ISMP Adverse Drug Reactions

Propofol-Related Infusion Syndrome (PRIS)^{1,2} Ivermectin-Induced Stevens-Johnson Syndrome Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis From Fexofenadine Memantine-Related Drug Eruption

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Propofol-Related Infusion Syndrome (PRIS)^{1,2}

Propofol-related infusion syndrome (PRIS) is a rare but often lethal complication associated with the use of propofol. The most common risk group for the development of PRIS are young, critically ill patients after neurosurgery while receiving vasopressors with the administration of propofol at a mean dose ≥ 4 to 5 mg/kg/h, over more than 48 hours duration. The clinical symptoms of PRIS include unexplained metabolic acidosis, rhabdomyolysis, renal failure, fever, hyperlipidemia, hyperkalemia, hepatomegaly, arrhythmia, and rapidly progressive cardiac failure. Proposed laboratory markers to monitor for patients with PRIS include lactate, troponin, creatine kinase, myoglobin, triglycerides, and the analysis of acylcarnitines. The analysis of acylcarnitines has become widely accepted as a helpful instrument to confirm the diagnosis of PRIS.

Patient 1¹ was a 30-year-old woman who underwent laparoscopic surgery with sedation provided by a propofol infusion at an average hourly rate of 3.3 mg/kg for approximately 6 hours. Three hours later, the patient demonstrated a mild unpredictable hypotension of 90/60 mm Hg for which dopamine was initiated for blood pressure support. At this time, a blood glucose measurement was 58 mg/dL (normal range, 70–110 mg/dL) followed by an arterial blood gas revealing metabolic acidosis with measurements of pH 6.91 (normal range, 7.33–7.45), pCO₂ 44 mm Hg (normal range, 35–45 mm Hg), pO₂ 104 mm Hg (normal range, 75–105 mm Hg), and blood glucose of 38 mg/dL. Over the next few hours, the patient's arterial pH ranged from 7.06 to 7.49 with a blood glucose of 198 to 216 mg/dL and an elevated lactate level. The patient remained unresponsive 3 hours after the conclusion of the propofol infusion, and a neurological examination yielded suspected brain damage. The patient subsequently had an magnetic resonance imaging (MRI) of the head, which revealed prominent bilateral lesions in the basal ganglia, temporal lobe, and cerebellum. The possible causes of bilateral basal ganglia MRI abnormalities include hypoxic-ischemic, toxic and metabolic, infectious, immune-mediated, mitochondrial, and neurodegenerative disorders.

Ten hours after the onset of this event, the patient had a creatinine kinase of 1644 IU/L (normal range, woman ≤ 170 IU/L). Two days later, the patient had a brain natriuretic peptide level of 1270 pg/mL (normal range, <100 pg/mL) which is suggestive of heart failure. It should be noted that the patient did not experience arrhythmias or hypoxia throughout their surgical procedure. The combination of lactic acidosis, elevated creatine kinase, and cardiac insufficiency in the context of propofol anesthesia suggested the diagnosis of propofol-related infusion syndrome (PRIS). As PRIS has been associated with mitochondrial DNA (mtDNA) mutations, a complete mtDNA sequencing was conducted and revealed no abnormalities. The patient's relatives refused further investigation and the patient eventually died due to refractory circulatory failure 16 days from the onset of her condition.

Patient 2² was a 19-year-old previously healthy man who was admitted to the hospital with left-sided hemiparesis after first-time alcohol intoxication. His medical history was negative for any disease state, allergies, or drug abuse. A large intracerebral hemorrhage was discovered on computed tomography (CT) scan and the patient was sent for surgery. The patient was intubated and propofol 5 mg/kg/h was initiated. Surgery included a craniotomy with resection of an arteriovenous malformation and evacuation of the intracerebral hemorrhage.

During the first 4 days, postoperatively the patient experienced inflammation, impaired coagulation, continuously elevated intracranial pressure, diabetes insipidus, and brain edema. On the fifth postoperative day, the patient underwent a second surgery to release intracranial pressure. After surgery, the patient experienced tachyarrhythmias with a heart rate of 130 to 140 bpm. Elevated doses of catecholamines were

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necessary to maintain cardiovascular circulation. The patient also had an elevated troponin of 16.5 $\mu\text{g/L}$ (normal range, ≤ 0.1 $\mu\text{g/L}$). In light of the elevated troponin, the patient underwent a coronary angiography, which revealed unremarkable coronary arteries; however, the patient did have impaired systolic left ventricular function. Within a few hours, bradyarrhythmias with subsequent asystole emerged requiring an external pacemaker and frequent mechanical resuscitation. In addition, the patient developed a fever, anuria, hyperkalemia, and metabolic acidosis. Sadly, the patient expired 8 hours after his second surgery. He had received a propofol infusion for a total of 132 hours at an average dose of 4.6 mg/kg/h.

