CASE STUDY

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Stevens - Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) associated with Metronidazole Usage: Adr Analysis at a Hospital (GGH-RIMS), Kadapa

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ABSTRACT: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe skin reaction most often triggered by particular medications. Stevens-Johnson syndrome (SJS) is a life threatening adverse drug reaction. 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 or those used as self-medication may cause difficulties in diagnosis and management. Metronidazole alone rarely causes SJS. We present a case of an elderly female patient had past medication history of metronidazole use, developed neurological symptoms followed by pain and blisters on both soles, erythema of face and neck, scrotal itching and erosion, and hemorrhagic encrustation around the lips and oral mucous membrane. As metronidazole is a widely used drug, physicians should be aware of this adverse reaction for early detection and intervention. The patient should also be encouraged to report any abnormal manifestation following use of metronidazole to prevent such potentially life-threatening conditions. 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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INTRODUCTION:

Metronidazole is a well-established antimicrobial drug and is clinically effective in trichomoniasis, amoebiasis, and giardiasis, as well as in a variety of infections caused by obligate anaerobic bacteria, including Bacteroides, Clostridium and microaerophilic bacteria such as Helicobacter and Campylobacter species. Metronidazole accepts an electron from the sufficiently negative electron transport chain of anaerobic and microaerophilic pathogens to form a highly reactive

nitro radical anion that kills them by radical-mediated mechanisms that target DNA and possibly other vital biomolecules. Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe skin reaction most often triggered by particular medications [1]. Although Stevens-Johnson syndrome and toxic epidermal necrolysis were once thought to be separate conditions, they are now considered part of a continuum. Stevens-Johnson syndrome represents the less severe end of the disease spectrum, and toxic epidermal necrolysis represents the more severe end. SJS/TEN often begins with a fever and flu-like symptoms. Within a few days, the skin begins to blister and peel, forming very painful raw areas called erosions that resemble a severe hot-water burn. The skin erosions usually start on the face and chest before spreading to other parts of the body. In most affected individuals, the condition also damages the mucous membranes, including the lining of the mouth and the airways, which can cause trouble with swallowing and breathing. The painful blistering can also affect the urinary tract and genitals. SJS/TEN often affects the eyes as well, causing irritation and redness of the conjunctiva, which are the mucous membranes that protect the white part of the eye and line the eyelids, and damage to the clear front covering of the eye (the cornea) [2].

Severe damage to the skin and mucous membranes makes SJS/TEN a life-threatening disease. Because the skin normally acts as a protective barrier, extensive skin damage can lead to a dangerous loss of fluids and allow infections to develop. Serious complications can include pneumonia, overwhelming bacterial infections (Sepsis), shock, multiple organ failure, and death. About 10 % of people with Stevens-Johnson syndrome die from the disease, while the condition is fatal in up to 50 percent of those with toxic epidermal necrolysis. Among people who survive, long-term effects of SJS/TEN can include changes in skin coloring (pigmentation), dryness of the skin and mucous membranes (Xerosis), excess sweating (Hyperhidrosis), hair loss (Alopecia), and abnormal growth or loss of the fingernails and toenails. Other long-term problems can include impaired taste, difficulty urinating, and genital abnormalities. A small percentage of affected individuals develop chronic dryness or inflammation of the eyes, which can lead to increased sensitivity to light (Photophobia) and vision impairment [3].

Symptoms resembling an upper respiratory tract infection such as fever > 39 °C, sore throat, Cold, Cough, headache and body pain. Target lesions: These lesions that are darker in the middle surrounded by lighter areas are considered diagnostic of SJS. Painful red or purplish rash, blisters on the skin, mouth, eyes, ears, nose and genital areas. As the disease progresses, the flaccid blisters may merge and rupture thereby exposing painful sore. Eventually the top layer of the skin forms a crust and is shed. Facial swelling, swollen lips covered in crusty sores and mouth ulcers. Ulcers in the throat can cause difficulty in swallowing, while those in the digestive tract can cause diarrhea, ultimately causing dehydration. Swelling of eyelids, inflammation of the conjunctiva/ photosensitivity, where eyes are sensitive to light [4].

METRONIDAZOLE DRUG:

Bactericidal, trichomonacidal and amebicidal actions. The nitro group of metronidazole is reduced inside the infecting organism; this reduction product disrupts DNA and inhibits nucleic acid synthesis. Drug is active in intestinal and extra intestinal sites. It's active against most anaerobic bacteria and protozoa including *Bacteroides fragils*, *B. melaninogenicus*, Fusobacterium, Veillonella, Clostridium, Peptostreptococcus, *Trichomonas vaginalis*, *Giardia lamblia* and *Balantidium coli*. The half-life of metronidazole in plasma is about 8 h, and its volume of distribution is approximately that of total-body water. Less than 20 % of the drug is bound to plasma proteins. With the exception of the placenta, metronidazole penetrates well into body tissues and fluids, including vaginal secretions, seminal fluid, saliva, and breast milk. Therapeutic concentrations are also achieved in CSF. After an oral dose, over 75 % of labelled metronidazole is eliminated in the urine largely as metabolites; only about 10 % is recovered as an unchanged drug. The liver is the main site of metabolism, and this accounts for over 50 % of the systemic clearance of metronidazole. The two principal metabolites result from oxidation of side chains, a hydroxy derivative and an acid. The hydroxy metabolite has a longer half-life ~12 h and contains nearly 50 % of the anti-trichomonal activity of metronidazole. Formation of glucuronides also is observed.

Small quantities of reduced metabolites, including ring-cleavage products, are formed by the gut flora. The urine of some patients may be reddish brown owing to the presence of unidentified pigments derived from the drug [5,6].

