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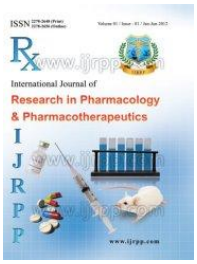

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Case report ***Open Access***

Phenobarbitone induced steven johnson syndrome (SJS) Case report

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ABSTRACT

Introduction

Adverse drug reactions (ADRs) are one of the leading causes of death in hospitalized patients. ADR is a response to a drug which is noxious, unintended and occurs at doses normally used in human for prophylaxis and treatment. Steven Johnson syndrome is an immune complex mediated hypersensitivity complex that typically involves the skin and mucous membranes. Steven Johnson syndrome and toxic epidermal necrolysis are rare (TEN 90% SJS less than 10% body surface area detachment) but life threatening cutaneous adverse drug reactions. Drugs like antiepileptics (Phenobarbitone, phenytoin, lamotrigine), antibiotics (penicillin, cephalosporins, sulphonamides) anti gout drug allopurinol are considered as one of the most common causative factor for these serious ADRs.

Discussion

A four year old girl, known epileptic for the last two years, has generalized idiopathic epilepsy. She had been on Sodium Valproate and well controlled. The mother stopped the Valproate having been seizure free for two years .Two weeks later she had a generalized seizure lasting for ten minutes. The mother consulted some other doctor who prescribed Phenobarbitone 20 mg twice daily. Two weeks later she developed a skin rash on the face which spread to the trunk, upper and lower limbs and lastly the mucous membrane of the mouth and genitalia. The rash was very itchy. She also complained of inability to swallow and burning micturition due to genital ulcers. She was admitted to pediatric intensive care unit (PICU) in tertiary care hospital. The symptomatic and supportive treatment with corticosteroids and liquid paraffin was given for the initial management of SJS. Patient was discharged after 24days treatment.

Conclusion

By the withdrawal of the drug, the condition of the patient was improved. So the drug withdrawal is the first line for management of drug induced Steven Johnson syndrome.

Keywords: Adverse drug reactions, epilepsy, Steven Johnson syndrome.

INTRODUCTION

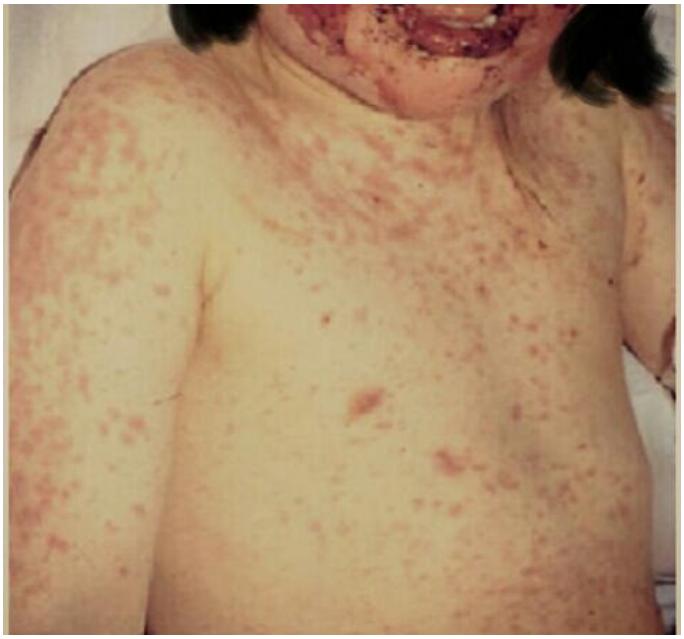
Serious allergic cutaneous reactions especially Steven Johnson syndrome(SJS) and Toxic epidermal necrolysis (TEN) are major complications of antiepileptic drug(AED) therapy[1] Phenobarbitone, phenytoin, lamotrigine are most