Postmortem tissue samples had been obtained of the patient's heart muscle from the ventricles, skeletal muscle, and liver. Autopsy results revealed massive steatosis of the liver and biventricular cardiac thickening. Also detected were microvesicular fatty degeneration of the hepatocytes, myocardial edema, and disseminated necrosis of heart muscle cells. Histological analysis of the skeletal muscle indicated the patient had rhabdomyolysis. The mitochondria of skeletal muscle samples revealed a disintegration of the outer membrane and a loss of cristae. Prior to the patient's death, blood samples were drawn and analyzed for acylcarnitines. Concentrations of several short-chain acylcarnitines showed considerable increases in comparison with a healthy individual: C2-carnitine, 16.712 $\mu\text{mol/L}$ vs 1.036 $\mu\text{mol/L}$; C4-carnitine, 7.125 $\mu\text{mol/L}$ vs 0.059 $\mu\text{mol/L}$, and C5-carnitine 4.957 $\mu\text{mol/L}$ vs 0.073 $\mu\text{mol/L}$.

Prior research has hypothesized that the impairment of mitochondrial fatty acid oxidation is the probable main cause of PRIS. Vollmer et al² conducted electron microscopic analysis of the patient's heart muscle tissue which showed prominent electron dense structures clearly associated with the mitochondria. These electron dense structures might be composed of accumulated free fatty acids that did not pass the mitochondrial membrane caused by propofol. Their analysis gives evidence that mitochondria of cardiac muscle seem to be the centrally affected structure in PRIS and may explain the dramatic and self-accelerating process with initial arrhythmias rapidly leading into progressive cardiac decompensation. The authors call for the development of suitable diagnostic and predictive tools for the detection and prevention of PRIS.

Ivermectin-Induced Stevens-Johnson Syndrome³

A 38-year-old man received a 12 mg oral dose of ivermectin as part of a nationwide campaign against worm parasitic disease in the Republic of Cameroon. The next day, the patient noted that he had blisters on his lips, which later extended to involve his oral mucosa. These symptoms were also associated with pain while chewing and soreness of his entire oral mucosa, which impaired his ability to eat. The patient also developed a rash on his face. The rash was scaly and extended

toward the patient's hairline. The next day, the patient noted that his eyes became reddish, itchy, painful, and began to discharge a clear fluid. At this time, the patient decided to seek medical attention for his condition.

A medication history revealed that the patient had not ingested any other drug besides ivermectin. He did remember receiving a dose of ivermectin 1 year earlier during a similar disease campaign but he did not experience any adverse effects. The patient reported he was human immunodeficiency virus (HIV) negative based on an HIV test conducted 6 months earlier but he did not have any documentation. However, he reported his wife is HIV positive and was currently receiving highly active antiretroviral therapy. The patient reported he did not have any chronic diseases and denied having any food or drug allergies. Physical exam revealed desquamating hyperpigmented rashes on his face with whitish plaques. The rashes were on the nasal bridge and extended to the malar area, sparing the nostrils. There were black eschars and erythematous erosions on the lips with sores and blisters in the oral mucosa. His eyes were erythematous, tearing, and had sticky secretions that made his eyelids difficult to separate.

The patient was suspected of having Stevens-Johnson syndrome (SJS). He was tested for HIV and a first-line HIV test was positive. In addition, a repeat first-line HIV test and a second-line HIV test confirmed his HIV positive status. A subsequent CD4 count was 568 cells/mm³ (normal range, 500-1400 cells/mm³). Baseline laboratory tests were unremarkable as they demonstrated a normal complete blood count, liver enzymes, and kidney function. The patient was treated with an intramuscular dose of dexamethasone 4 mg followed by 15 days of a prednisone taper starting at 20 mg of prednisone twice daily. He was also given oral antihistamines, ciprofloxacin eye drops, and oral hygiene. Within 1 week, the patient's symptoms improved and most lesions had resolved within 3 weeks.

