ISMP Adverse Drug Reactions

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of revention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA) MedWatch program (800-BDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with ur readers. E-mail Dr. Mancano michael.mancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

Adalimumab-Induced Aseptic Meningitis¹

A 40-year-old woman received adalimumab for 11 days (80 mg then 40 mg 1 week later) to manage her chronic plaque psoriasis when she developed persistent frontotemporal headaches, vomiting, photophobia, neck ache, and fever. For the 15 months before initiating adalimumab, she was taking cyclosporin 250 mg/day which was then dose reduced to 200 mg/day once she started adalimumab. Based on her symptoms and physical examination which included mild nuchal rigidity without focal deficits and psoriatic plaques all over her trunk and thighs, she was treated for meningoencephalitis with ceftriaxone, ampicillin, and acyclovir.

The patient's abnormal lab values included the following: serum C-reactive protein of 47.5 mg/L (normal range, $\leq$ 5mg/L), hemoglobin of 9.6 g/dL (normal range, 11-15 g/dL), a white cell count of 9.5×10^9 /L (normal range, $3.6-9.3 \times 10^9$ /L), a platelet count of 516×10^9 /L (normal range, $170-420 \times 10^9$ /L), CSF: 752 red cells/ μ L (normal range, <1 cell/ μ L), and 37 nucleated cells/ μ L (normal range, 0-5 cells/ μ L), and cerebrospinal fluid (CSF) protein of 0.84 g/L (normal range, 0.1-0.4 g/L). The following tests were all negative or unremarkable: gram stain, bacterial culture, complement fixation testing for herpes simplex virus, mumps virus, and measles virus in CSF and herpes polymerase chain reaction (PCR) assay. Because she was just initiated on adalimumab, it was discontinued and the patient improved over 1 week with resolution of her symptoms and no neurological sequelae. Because of her symptoms and CSF studies, she was diagnosed with aseptic meningitis with the most probable cause being adalimumab.

Drug-induced aseptic meningitis is a rare disease with only 194 cases reported in literature. Common culprits in drug-induced aseptic meningitis are monoclonal antibodies, in particular tumor necrosis factor α inhibitors which have neurological side effects of headache, demyelinating events, and aseptic meningitis. Because there has been an increased use of monoclonal antibodies, the risk of experiencing this adverse effect has also increased. TAAM, also known as TNF- α inhibitor (TNF α -i)-associated aseptic meningitis, differs from drug-induced aseptic meningitis in that CSF pleocytosis can be either lymphocyte or neutrophil predominant and it equally affects both genders. The authors note that the pathophysiology of TAAM remains unclear. Direct toxic effects appear unlikely, because TNF α -i cannot cross the blood-brain barrier. In cases with associated myalgia and arthralgia, a type III hypersensitivity reaction akin to serum sickness mediated by drug auto-antibodies has been postulated.

Pill Desiccant-Induced Acute Hypoxic Respiratory Failure²

A 77-year-old man with a medical history of diabetic retinopathy and vitreous hemorrhage causing visual impairment

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presented to the hospital with an inability to swallow liquids or handle secretions. He reported not being able to tell the difference between his amoxicillin/clavulanate tablet and the desiccant in the bottle. The patient apparently accidentally ingested the desiccant. After presentation to the hospital, he quickly developed respiratory distress due to aspiration of his secretions and needed to be intubated. Esophagogastroduodenoscopy (EGD) was performed and the desiccant was pushed into his stomach to prevent further harm because removal upward would cause significant esophageal trauma. The next day, the patient self-extubated and returned to normal swallowing and bowel function but refused reintubation despite the desiccant not being recovered. The patient continued to have respiratory distress and died within a few days from hypoxic respiratory failure.

The authors state that many ideas have been recommended to help prevent these types of adverse drug reactions, most importantly educating the patients about their unique risk for accidental adverse drug events. Additional ideas include making the desiccant a different color and shape than the pill, anchoring the desiccant to the bottom of the pill bottle and for pharmacists to counsel on the presence of a desiccant to elderly patients. Specific strategies for elderly patients need to be created and practiced to ameliorate patient safety and overall health.

