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Case Report

Can idiosyncratic drug reactions occur in quick succession? a case of cross sensitivity between levetiracetam and phenytoin

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ABSTRACT

The occurrence of adverse drug reactions (ADRs) to more than one drug in quick succession can cause diagnostic dilemma to the doctor and increased burden of suffering to the patient. We present a single case report of a 23 year old female who developed rash and agranulocytosis in quick succession as ADRs to phenytoin and levetiracetam respectively. These antiepileptic drugs (AEDs) were prescribed as prophylaxis against post traumatic seizures (PTS). Hence a proper rationale for the prophylactic treatment of PTS and pharmacovigilance for early detection of adverse drug reactions is the need of the hour.

Keywords: Adverse drug reaction, Drug induced agranulocytosis, Idiosyncratic drug reaction, Levetiracetam, Phenytoin

INTRODUCTION

Use of antiepileptic drugs (AEDs) for the treatment of seizures post craniocerebral trauma is a common practice. A debate still exists regarding the use of AEDs to prevent post traumatic seizure (PTS) and subsequent epilepsy after traumatic brain injury.[1] The use of AEDs for the prophylaxis of such seizures has its own risk of adverse effects.[2] As AEDs have a narrow therapeutic range, they are more likely to cause adverse effects with diverse manifestations. Here we report a case of a young female with head injury as a result of motor vehicular accident, on seizure prophylaxis, developing adverse drug reactions (ADRs) to AEDs one after the other. This case highlights the need to keep a constant vigilance against ADRs in order to prevent morbidity and mortality

CASE DETAILS

The patient is otherwise healthy 23 year old female who presented with head injury following a motor vehicular accident. She did not have any prior history of seizures. She was conscious, oriented and did not develop any seizures post head injury. CT scan revealed a small subdural hemorrhage in right frontoparietal region without mass effect. Loading dose of phenytoin injection (700mg) was given intravenously initially followed by 100 mg 8 hourly for prophylaxis of seizures. She was discharged 5 days later after conservative management in the hospital. She was advised to continue oral phenytoin 100mg twice daily for one month as prophylaxis against post traumatic brain injury seizures.

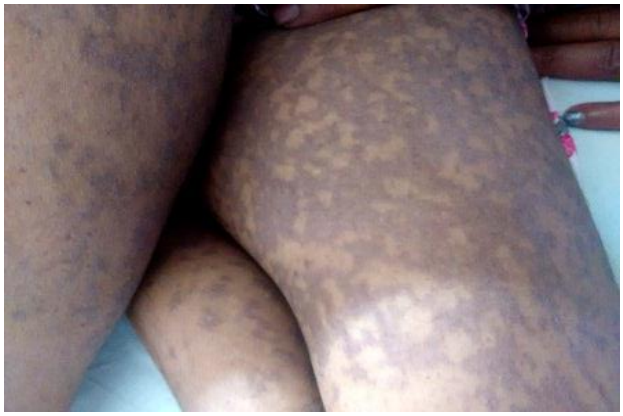

Figure 1: Retiform rash present on both thighs due to phenytoin hypersensitivity.

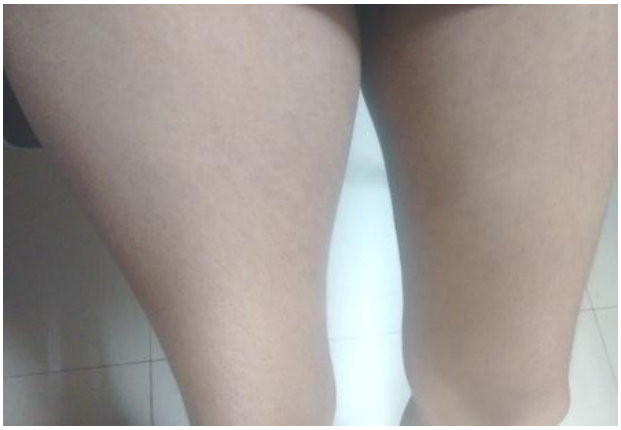

Figure 2: Rash subsided after discontinuation of phenytoin.

