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Editorial

Levamisole in Medicine

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Levamisole is a common antihelminth used in veterinary medicine. It caught the attention of the medical community in 2008 when it was discovered to be the cause of agranulocytosis in people using illicit substances contaminated with levamisole. Subsequently multiple other deleterious effects have been recorded with the use of cocaine laced with this drug as discussed below.[1] Prior to the widespread use of levamisole in cocaine, it was shown to cause the same deleterious effect in the pediatric population in whom it was used in chemotherapy regimen.[2]

WHAT IS LEVAMISOLE

Levamisole is available as tablets, pastes, gels, soluble powder, feed premixes, topical solutions, and injectable solutions in veterinary pharmaceutics where it is used to treat worm infestations in the cattle, sheep, and pigs. Historically, it has been used to treat rheumatologic disorders and malignancies since it possesses immunosuppressive and immunomodulatory effects. United States Food and Drug Administration (US FDA) has approved it to be used along with 5% fluorouracil in the treatment of advanced colon cancer, but was later banned by the FDA.[3]

MECHANISM OF ACTION FOR VASCULITIS AND OTHER SIDE EFFECTS

Levamisole causes small vessel involvement of the skin among other organs by the direct toxic effect on the endothelial cells resulting in occlusion of the small cutaneous blood vessels. It acts as a hapten exposing the neutrophils to autoantibodies resulting in opsonization and destruction of the leucocytes. Levamisole also increases T-cell activation and proliferation.[4]

LEVAMISOLE AND COCAINE

A legal substance that is added to an illicit drug to increase the weight or volume of the drug is called a cutting agent. There are many theories to explain the use of levamisole as a cutting agent though not one can be proven to be definite. It is postulated that even though levamisole is not addictive, it can make cocaine more addictive. Levamisole may have been initially added to cocaine to trace its source of origin but given its current widespread use (69 % cocaine in the USA is contaminated with levamisole) it may have lost its relevance in that sense. Levamisole is known to cause local skin issues along with systemic problems. Local skin issues include retiform purpura, hemorrhagic bullae, purpuric plates, pyoderma gangrenosum. Systemic complications include agranulocytosis with leukopenia, arthralgia, necrotizing glomerulonephritis with pauci-immune deposits leading to renal failure, alveolar hemorrhage with pulmonary hemorrhage, leucoencephalopathy and seizures.

SEROLOGY

Serologically the antineutrophil cytoplasmic antibodies (ANCAs) are useful for diagnosis since they are discordant in their sensitivities. Perinuclear anti-neutrophil cytoplasmic antibodies tests positive for proteinase 3 (PR3) and cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) tested positive for myeloperoxidase (MPO). Atypical ANCA against hydroxynonenal (HNE), lactoferrin and cathepsin-G. Antinuclear antibodies (ANA) and antiphospholipid antibodies (APLA) are also found in low-levels.[5]

HEMATOLOGICAL MANIFESTATIONS

Patients with agranulocytosis present with nonspecific symptoms like weakness, malaise, muscle cramps, and chills. The neutrophils falls less than 20% of the normal number. Levamisole on repeated exposures is hypothesized to induce antibodies to neutrophils causing destruction. Antithrombin antibodies are also found in these patients.[6]

DERMATOLOGICAL MANIFESTATIONS

Levamisole is classically associated with purpura in the ear lobules and tip of the nose and upper extremities. They are reticulate in appearance and skin in the center undergoes necrosis with resulting ulceration. The pathology is proposed to be caused by immune deposits in the peripheral capillaries. Skin histopathology reveals vascular thrombosis along with vasculitis in some cases.[7] It has also been associated with eruptions of serpiginous ulcerated lesions with necrotic ulcer beds. Seen in both upper and lower extremities they resemble classic Pyoderma Gangrenosum lesions with necrotic ulcer beds.[8]

NEUROLOGICAL MANIFESTATIONS

Recently a patient with spastic paresis and severe stupor presented with magnetic resonance imaging (MRI) features of multifocal leukoencephalopathy. She tested positive for cocaine (laced with levamisole) and it resolved with immunosuppression. Levamisole in medical use has also been associated with ataxia and other neurological symptoms.[9]

NEPHROLOGICAL MANIFESTATIONS

What is interesting is that levamisole is known to decrease the recurrence of steroid-dependent membranous nephropathy in children. But in adults using cocaine adulterated with levamisole multiple cases of crescentric glomerulonephritis with ANCA associated vasculitis have been described. The patients present with fever, fatigue, skin ulcerations, dark urine, polyarthritis, and fluid overload among other symptoms.[10] The electron microscopic features include unusual deposits with medium electron density composed of granules, microspherules, and rare single fibrils.[11]

PULMONARY MANIFESTATIONS

Two patients were reported with findings of lung involvement on their autopsy. Lungs showed numerous lymphocytes surrounding and infiltrating the wall of small pulmonary vessels and a perivascular fibrosis with transforming fibroblasts.[12] Though the cause of demise was not from pulmonary involvement this gives to rise to speculation of underlying damage that is wreaked by using cocaine laced with levamisole. In patients presenting with hemoptysis, this can definitely be considered as a differential.

CONCLUSION

Given the widespread use of drugs of recreation, it is important for physicians to be aware of the various side effects caused by these drugs which may mimic known disease processes. Cocaine/Levamisole adulterated autoimmune syndrome (CLAAS) is one such phenomenon which can be life-threatening in some patients with widespread organ damage.[13] Neutrophil activation is key to neutrophil extracellular trap formation resulting in ANCA positivity. In most patients, stopping the cocaine use usually helps with disease cessation but immunomodulators are sometimes required. There is always a danger of recurrence with repeated cocaine use. In this era, where opioid use epidemic is a national emergency, we have to educate the patients and the medical community about the ever increasing burden of consequences of drug abuse.

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