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RESEARCH ARTICLE

PHARMACOLOGY

AROMATIC ANTIEPILEPTIC DRUG REACTIONS

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ABSTRACT

Drug eruptions to aromatic antiepileptics are on increase . Reactions noticed are protean in nature and early detection is important which needs diligent observation. In our experience we had three cases with three different types of drug reactions to carbamazepine. One case had a morbilliform drug eruption with carbamazepine. We had another case with diagnosis- DRESS syndrome to Carbamazepine. (DR –delayed reaction, E- eosinophilia SS- systemic signs. The third case was steven johnsons syndrome. : In all the cases, the offending drug Carbamazepine was stopped immediately. Symptomatic treatment was given and antiepileptic drug structurally unrelated to carbamazepine was started. All cases responded well.

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KEYWORDS

carbamazepine, aromatic antiepileptics, morbilliform drug eruptions, dress syndrome, steven johnsons syndrome

INTRODUCTION

CARBAMAZEPINE: It is an antiepileptic and mood stabiliser.: It is an iminostilbene compound. (Tricyclic). It acts by slowing rate of voltage. Activated Na+ channels decrease synaptic transmission by acting presynaptically. They increase synaptic GABA action.

***Pharmacokinetics*:** Oral absorbtion :slow. Bioavailability:90%. t1/2:20-40 hrs.

***Adverse Reactions*:** Dose Related, Acute: Stupor, coma, hyperirritability, convulsions. Chronic; Drowsiness, ataxia, diplopia, vertigo, blurred vision, hypo natraemia, water intoxication, foetal malformations.

***Idiosyncratic Reactions*:** Blood dyscrasias, agranulocytosis, aplastic anaemia, leukopenia, thrombocytopenia,eosinophilia,erythematous rash,hepaticdysfunction,splenomegaly,pancreatitis,lupus Steven Johnson syndrome, DRESS syndrome

MATERIALS AND METHODS

Three patients on carbamazepine who suffered from different types of skin reaction were included and studied

1) A 74yr male patient presented with itchy rash all over body for 15 days. Rash progressed in cephalocaudal direction associated with high grade fever and chills. Patient is a known case of Diabetes mellitus, Hypertension and suffered from ischeaemic heart disease last year. He was started on carbamazepine after an episode of partial seizures 6weeks ago by a general practitioner. No other significant history of seizures in the past.
2) A 58yr male patient presented with fever and redness all over body for 4days associated with loose motions & vomittings. H/O pain and difficulty in swallowing.H/O redness and watering of eyes. Patient is a Known case of Diabetes mellitus since 1year on regular treatment.
   Patient was started on carbamazepine one month ago for partial seizures(1st episode
3) A 55yr female patient presented with skinrash, blisters and erosions for 10days associated with fever. H/O burning micturition for last 3 days.
   H/O surgery for maxillary sinusitis (SMR) 1month ago. Patient was started on Carbamazepine for trigeminal neuralgia 3weeks ago.H/O DM detected 1 month back and started on Tab.Glyciphage ½ bd.

OBSERVATIONS AND RESULTS

1. ***FIRST CASE*** On examination patient was found drowsy ,there is no pallor, no cyanosis, no lymphadenopathy. Pitting pedal edema was present. Vitals were normal.
   Cutaneus examination revealed erythematous maculopapular rash all over the body including face and scalp. Palms and soles are not involved. Exfoliation is seen in few areas.Oral mucosal involvement is seen.Genitalia were spared.
   Investigations have showed leucocytosis with raised absolute eosinophil count. Renal parameters were raised with Urea-52mg%,

Serumcreatinine:2.2mg%.USGabdomen:Grade Renalparenchymaldisease.
Diagnosis arrived at was Morbilliform drug eruption to carbamazepine.

2. ***SECOND CASE :*** on General examination showed pallor, cervical lymphadenopathy, Bilateral pitting pedal edema. Cutaneous examination showed erythema all over body including oral mucosa. Genitalia are not involved. Palms and soles are involved. [Please go through all these lines]
P/A: Mild Splenomegaly is present. Other systems normal.
Investigations showed peripheral eosinophilia (TC-10,500.,DC-P52,L40,E8,AEC:850cells/cumm.). Other blood investigations were normal. USG abdomen- Splenomegaly is present .
Diagnosis-DRESS syndrome to Carbamazepine. (DR –delayed reaction, E-eosinophilia SS- systemic signs)

DRESS SYNDROME WITH RASH , PEDAL EDEMA AND ADENOPATHY

Figure 1
acral edema with scaly rash.