Fourteen days after initiating phenytoin, the patient developed a progressively pruritic dusky violaceous retiform rash all over the body predominantly involving trunk, both thighs and arms, but sparing her face, palms and soles. The rash was associated with scaling. There was no fever or regional lymphadenopathy. It was suspected to be due to phenytoin hypersensitivity. Blood investigations were found to be normal and there was no leucopenia. She was symptomatically treated with oral chlorpheniramine 25mg at night and calamine lotion as local application. Phenytoin was withdrawn and oral levetiracetam 500mg was started twice daily as prophylaxis for seizures. The rash started subsiding subsequently after phenytoin withdrawal and no new lesions appeared the following day (Figure 1 and 2). The patient developed fever on the fourth day of initiating levetiracetam. Fever was high grade with chills and associated with myalgia. There was no history of headache, vomiting, abdominal pain, loose motions, altered sensorium, seizures, nasal discharge, cough or burning micturition. On examination it was found that the rash due to phenytoin hypersensitivity was already subsiding. Patient was not found to have any other focus of infection on systemic examination and her vitals were stable.

Investigations

The complete hemogram done during fever revealed hemoglobin 11.2g/dl, total leukocyte count 1,400cells/mm^3, with an absolute neutrophil count of 280cells/mm^3. Platelet count was 2.2lakh cells/mm^3. These findings suggested agranulocytosis with severe leucopenia. Other tests like liver function tests, renal function tests, serum lipids, urine analysis, blood sugar were within normal limits. The tests carried out to rule out infective causes of fever like malaria, dengue, leptospirosis, typhoid were also negative.Radiological investigations like chest xray, abdominal ultrasound and CT scan of brain, thorax and abdomen also did not reveal any focus of infection.Thus patient had agranulocytosis, and thorough investigations to find out the cause of agranulocytosis gave no results. The blood counts were decreasing each day with an absolute neutrophil count decreasing below 200cells/mm^3. Patient subsequently developed oral and vaginal candidiasis due tosuppressed immunity secondary to leucopenia. The patient was managed symptomatically with broad spectrum antibiotic (ceftazidime 1gm iv thrice daily), which was started prophylactically in view of her immunosuppressed state. Blood counts were monitored daily (Table 1).

Table 1: Blood counts during the course of admission.

Blood parameters	On admission	Day 2	Day 3	Day 4 (levetiracetam discontinued)	Day 5	Day 6
Hemoglobin (in g/dl)	11.2	11.2	11.0	11.4	11.0	10.8
Total Leukocyte Count (in cells/mm^3)	1400	757	473	2000	5300	7340
Differential count (on 100 cells)						
Neutrophils	20	18	14	35	40	41
Lymphocytes	76	78	80	33	45	54
Monocytes	04	04	06	30	15	2
Eosinophils	-	-	-	01	-	3
Basophils	-	-	-	01	-	-
Absolute neutrophil count (in cells/$mm^{3)}$	280	136	66	700	2120	3009
Platelet count (in lakh cells/ mm^3)	2.2	2.7	2.9	3.2	3.14	3.0

As there was no obvious cause of fever, leucopenia was suspected to be secondary to levetiracetam. It was noted that, immediately after stopping levetiracetam, counts started rising steadily and the patient became afebrile the next day.

Causality assessment was carried out for the ADRs due to phenytoin and levetiracetam based on the available clinical information (Table 2). Further rechallenge with oral phenytoin and levetiracetam was not done in the interest of the patient and due to ethical constraints. Patient was discharged after clinical improvement and laboratory studies revealed normal leucocyte count. She was discharged without any AEDs and was asked to follow up in case of occurrence of seizures.

Table 2: Causality assessment of ADRs.