The authors point out that the antimicrobials that are commonly associated with causing SJS include sulfonamides and aminopenicillins. Those less frequently associated with SJS are cephalosporins, fluoroquinolones, vancomycin, and anti-tuberculosis medications. Additional antimicrobials such as fluconazole and streptomycin have also been associated with causing SJS. This patient had previously ingested ivermectin at the same dose 1 year earlier with no reaction. However, after his current dose of ivermectin, he experienced SJS. This may suggest that this case of SJS caused by ivermectin may be idiosyncratic because it seems to be dose-independent. An interesting fact is that 1 year earlier when the patient received his first dose of ivermectin, the patient was confirmed HIV negative. However, he developed SJS during the current ingestion of ivermectin when he confirmed to be HIV positive. The authors conclude that there may be a link between HIV infection and ivermectin-induced SJS, as underlying diseases especially those that impair immunity may have a role in the development of SJS and HIV-seropositive patients have a higher incidence of SJS.

Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis From Fexofenadine⁴

A middle-aged woman presented to her physician with a sore throat, eye redness, and rhinitis. She was prescribed amoxicillin clavulanate for 5 days along with fusidic acid eye ointment. The patient's symptoms continued to worsen and she self-medicated with acetaminophen and ibuprofen. Six days after visiting her physician, she started fexofenadine with pseudoephedrine twice daily. After 2 doses of fexofenadine/pseudoephedrine, the patient noticed lip swelling. Her other symptoms persisted, and her ear, nose and throat specialist changed her antibiotic to clarithromycin and she was advised to continue taking her fexofenadine/pseudoephedrine.

The patient took 2 more doses of fexofenadine/pseudoephedrine, and on day 8, she developed more swelling and blisters on her lips and presented to the emergency department. She was treated with intravenous hydrocortisone, oral promethazine, and cetirizine/pseudoephedrine. The next day the patient was admitted to the hospital with a high fever of 39.5°C (103.1°F) and erythematous non-blanchable, dusky target lesions over her face, trunk, and limbs which affected 20% of her body surface area. She also had blistering with a positive Nikolsky sign (this sign is present when slight rubbing of the skin results in exfoliation of the outermost layer) over less than 1% of her skin and bilateral conjunctivitis, hemorrhagic cheilitis, and buccal mucosal erosions.

The patient was treated for Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) overlap with topical corticosteroids, cetirizine, and cyclosporin 1.5 mg/kg twice daily. The patient had a skin biopsy, which revealed full-thickness epidermal necrolysis. In addition, all tests for Epstein-Barr virus, cytomegalovirus, HIV, hepatitis, human herpesvirus, and *Mycoplasma pneumoniae* as well as others were negative. The patient recovered and had full reepithelialization of her skin after 50 days.

Ten weeks after her reaction, the patient underwent skin tests for all of the medications she had received prior to her episode of SJS/TEN. A patch test was clearly positive for fexofenadine/pseudoephedrine while all other medications were negative. Additional testing of fexofenadine alone versus fexofenadine/pseudoephedrine revealed a positive patch test for both test patches. The patient was advised to not consume products containing fexofenadine in the future.

Memantine-Related Drug Eruption⁵

An 89-year-old man was treated for the past 2 months with memantine and donepezil for his Alzheimer disease. The patient noticed erythematous eruptions on his trunk and extremities and sought medical attention. The patient's physical exam revealed palpable scaly erythema and papules located on his extremities and trunk. His skin eruptions were mainly concentrated on bent or curved areas of his trunk and extremities. A medication history revealed the patient was receiving no additional medications and was only receiving donepezil and memantine. The patient also did not have a history of allergic skin disease.

The patient's physician performed a lymphocyte stimulation test (LST) to identify the causative drug. The results of the LST revealed a significant stimulation index for memantine, which indicated that this was the causative agent for the patient's skin eruptions. The patient denied further cutaneous testing. Treatment was initiated with betamethasone ointment, and memantine therapy was discontinued immediately. The patient's skin eruptions began to improve with this treatment and the continuation of donepezil. The patient's skin eruptions did not reappear after the discontinuation of betamethasone.

The authors examined the chemical structure of memantine and noted that it is an adamantane derivative with 3 connected cyclohexane rings. There are several adamantane derivative medications on the market worldwide and they are amantadine and vildagliptin. The possible cross-reactivity between drugs, which are adamantane derivatives, can be a clinical concern for future pharmacotherapy in this patient. The authors conducted an LST with the patient's lymphocytes, which reacted to amantadine, and vildagliptin with an elevated LST index. This indicates that the patient might experience cutaneous adverse reactions with these adamantane derivatives because of cross-reactivity to the adamantane chemical structure.

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