widely used anticonvulsants for seizureprophylaxis."A new eruptive fever with stomatitis and opthalmia" was described as a severe variant of erythema multiforme & was termed by Steven and Johnson in 1922. By the 1940's it was commonly called as "Steven Johnson's syndrome (SJS)" [(2)]. In 1956, Lyell first used the term toxic epidermal necrolysis (TEN) when he reported four cases of cutaneous disease that he likened to scalding[(3)]. The two forms of disease are characterized by an intense inflammatory reaction of the skin that gives rise to blistering and erythematous plaques, frequently also affecting the ocular and oral mucosa, and the general condition of the patient through fever and malaise followed by the sudden onset of a morbilliform rash that rapidly becomes confluent with diffuse erythema of the entire body, epidermal necrosis resulting in painful blistering exanthema, diffuse denuding of skin and involvement of mucous membranes[(4,5)]. The only difference between them is the extent of skin involvement: TEN affects greater than 30% of the skin surface and SJS less than 10 %[(6)].Mortality is as high as 60–70% in older series of patients. In recent studies the mortality rate is about30% when the patient is managed in a burn unit [(7)]. Stevens Johnson syndrome (SJS) is a severe hypersensitive reaction that can be precipitated by infection such as herpes simplex virus or mycoplasma, vaccination, systemic diseases, physical agents, foods and drugs [(8, 9)]. Initially in the disease process, the epidermis becomes infiltrated with CD8 cells, T-lymphocytes and macrophages, while the dermis shows CD4-cells predominance. It is postulated that the lymphocytes release cytokines, which mediate the inflammatory reaction and apoptosis of epithelial cells. The reported mortality varies from 3 to 10% for SJS and 20 to 40% for TEN [(10)]. The drugs that cause SJS commonly are antibacterials (sulfonamides), anticonvulsants (phenytoin, phenobarbital and carbamazepine) non-steroidal anti-inflammatory drugs (oxicam derivatives) and oxide inhibitors (allopurinol) [(11, 12)]. ADR monitoring system with a feedback to and the education of the prescribers can help prevent, identify and manage this life threatening condition much more effectively. Here we report a case of Steven Johnson syndrome which was induced by phenobarbitone.

CASE PRESENTATION

A four year old girl, known epileptic for the last two years, has generalized idiopathic epilepsy. She had been on Sodium Valproate and well controlled. The mother stopped the Valproate having been seizure free for two years .Two weeks later she had a generalized seizure lasting for ten minutes. The mother consulted some other doctor who prescribed Phenobarbitone 20 mg twice daily. Two weeks later she developed a skin rash on the face which spread to the trunk, upper and lower limbs and lastly the mucous membrane of the mouth and genitalia. The rash was very itchy. She also complained of inability to swallow and burning micturition due to genital ulcers. She was admitted to pediatric intensive care unit (PICU) in tertiary care hospital. And it was observed that patients prodrome of cutaneous lesions consists initially of erythmateous macules that rapidly & variably develop central necrosis to form vesicles, bullae, areas of denudation on face, trunk and extremities. Laboratory investigations revealed that patient has elevated level of increased erythrocyte sedimentation rate (ESR) showed inflammatory condition (The most common cause of high ESR is an increased protein level in the blood, such as the increase in acute phase protein in inflammatory disease), followed by decreased level of serum albumin showed oedema in the body (Albumin has an important role in binding calcium, bilirubin and many drugs. A reduction in serum albumin will increase free level of agents which are normally bound and adverse effect can result if the "free" entity is not rapidly cleared from the body will cause edema [(13)]. Increased liver enzymes showed hepatic impairment and further with Ultrasonography was confirmed. Leukocyte count also increased, it shows that sign of inflammatory response. A Clinical diagnosis of Stevens Johnson syndrome was made Phenobarbitone was stopped immediately. During the hospital administration, patient was managed symptomatically for pain control, fever, burning sensation, skin and mouth ulceration. . For supportive care the patient protected from secondary bacterial infection, maintained proper nutrition, fluid and electrolytes balance and glycerin swabs used to protect oral cavity. Proper skin dressing for fast wound healing. For systematic treatment, tobramycin eye drops with lubricant were administered. Short term course of parenteral corticosteroid shows the erythema reappeared from the skin. The dose of corticosteroid reduced gradually based on the serial

laboratory reports and patient recovery. Vitamin B complex given for manages the mouth ulcers. Topical Fusidic acid cream was added. Sodium valprote was started for her epilepsy ceftriaxone was given to prevent the secondary infections. Finally the patient recovered fully and discharged on the 24th day of admission with special warnings to hypersensitive drugs and also advised some discharged medications such as vitamin B Complex, Ceftriaxone and glycerin swabs.



