Lasagna scale and analysis of observed ADR (Table 1 & Table 2)

Table 1: Causality assessment of suspected ADR

Adr scale	Who-umc	Naranjo's	Karsch & lasagna
Assessment	Probable	Probable	Possible

Table 2: Analysis of observed ADR

Severity assessment	Level-4 (b)
Predictability	Type-A
Preventability	Probably preventable

Results and Discussion

Epilepsy is a collective chronic neurological condition characterised by continuing seizure activity (recurrent attack of seizures). These seizures are brief signs and symptoms of irregular, excessive or synchronous neurological activity of brain. If seizures occur repeatedly, neurons can be injured, may leads to change in memory and cognitive functions. Epilepsy is generally organised, but cannot be healed with medications. Patients undergoing surgeries may also have subtle and stormy adverse drug reactions[7]. Here, in this case report, as patient had a history of epilepsy since 20 years she was on treatment with Tab. Carbamazepine which had lead to aplastic anaemia due to chronic usage. Aplastic anaemia is a hematopoietic stem cell disorder characterised by pancytopenia of the peripheral blood and hypo-cellular bone marrow [8]. It is a type of anaemia in which bone marrow fails to produce all types of blood cells. Aplastic anaemia is one of very rare side effect, although it is the most serious as it has high mortality rate. Most of the cases related to the aplastic anaemia are seen 3 to 4 months after treatment of epilepsy and the risk period is less than 12 months. The choice of treatment

is bone marrow transplantation in patients under the age of 50 and in older patients the recommended treatment is immunosuppressive drugs. Therefore, the early diagnosis of aplastic anaemia is essential, although the difficulty lies in determining how often haematological controls are to be performed, since some cases have appeared a few days after beginning treatment. The appearance of aplastic anaemia does not seems to be related to age, either disease treated or to be dose dependant [9]. Carbamazepine was given to treat epilepsy for reducing hyper excitability. Common ADRs include hypertension, pulmonary hypersensitivity, Steven Johnson syndrome, erythema multiforme, excessive diaphoresis stomatitis, glossitis and dry mouth and aplastic anaemia. In this case, patient had a history of carbamazepine usage since 18 years which had lead to the development of aplastic anaemia and this is the reason for the patient's hospital admission. During patient interviews, clinical pharmacists have recognised adverse drug reactions case, based upon the literature reviews and laboratory investigations, concluded that this condition is because of the carbamazepine and performed causality assessment, severity, preventability & predictability. After identifying suspected adverse drug reaction, physician immediately withdrawn carbamazepine and provided appropriate treatment [10].

Conclusion

As carbamazepine is associated with nine fold increased risk of aplastic anaemia, better vigilance for implementation of safe and effective treatment for each individual is needed. In order to prevent serious adverse drug reactions of drugs, close monitoring during treatment course, creating awareness, recognition of the patient and careful management of all patients is essential. Physicians should be alert to the possibility of anti-epileptics ADRs, especially carbamazepine associated aplastic anaemia.

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Conflict of interest

None declared

Ethical Approval

Not required

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