Case Report

Carbamazepine and sodium valproate cross reactivity

Epilepsy is defined as recurrent seizures provoked by any immediate identifiable cause. Drug therapy is the mainstay of treatment for patients with epilepsy. Phenytoin, sodium valproate, carbamazepine and ethosuximide are generally used as first line therapy for most seizure disorders. Carbamazepine is one of the most widely used medications for the treatment of partial-onset seizures. Sodium valproate is a broad-spectrum antiepileptic that has proven efficacy against all seizure types, which makes it a useful antiepileptic when exact seizure classification is unknown or multiple seizure type exists. The patients who do not respond to first line antiepileptics or develop side effects to them are invariably prescribed alternative drugs. Clobazam, a long acting benzodiazepine, is one such drug that is given as an adjunctive therapy in these patients.

The aromatic antiepileptics viz. phenytoin, carbamazepine, phenobarbitone and primidone can cause hypersensitivity reactions.[1] For example, carbamazepine can cause pruritic and erythematous rashes, urticaria, photosensitivity reactions, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, Stevens-Johnson syndrome and Toxic epidermolysis.[2] In such a case carbamazepine is discontinued and nonaromatic antiepileptics like sodium valproate or a benzodiazepine is usually recommended as an alternative therapy. Here, we present a case in which there was development of acute hypersensitivity reaction to both aromatic and nonaromatic antiepileptics – a rarely reported phenomenon.

Case report

As a part of spontaneous drug reaction monitoring, a case was referred from the department of Dermatology Lok Nayak Hospital, New Delhi, regarding 18-year-old male patient who had an episode of focal seizures followed by unconsciousness and postictal headache. Prior to this episode the patient had no history of epileptic seizures. The patient was prescribed tablet carbamazepine 200 mg, three times a day. After an asymptomatic period of 10 days, the patient started developing reddish skin lesions over the body, associated with itching. These appeared initially over the trunk and later involved bilateral upper and lower limbs and face as well. The itching was severe in character, aggravated at night and disturbed his sleep. Two days later the patient developed high-grade fever and came to the emergency department with these complaints.

On examination, the patient was found to have generalized erythematous maculopapular rash with scaling, mainly on extensor surfaces. The scales were thin, whitish and easily removable. Palms and soles showed similar areas of blotch-like erythema. He had generalized lymphadenopathy with lymph nodes varying in size from 2 x 2 to 5 x 5 cm discrete, mobile and nontender in nature. There was bilateral nonpitting pedal edema. Conjunctiva showed bilateral mild congestion. There is no known history of hypersensitivity to any drugs.

All routine hematological and biochemical investigations including liver function tests were normal. Skin biopsy of the lesion revealed a normal epidermis with scattered perivascular and peri-appendageal lymphohistiocytic infiltrate in the dermis. Fine needle aspiration cytology of cervical and axillary lymph nodes revealed a lymphoid hyperplasia. A diagnosis of erythroderma due to anticonvulsant hypersensitivity syndrome was made.

Carbamazepine was stopped and patient was given tablet Pheneramine 25 mg three times a day and white soft paraffin for local application. Body temperature, pulse rate, oral intake and output were monitored. Patient was prescribed tablet sodium valproate 200 mg; two times a day and tablet clobazam 10 mg at bedtime. Inspite of changeover to two new drugs, all the symptoms persisted and there was no improvement in the condition of patient for another 3 weeks. Subsequent to that sodium valproate was tapered and finally stopped. Patient was allowed to continue with only tablet clobazam 20 mg at bedtime. One week after sodium valproate was stopped, the condition of patient improved with regression of edema and lymphadenopathy. At this time itching also decreased in intensity and erythema and scaling became less severe. However, while the patient was on clobazam alone, the symptoms did not relieve completely. Hence, clobazam was also stopped after 2 weeks of discontinuation of sodium valproate and patient was maintained on tablet diazepam 10 mg/day. Two weeks after stopping clobazam all the lesions completely disappeared. There was no episode of seizures throughout this period. The patient has since been maintained on diazepam. Rechallenge was not attempted on this patient.

Discussion

The antiepileptic drug hypersensitivity syndrome (AHS) is an adverse drug reaction associated with aromatic antiepileptic drugs. The hallmark of this syndrome is fever, rash and lymphadenopathy, which are accompanied with multi-organ system abnormalities.[3] This rare syndrome seems to be related to arene-oxide metabolites of aromatic anticonvulsants.[4]

Cutaneous adverse reactions are frequently described with anticonvulsant drugs especially with aromatic drugs such as carbamazepine, phenytoin and phenobarbitone.[5] Although sodium valproate is chemically unrelated to other
antiepileptics, this drug shares the same order of risk for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis. Nonaromatic antiepileptics like sodium valproate can be prescribed as an alternative therapy in patients with hypersensitivity reaction to aromatic antiepileptics. In our patient, initially the hypersensitivity reaction developed with the use of carbamazepine. Even after replacing it with sodium valproate and clobazam, there was no relief in the condition of patient. After stopping sodium valproate the signs and symptoms regressed but did not disappear completely. Incomplete disappearance of signs and symptoms with clobazam alone and complete disappearance after stopping it puts the status of clobazam also under doubt. It is unclear, whether clobazam contributed to the occurrence of such a hypersensitivity reaction or it was a residual effect of sodium valproate. Since, at present the patient is receiving diazepam, which is closely related to clobazam, it is less likely that clobazam could contribute to such a reaction. The causal relationship was established and we conclude that the reaction can be put in the category of probable/likely adverse drug reaction with carbamazepine and valproate as it is unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

In the present case, the patient developed hypersensitivity reaction to two structurally different antiepileptics. Hence physicians while prescribing alternative drugs in case of hypersensitivity reaction to the first line antiepileptics should keep in mind the possibility of cross reactivity between structurally unrelated antiepileptics like carbamazepine and sodium valproate.

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References