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A SYSTEMATIC REVIEW ON NSAID INDUCED STEVEN JOHNSON SYNDROME

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are the medicines that are frequently prescribed and taken by people all over the world. NSAIDs are among the many medications that have the significant potential for causing TEN or SJS. Skin responses involving mucosal or skin membrane separation include SJS and TEN. Males were less impacted than females. Drugs, infections, and genetic factors (HLA-A and HLA-B) were the main causes of SJS or TEN (mycoplasma pneumonia and herpes simplex virus). It's unclear exactly how SJS or TEN cause disease. The majority of SJS or TEN cases involve people over the age of 40. The optimum course of treatment for people with SJS or TEN is currently not supported by enough evidence due to the rarity of these disorders. The majority of medications, including antibiotics, anticonvulsants, and NSAIDs, cause SJS or TEN. To diagnose SJS or TEN, diagnostic tests such skin prick tests, PCR tests, and serology tests were utilised. In addition to receiving the greatest supportive care, patients are also given numerous medications such immunomodulators (IVIG), cyclosporine, systemic corticosteroids, TNF inhibitors, and plasmapheresis.

Keywords : Steven Johnson syndrome, tumour epidermal necrolysis, non steroidal anti inflammatory drugs, acetaminophen, adverse drug reactions.

INTRODUCTION

Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare disorders of the skin which involves detachment of skin and mucosal membrane. This disorder causes the skin to develop rashes, blisters and then peel.[1-3]It affects the mucous membrane including eyes, genitalia and mouth. SJS is less intense than TEN. SJS affects less than 10% of the entire body while TEN affects more than 30% of the body.[4] Many factors may be involved in developing these disorders, which includes genetic bias. One of these genetic factors include specific human leukocyte antigens (HLAs) which may increase the risk of developing SJS. These gene might be triggered by environmental factors. Medications which are most likely to cause SJS include Antibacterial sulfa drugs,Anti-epileptic drugs (including phenytoin ,carbamazepine, lamotrigine, and Phenobarbital),Allopurinol, Non-steroidal anti-inflammatory drugs (NSAIDs), (including piroxicam nevirapine, and diclofenac).[5]

NSAIDS are one of the most often prescribed and used class of drug in the world, and it is believed that these medications are the main factor in adverse drug reactions.[6] NSAIDS may induce SJS in 15.93% of cases (in the study of tejask. Patel et al). The majority of studies show that NSAIDS such acetaminophen, propionic acid, and aspirin are the main medications involved in SJS or TEN. SJS and TEN had mortality rates of 1–5% and 23–45%, respectively. [1,6-9]

MECHANISM OF NSAIDS

Acetaminophen, acetic acid, and propionic acid (ibuprofen and naproxen) are some of the typical culprit medications causing severe cutaneous reactions.[10] The US Food and Drug Administration stated in august 2013 that there was a possibility that acetaminophen could result in SJS or TEN.[11] The USFDA documented 91 cases of SJS or TEN between 1969 and in 2012. 8 cases of SJS or TEN were reported in the study by Shang-Chen Yang et al. there were 5 cases of SJS described in the study by Oshikoya, Ogunyinka, and colleagues. A grading system called SCORETEN was developed to assess the seriousness and prognosis of SJS or TEN. [12]

The study's objective is to assess the epidemiology, aetiology, diagnostic criteria, management, and treatment of SJS or TEN that have been caused by medicines (NSAIDS).