3. ***THIRD CASE :*** on General examination showed slight pallor. Vitals were normal.
Cutaneous examination showed target lesions, purple macules and patches,erosions, few blisters, all over the body. Oral and genital mucosa is involved. Other systems normal.
Investigations: TC- 18600cells/cumm.DC-P86,L1O,E4.,Other investigations were normal. Skin biopsy was done and HPE: Showed hyperkeratosis, vacuolar changes in the basal layer of the epidermis, necrotic keratinocytes in the papillary dermis and infiltration of lymphocytes and eosinophils.
Diagnosis: Steven-Johnsons syndrome to carbamazepine.

STEVENJOHNSON SYNDROME

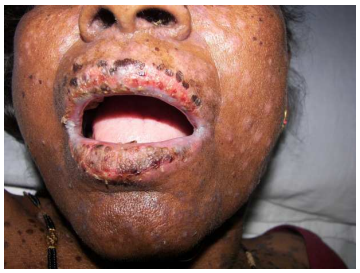

Figure 2
Steven-Johnson syndrome with haemorragic crusts with mucocutaneous involvement.

DISCUSSION

Carbamazepine was discovered by Walter Schindler(Switzerland). Its anti mania effect was described by Takezaki, Hanaoka and Okuma. Its is structurally related to tricyclic anti depressants. It acts by blocking use dependent sodium channels. Its therapeutic plasma levels are 4-8 microgm/ml. It is a enzyme(Cyp3A4) inducer. It's a drug of choice for the partial as well as the generalized tonic-clonic seizures.
Non antiepileptic uses: trigeminal neuralgia, Glosopharingial neuralgia, Post herpetic neuralgia, manic depressive psychoses.
Off label uses: cranial diabetes insipidus, intermittent explosive disorder, complex regional pain syndrome, phantom limb, neuromyotonia.

Adverse Reactions: Dose Related:Acute: Stupor,coma,hyperirritability,convulsions.
Chronic; Drowsiness, ataxia,diplopia, vertigo,blurred vision,hypo natraemia,water intoxication,foetal malformations.

Idiosyncratic Reactions:Blood dyscrasias, agranulocytosis, aplastic anaemia, leukopenia, thrombocytopenia,eosinophilia,erythematous rash, hepaticdysfunction, splenomegaly, pancreatitis, lupus.[more or less the same of the opening page]
A strong association between the risk of developing sjs/ten and the presence of Hla-b*1502, an inherited allelic variant of the Hla-b gene. Hla-b*1502 is found almost exclusively in patients with ancestry across broad areas of asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of Hla-b*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk

Steven Johnsons syndrome:.
It is characterised by a prodrome of flu like symptoms and extensive EMF lesions on trunk,with occasional skin blister and erosions covering < 10% BSA.Lesions almost always involve mucousmembranes, Oropharynx, eyes, genitalia and anus in that order of frequency.
Painful erosions, crusted lips,increased salivation and redness of eyes with photophobia are the common features.
Skin Biopsy helps to confirm the diagnosis

DRESS SYNDROME:
It is an adverse idiosyncratic drug reaction characterised by triad of fever, skin eruption,internal organ involvement. Drugs most commonly associated are: Aromatic anticonvulsant agents- Phenytoin, carbamazepine, phenobarbital(cross reaction).

Pathogenesis: Defective detoxification of reactive oxidative metabolites by the liver,genetic predisposition(like slow acetylator status) are implicated.

ClinicalFeatures: Occur usually 1-6 weeks later. Fever, pharynigitis, cervical lymphadenopathy, pruritic generalized (maculopapular) exanthem.
Edema is the hallmark of DRESS Syndrome.
Liver abnormalities(severe hepatitis) ,Renal involvement, lungs and CNS involvement can occur.
Haematological manifestations like atypical lymphocytosis, eosinophilia,neutrophilia and hemolytic anemia can occur

In all the cases, the offending drug Carbamazepine was stopped immediately.

Symptomatic treatment was given and antiepileptic drug structurally unrelated to carbamazepine was started. All cases responded well.

CONCLUSION

Antiepileptics with aromatic ring commonly produce drug eruptions any time from second week. These case reports are presented to bring to light the spectrum of rashes caused due to Aromatic antiepileptics. It is also important that all structurally related drugs like phenytoin, phenobarbital, imipramine, desipramine, amitriptyline, promethazine should be avoided in these patients. It should be noted that a second exposure to the same or related drug may cause fatal reactions.

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