Suspected drugs	WHO-UMC	Naranjo's scale	Modified Hartwig's scale
Phenytoin	Probable	Probable (+6)	Level 2
Levetiracetam	Probable	Probable (+7)	Level 4

DISCUSSION

Post-traumatic epilepsy can be classified into three types based on the occurrence of seizures in relation to the time of traumatic brain injury: immediate seizures, occurring within 24 hours of injury; early seizures, occurring within 7 days of injury; and late seizures, occurring more than 7 days after injury.[3] AEDs are used in the treatment of posttraumatic epilepsy. There is still a difference of opinion amongst the physicians for the use of AEDs to prevent PTS after traumatic brain injury.[2] AEDs have a beneficial role if used in the first week after traumatic brain injury.

The available literature supports the use of AEDs for early PTS prophylaxis during the first week after a traumatic brain injury. The American Academy of Neurology and Brain Trauma Foundation guidelines recommend the use of phenytoin for the above indication. Levetiracetam may also be used as an alternative since it has demonstrated comparable efficacy to phenytoin for early PTS prophylaxis.[4]

The American Academy of Neurology recommends prophylaxis with phenytoin for adult patients with early PTS (typically with prolonged loss of consciousness or amnesia, intracranial hematoma or brain contusion on CT scan, and/or depressed skull fracture), beginning with an early intravenous loading dose (Level A). Prophylaxis with phenytoin, carbamazepine, or valproate is not advised beyond the first 7 days after injury as (Level B). The prophylaxis with AEDs beyond the first week is more likely to be associated with adverse effects.[2]

Idiosyncratic drug reactions are unpredictable immune mediated reactions, which are dose independent and can be life threatening. The skin, liver and blood cells are the most common targets, though they can affect other organs as well.[5] These have been a major source of concern as they constitute most life threatening adverse effects of AEDs. In this case phenytoin was found to affect skin causing retiform rash, and, agranulocytosis was attributed to levetiracetam. These idiosyncratic reactions resolved on discontinuation of the above drugs.

Phenytoin is one of the widely used AEDs which is effective against all types of partial and tonic clonic seizures except absence seizures. This hydantoin derivative acts primarily by slowing the rate of recovery of voltage activated Na^+ channels from inactivation. It is known to have a diverse adverse effect profile such as dose related cerebellar-vestibular effects, behavioural changes, gastrointestinal symptoms, hirsutism, gingival hyperplasia, osteomalacia and megaloblastic anemia. Phenytoin induced hypersensitivity reactions include morbilliform rash which is found in 2-5% of patients and occasionally more serious skin reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis can occur.[6] Levetiracetam is a pyrrolidine drug and is approved by FDA for adjunctive therapy for myoclonic, partial onset, and primary generalised tonic-clonic seizures in adults and children above 3 years of age. It exerts its anticonvulsant action via synaptic vesicle protein, SV2A. Levetiracetam is generally well tolerated. The adverse effects most frequently reported are somnolence, asthenia, dizziness and psychiatric disturbances.[6] Levetiracetam is not known to cause hematological side effects but isolated cases of mild thrombocytopenia, leukopenia, or anemia have been reported. Few cases of pancytopenia have also been reported.[7]

Cutaneous reactions constitute 3-15% of ADRs to AEDs. These hypersensitivity reactions can be attributed to the aromatic ring in AEDs as seen in phenytoin, phenobarbitone and carbamazepine. Cross sensitivity in AEDs is more often seen with aromatic AEDs. Cross sensitivity between levetiracetam and other AEDs is rarely seen.[8] This is one such rare case where two ADRs occurred in same patient in quick succession where cross sensitivity of levetiracetam with phenytoin was also demonstrated.

A high index of suspicion should be maintained with respect to the idiosyncratic drug reactions and their early detection is required to decrease morbidity and mortality. Although levetiracetam is considered to have a low adverse effect profile, it should be administered with caution and careful monitoring in a patient with previous hypersensitivity to phenytoin.

CONCLUSION

ADRs add to healthcare costs and worsen the quality of life of patients. Detection and notification of idiosyncratic ADRs is of importance as these may not be evident during

clinical trials. Controversy exists regarding prophylactic treatment of PTS and execution of the guidelines for the same are the need of the hour. Careful monitoring is required when patient is initiated on AEDs and also during change of AEDs to detect cross sensitivity induced idiosyncratic ADRs.

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