DISCUSSION

Stevens-Johnson syndrome is a severe, episodic mucocutaneous intolerance reaction described by Hebra [(14)] in 1866 and Albert Mason Stevens and Frank Chambliss Johnson in 1922. Erythema multiforme (EM), Stevens-Johnson syndrome and Toxic epidermal necrolysis (TEN) are part of a clinical spectrum [(15)].TEN is the most severe form of drug-induced skin reaction and is defined as epidermal detachment of >30% of body surface area. SJS presents with epidermal detachment of <10% of body surface area, whereas involvement of 10%-30% of body surface is defined as SJS/TEN overlap[(16)]. The association between anticonvulsant consumption and skin reactions is well known. The antiepileptic drug hypersensitivity syndrome refers to a severe idiosyncratic reaction with erythematous skin eruption, fever, lymphadenopathy, hyper eosinophilia and visceral involvement (mainly hepatitis, pneumonitis, nephritis and carditis) [(17)]. Its incidence has been estimated to 1 reaction per 5,000 to 10,000 exposures to phenytoin, carbamazepine and phenobarbital [(4)]. Antiepileptics such as phenytoin, phenobarbital, and carbamazepine play an important role in the development of drug-induced serious skin reactions such as SJS and TEN [(18)].These reactions generally appear in the first 8 weeks of treatment, and the risk is most acute during the first 2-8 weeks of antiepileptic treatment [(19)]. Phenobarbitone is not the right choice for this age group and is rarely used for primary idiopathic generalized epilepsy. There is still controversy about whether all antiepileptic drugs are associated with severe cutaneous reactions i.e. Stevens-Johnson syndrome. Berthold Rzany et al found that about 16% of SJS cases are associated with short-term use of antiepileptic drugs. They also found a greatly increased risk of SJS for short-term use of phenobarbital, phenytoin, and carbamazepine [(20)]. The relative risk for aromatic anticonvulsants including phenobarbital to cause SJS is 11 to 15. The greatest risk is during the first two months of treatment with Phenobarbital [(6)].Commonly some of the drugs like Carbamazepine, Phenobarbital, Phenytoin and Valproic acid have high incidence to cause SJS/TEN and also these minds of reactions are independent on dose of drug and are idiosyncratic [(21)]. A study with adverse reactions of SJS/TEN due to anti-seizure drugs revealed that they had the higher chance (81.8%) of causing severe eruption that is SJS/TEN than NSAIDs (53.84%) and antimicrobials (34.48%). This is higher as compared with the previous report (70%)

[22].The exact mechanism of SJS/TEN still remains largely unknown. In immunological mechanisms reactive drug metabolites or interactions between these two are proposed. Interactions between CD95 L and Fas (CD 95) are directly involved in the epidermal necrolysis. Granulysin is also considered as a keymediator for disseminated keratinocyte death in SJS/TEN [23]. The lesions occur as a consequence of cell death causing separation of epidermis from the dermis. The keratinocytes undergo apoptosis through an interaction between cell-surface death receptor like Fas and its receptive ligand. Apoptosis is induced by proinflammatory cytokines like TNF-α, IL-6 and soluble CD40 ligand [24].Various systematic approaches have been developed to determine whether an ADR is actually due to the drug or a result of other factors. In the present case, Naranjo's algorithm was used to determine a plausible reaction due to phenobarbital. The following criteria were considered: there are conclusive reports and studies suggesting the role of phenobarbital in the development of SJS (score +1); lesions accompanied with prodromal symptoms developed following phenobarbital administration; the patient was apparently normal before the intake of drug (score +2); the condition improved within 2 days of discontinuation of phenobarbital (score +1); the differential diagnosis of viral fever or any underlying systemic condition with similar manifestations were ruled out (score +1) and the lab investigations were suggestive of SJS (score +1). Based on the total score of +6, the patient was categorized as probable adverse reaction due to phenobarbital administration. Removal of the causative agent and palliative therapy are the mainstay of treatment of SJS. Oral lesions usually subside within 14 days of removal of the offending drug. Administration of systemic steroids and intravenous immunoglobulin's helps in blocking the apoptotic pathways. The use of systemic steroids in the management of SJS is controversial but early short-term systemic steroids do not cause any significant side effects or increased mortality or morbidity in children. Anesthetic ointments can help in reducing the oral symptoms.

CONCLUSION

SJS is a life threatening adverse drug reaction. In conclusion, our study showed that SJS was more commonly seen in children who were susceptible to viral infections; mortality was higher in the elderly. This serious ADR when caused by unknown drugs may cause difficulties in diagnosis and management. Our findings suggest that reporting of ADR by health care professional should be encouraged. A robust ADR monitoring system with a feedback to and the education of the prescribers can help prevent, identify and manage this life threatening condition much more effectively.

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