LITERATURE:

SJS and TEN are part of the same spectrum of the disease, with nonspecific clinical manifestations and main characterization factors due to the extent and severity of the skin lesions. Integral management with different therapeutic alternatives can represent a crucial part in the multi systemic management of SJS and TEN. Most of the complications must be referred and resolved by their respective specialist, but there are prevention measures for the most common complications among which are highlighted [7].

CASE REPORT:

A 45 - Years female patient was brought to the Rajiv Gandhi Institute of Medical Science tertiary care teaching hospital, Kadapa, India. On the day of admission, patient was presented with the complaints of crusting lesions over the lips and erosions over the buccal mucosa and ears for 15 days. Lesions started and then ruptured on its own and the oozing serous discharge from ears and blood discharge from lips. Her past medication was tablet metronidazole 400 mg thrice in the day (prescribed by a registered medical practitioner). Patients were diagnosed as metronidazole induced Stevens Johnson syndrome.

PATIENT'S INVESTIGATION:

They have performed a cutaneous examination. Cutaneous examination well defined symmetrical crusting lesions present over the lips and ears and erosive lesions present over the mucosa hair-loss present.

ADR ANALYSIS:

However, upon analyzing the product information of antibiotic drugs, it was found that the most suspected drug (Metronidazole) induced Stevens - Johnson syndrome. However further assessment was done by performing causality assessment with the standard methods such as Naranjo's scale, Karch and Lasagna scale and WHO-UMC causality assessment system. Upon assessment of the reported event, there is a probable causality relationship between medical and medical history for the reported event [8]. We made a further assessment on the severity, predictability and preventability through Modified Hartwig and Siegel severity scale, Schmock and Preventability scale which were represented. Outcome of the suspected drug was reported as drug withdrawn and outcomes of the event were recovered. However, the patient was treated with supportive therapy for the developed event [9].

DISCUSSION:

Stevens–Johnson syndrome is a serious, idiosyncratic reaction of the skin and mucous membranes to a drug. It results in blistering and subsequently widespread epidermal loss and can have a high mortality rate. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are terms used to describe a life-threatening, mucocutaneous drug hypersensitivity syndrome characterized by blistering and epidermal sloughing. In SJS, there is epidermal detachment of <10 % BSA, in TEN there is detachment of > 30 % of the BSA, while cases with 10 to 30 % involvement are labelled SJS/TEN overlap. The systemic problems which accompany widespread epidermal loss such as high losses of heat and fluid, and the heightened risk of infection due to diminished barrier function can cause serious morbidity, similar to extensive burns. TEN carries a mortality rate of approximately 30 %, but this can rise to 90 % mortality in the presence of co-morbidities. HIV-infected patients and patients with systemic lupus erythematosus (SLE) have an enhanced risk of developing SJS/TEN. A prodrome of fever, malaise, and upper respiratory tract symptoms may precede the eruption by a few days. Involvement of the mucous membranes of the eyes, mouth, and nose is a prominent early feature. Eye involvement results in blepharitis, haemorrhagic conjunctivitis, mucus secretion, and pseudo-membranes. Ophthalmological input is required early if long-term sequelae such as blindness from corneal opacities and synechiae are not to occur. Urethral involvement must also be anticipated and the patient catheterized if strictures are not to complicate the disease course. Mouth involvement causes an erosive and haemorrhagic mucositis. On the skin, dusky red macules 1 to 3 cm in diameter appear at any site and evolve to become confluent. The skin lesions pass through vesicular and bullous phases before epidermal detachment occurs. Shearing pressure to the skin causes detachment of involved epidermis (Positive Nikolsky's sign). In TEN, there is widespread epidermal loss and sloughing of the necrotic epidermis which peels back to leave large areas of exposed dermis. Denuded dermis exudes serum, becomes secondarily infected and readily bleeds. The patient is in severe pain and is usually extremely ill. The visceral manifestations that result from widespread epithelial loss include pneumonia,

pancreatitis, thromboembolic disease, renal and hepatic impairment [10].

The patient with SJS/TEN will require full supportive care, preferably in an intensive care unit. Patients with SJS with less extensive involvement may be managed in a lower dependency environment, but should be monitored closely for signs of progression in the first 48 h of admission. A multidisciplinary approach, including dermatologists, ophthalmologists and intensive care physicians, is critical to a successful outcome. Following drug withdrawal, the management is supportive, including prompt treatment of infection, careful attention to thermoregulation, fluid balance and skin care, and introduction of appropriate eye and lid care. The literature has failed to identify one treatment which definitely improves outcomes, but agents which have been used include systemic steroids, cyclosporine and intravenous immunoglobulin. Pharmacogenetics involves the cutaneous ADRs Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Both are serious reactions associated with substantial morbidity and mortality in which up to 40 % of patients with TEN may die. SJS and TEN have been associated with numerous drugs, although the incidence of these reactions is extremely rare. The reactions are more common in South East Asian populations, including those from China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan and, to a lesser extent, India and Japan. The presence of HLA allele, HLA-B*1502, for which genetic testing is available, indicates an increased risk of skin reactions. Type IV (delayed type) Antigen presentation with major histocompatibility complex protein to T - cells and cytokine and inflammatory mediator release. Usually occurs after 7 to 20 days. Macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, associated with Antibiotics [10,11].

CONCLUSION:

Our study aims to minimize the ADR like SJS by making alert to physicians and other healthcare professionals intern we can avoid hospital admissions because of ADR, reduce economic burden of the patients and health related quality of life of the patient can be improved.

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