EPIDEMIOLOGY

AGE

According to Thomas Harr's study, there were 1.89 instances of TEN per million people in 1996 in Berlin and western Germany. Incidence rates for SJS or TEN over the past 20 years were 1-2 per million annually. According to M. Mockenhaupt's study, the incidence rate for TEN was 1.2 per million per year in France and 0.93 per million per year in Germany. The average age of SJS or TEN patients was 53.4% (36 percent of SJS patients were under 40 years old).[13] In other nations, the annual incidence rates of TEN/SJS were 6 and 1.4 per million. In that study by Siew Eng Choon et al., NSAIDs were the culprit in 9.9% of instances.[14]

GENDER

On comparison to men, women were more affected to SJS or [15,16] Acetaminophen induced SJS and TEN were reported in 33.89% in female within the age group of 20-39 years.[15-17]

The incidence rate in Europe and the United States is roughly 2-3 / million people each year.[17] In Japan, it ranged from 0.28 to 0.52 per million people each year. The mean age was 45.7 years in the survey conducted between 2000 and 2006, and 56.6 years in the survey conducted between 2000 and 2013.[18] According to a recent US paediatric database cohort study, hospitalised children have 7.5/100000 SJS-TEN cases and 6.3 and 0.5 per 100000 cases of SJS and TEN, respectively.[19] Each year, 1-2 million people were affected with SJS or TEN.[20]

ETIOLOGY

1. INFECTIONS : Infections such as herpes simplex virus and mycoplasma pneumonia are mostly found to induce SJS or TEN.[21,22]
2. GENETIC FACTORS : Human Leukocyte Antigen(HLA) gene is said to be a susceptibility gene. in Japanese, Korean, European population HLA-A*gene + CBZ induced SJS or TEN is common whereas in Asian population (India, Malaysia, China) HLA –B*gene + CBZ induced SJS or TEN is common.[23]
3. DRUGS : The SJS or TEN is majorly induced by certain medications, such as antimicrobials (37.27%), antiepileptics (35.73%), and non-steroidal anti-inflammatory medicines (15.93%).[14]
4. IDIOPATHIC

DIAGNOSTIC METHODS

Since there is no specific diagnostic test to validate the involvement of triggering agents, SJS or TEN were primarily diagnosed using signs and symptoms. This makes it challenging to identify the specific causal agent. The ALDEN score, which takes into account algorithms for five factors including index day, half life, prechallange/rechallange, dechallange, and renown, can be used to determine the culprit drug. PCR and serology tests are used to detect infection.The test for lymphocyte transformation was utilised to determine the offending medication.[24,25]

SKIN TESTING

Both intra dermal testing and skin prick testing were employed. IDT procedures involved dilutions ranging from 1/10 to 1/100. A diameter increase of more than 3 mm over the course of 20 minutes is regarded as successful.[26]

Patch tests were an easy, quick, and secure way to identify NSAIDS-induced SJS or TEN. The mariosanchez-borges study found that Metamizole had the highest concentration of NSAIDS for patch testing (10–50), followed by ketoprofen, phenylbutazone, and oxyphenylbutazone (1–10), and Ibuproxan, Acetyl Salicyclic Acid, and Paracetamol.[27-29] A grading system called SCORETEN was developed to assess the seriousness and prognosis of SJS or TEN. [8,22]

MANAGEMENT

The prognosis or onset of SJS or TEN can be avoided with early identification and treatment. For the decreasing mortality, some treatments were advised.

It is essential to stop using the harmful substance right away and to treat SJS or TEN with supportive care. Additionally, the provision of oxygen, nutrients, topical anaesthetics for pain treatment, electrolytes, and fluid and electrolyte balance.[3,21]

Antibiotics and topical corticosteroids were utilised to treat minor illness conditions. Within a week, the amniotic membrane covering the ocular surface must be replaced urgently in severe cases.[30]

Intravenous immunoglobulin

In 1998, IVIGs became the initial option for treating TEN. With a high dose of 2-4g/kg, IVIg directly inhibits the FAS/FAS ligand interaction, which benefits patients with SJS or TEN by lowering mortality rates. IVIg did not have therapeutic benefits when given alone, however it is now employed in combination therapy to produce therapeutic benefits.[3,31,32,33]

