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Pathophysiology-Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Introduction
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, cutaneous, severe, drug-induced hypersensitivity reactions marked by widespread inflammation of the epidermis, ending in necrosis and the eventual sloughing of tissue. First described in 1952 by pediatricians Albert Stevens and Frank Johnson, both diseases are believed to be a result of the same disease process. They are the most serious of all drug-related hypersensitivity reactions which result in hospitalization (Ferrandiz-Perez & Garcia-Patos, 2013).

As a critical care nurse caring for a variety of trauma patients, it is crucial that staff is aware of potentially serious medication reactions. Some of the most serious of these start out with vague symptoms and may appear benign. However, some are very serious and potentially fatal.

Signs and Symptoms
• Fever, malaise, fatigue and mucosal involvement, including ocular, GI, GU, genital and upper respiratory tract.
• Mucosal involvement, which typically lasts over a week prior to the onset of the more identifiable rash.
• Marked erythema of skin leading to peeling, desquamation and toxic epidermal necrolysis (SJS/TEN): could be mistaken for Stevens-Johnson syndrome/toxic epidermal necrolysis.

Pathophysiology-Overview
SJS/TEN disease has long been presumed to appear as a result of an immune-mediated reaction to certain drug metabolites, although the exact mechanism of action has been poorly understood. Evidence has established a genetic predisposition for illness to various Asian populations, leading to FDA recommendations for pre-treatment genetic testing. Additional research has focused on the effects of vitamin A derivatives on the disease process.

Pathophysiology
SJS/TEN is marked by the widespread eruption of macules and papules which eventually lead to skin necrosis and sloughing. Until recently, SJS/TEN has been thought to be an idiopathic illness. Research seeking to clarify the genesis of the illness has found that morbidity can be a result of a genetic predisposition to a drug hypersensitivity reaction. Genetic research has identified several combinations of alleles and medications which, when combined, increase the risk of illness. Further research has sought understanding into the disease pathophysiology. In a paper published by Mawson, Enrar and Karre (2015), the authors theorize that disease occurs when a drug metabolite damages the liver, the organ responsible for storage of vitamin A, causing free-retinoid molecules to spill into the circulation creating an acute, systemic Vitamin A toxicity. Granulysin, a cytotoxic protein produced in massive quantities by both CD8+ T-lymphocytes and natural killer cells is the most prevalent molecule found in SJS/TEN elixirs. Granulysin is believed to act as a cytotoxic for destructive retinoid molecules (such as retinoid acid), combined together are believed to be responsible for keratinocyte apoptosis seen in SJS/TEN. As keratinocytes die off, the epidermis becomes detached from the dermis ending in tissue necrosis and sloughing (Teo & Walsh, 2016). Although not fully understood, the authors theorize that CD8+ T-cells become hyperactive when exposed to extreme levels of retinol and overproduce Granulysin. Granulysin then attracts retinoic acid which are both cytotoxic and together cause keratinocytes to die off. Keratinocytes make up 90% of the cells in the epidermis.

Many classes of medications have been linked to SJS/TEN, including anticonvulsants, antibiotics, NSAIDS, corticosteroids and allopurinol. These medications increase circulating retinoid levels, either through hepatic release as a result of liver injury, or through the inhibition of metabolism which leads to higher circulating retinoid derivatives, such as retinoid acid, a powerful cell-lysing agent (Mawson, Enrar, & Karre, 2015). Hepatic injury could explain the extended prodromal illness seen in this disease as patients often present with vague illness which typically lasts for over a week prior to the onset of the more identifiable rash.

Implications: Pathophysiology
Understanding pathophysiology is key for treating and limiting the risk of the disease mechanism for disease. Provided that retinal toxicity is involved with SJS/TEN, plasmapheresis could be used to reduce circulating levels and mitigate the destructive effects which retinal contributes in this disease. Plasmapheresis has been shown in small samples to reduce mortality versus typical treatment for patients with SJS/TEN (Mawson, 2015).

References

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
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