Cyclosporine

It is a calcineurin inhibitor, and when compared to IVIg, it has better therapeutic benefits for SJS/TEN and is beneficial in treating autoimmune illnesses and transplant-related complications. Early re-epithelialization and the prevention of the start of new lesions are both facilitated by it.[3,22,31,33,34]

Plasmapheresis

SJS/TEN can be effectively treated with plasmapheresis. Simple plasma exchange or double filtering is advantageous in this situation. Pathogenic elements such as drugs, drug metabolism, and illnesses that cause cytokinesis or chemokines in the patient's blood are removed by PP. Akito Hasegawa et al. reported that PP is a safe treatment with little negative medication responses. IVIG is used in conjunction with PP.[3,22,32]

Tumour necrosis factor inhibitor

Very few investigations on TNF inhibitors, skin lesions, and blister fluids with greater levels of TNF- have been published. Etanercept (25 mg/day) and infliximab (5 mg/kg) are two TNF-related medications that are used to treat SJS/TEN.[3,29,31,33]

Systemic corticosteroids

The most frequently prescribed medication for cutaneous infections is corticosteroidal. Utilizing corticosteroids at high doses for a brief period of time reduced mortality and improved infection control Acute stage of metyl prednisolone pulse treatment (500–1000mg/day for 4 days). oral prednisolone (0.8–1 mg/kg/day) comes next. High dose of corticosteroids for short-term pulse (4–8 mg/day of dexamethasone). [5,22,25,27,29,33]

Thalidomide and cyclophosphamide are two other medications used to treat SJS/TEN. A select few patients received IVIG and steroids in combination with medication therapy to reduce patient mortality.[13,19]

DISCUSSION

In Japan, an epidemiological investigation on SJS or TEN between 2005 and 2007 found that NSAIDs and acetaminophen were the most commonly suspected drug classes.[34] Recently, it was discovered that lactate dehydrogenase (LDH) was an additional valuable measure for assessing disease severity.[35]

The most frequent risk factor for developing SJS or TEN is medication use. When compared to persons under 40 years old, the mortality risk for SJS or TEN was higher in the over-40 age group.[36] The main cause of death in individuals with SJS or TEN is sepsis, with pulmonary problems occurring 15% of the time and multiple organ failure systems occurring 30% of the time.[37]

Acetaminophen is a safe and frequently prescribed medication for children's colds, but it may also be a major contributing factor in SJS or TEN. In the populations of Thailand and Japan, acetaminophen is the primary drug that causes SJS or TEN. In Brazil, dipyrone is the medicine that causes SJS or TEN the most frequently.[7] HIV patients had a 100-fold higher incidence of SJS or TEN than the general population.[38] In comparison to other NSAIDS, Oxicam posed a higher risk of SJS or TEN.[39] In the past, NSAIDs may have been linked to chronic difficulties in individuals with a particular genetic background. A recent study discovered that patients with SJS or TEN who take acetaminophen frequently had severe ocular surface involvement.[40]

Acetaminophen is one of the top five drugs most frequently linked to SIS or TEN. It was also a common drug for SJS or TEN, according to the Japanese ministry of health and welfare.[41] According to the selected research from 1995 to 2011, the patients in India and many other countries who were between the ages of 21 and 40 were most affected.[32] The incidence ratio in the most recent study should be in the range of 7.6 instances per million people each year, but it varies depending on the country. For example, in the UK study, the incidence ratio was 5.76 cases per million people, and in the US study, the IR was 12.7 cases per million people.[42]

CONCLUSION

NSAIDs are a class of medications whose worldwide usage is steadily rising. NSAID over-the-counter drugs have drastically increased. The two drugs known to most frequently induce SJS or TEN in the public are acetaminophen and NSAIDs. We were able to categorise the medications and their classes in this study, as well as the drug's mechanism (NSAIDs). In order to reduce the incidence of SJS or TEN, NSAIDs should be used appropriately. In order to prevent long-term severe visual impairment, ophthalmologist consultation and routine monitoring by corneal experts are crucial.

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