Rivastigmine Patch–Induced Angioedema³

An 84-year-old woman was admitted to the emergency department with complaints of nausea, vomiting, dizziness, confusion, lethargy, and swelling of the lips and tongue. The patient was started on rivastigmine patch 5 cm²/daily for Alzheimer dementia 1 month prior to this event and her dose was increased to 10 cm²/day 3 days prior. A medication history revealed that the patient was also receiving lisinopril plus hydrochlorothiazide 20/25 mg daily, nifedipine 30 mg daily for hypertension, escitalopram 10 mg daily for depression, calcium carbonate plus vitamin D3 880 IU daily, and alendronate 70 mg once weekly for osteoporosis. Therefore, the only new medication the patient had recently initiated was rivastigmine.

On presentation, her blood pressure was 120/56 mm Hg and other vitals were within normal limits. There was swelling of the lower lip, tongue, and upper and lower eyelids. She appeared confused and lethargic. Basic lab values including hematology, renal, and hepatic function were unremarkable. Her angioedema was treated with one dose of an antihistamine, methylprednisolone 60 mg, 5% dextrose 100 mL, and oxygen 2 L/min via nasal cannula. Her rivastigmine patch was discontinued; however, she continued to receive all of her chronic medications. The patient achieved a full recovery 2 days later and was ultimately diagnosed with angioedema due to rivastigmine.

Adverse skin reactions due to the rivastigmine patch are either local irritation or immunological allergic reactions. Angioedema is caused by the generation of bradykinin, the activation of mast cells, and the release of histamine. In this case, this cascade of events could have been caused by the active ingredient rivastigmine, various excipients within the patch, a combination of both, or concomitant use of lisinopril. The release of acetylcholine by parasympathetic neurons reportedly contributes to the development of hypersensitivity reactions. Acetylcholine esterase inhibitors increase the amount of acetylcholine at the synapses in the ganglion. This patient's advanced age, sex, and genetic tendency to develop allergic diseases could precipitate this allergic reaction. The authors are unclear whether cholinergic toxicity caused the inflammatory reaction in this patient. They recommend that while rivastigmine-induced angioedema is uncommon, health care professionals treating dementia should keep this type of adverse reaction in mind when prescribing and counseling patients and caregivers on transdermal rivastigmine.

Acute Liver Failure Due to Etodolac⁴

Taneja et al report on 2 patients who experienced acute liver failure due to etodolac. Patient 1 is a 27-year-old woman who received etodolac 400 mg and acetaminophen 500 mg fixed-dose combination twice a day as an analgesic for a right forearm fracture. Prior to admission, this patient's liver function tests were within normal limits and she had no history of liver disease. She developed nausea and vomiting with no associated abdominal pain, distension, constipation, obstipation, or fever within 48 hours of treatment. Her symptoms worsened the following day and she became drowsy and icteric and sought treatment. On admission, she was found to be drowsy but responsive, icteric, and had flapping tremors suggestive of grade 2 hepatic encephalopathy (West Haven Criteria).

Liver function tests drawn at this time revealed the patient had a total bilirubin of 4.3 mg/dL (normal range, 0.3–1.2 mg/dL), conjugated bilirubin of 2.0 mg/dL (normal range, $\leq$ 0.4 mg/dL), aspartate transaminase (AST) of 3623 U/L (normal range, 10–30 U/L), alanine transaminase (ALT) of 6060 U/L (normal range, 10–40 U/L), alkaline phosphatase of 229 U/L (normal range, 30–120 U/L), international normalized ratio (INR) 6.7 (normal range, 1–1.3), and serum creatinine of 1.6 mg/dL (normal range, female: 0.6–1.1 mg/dL). Arterial blood gas analysis revealed severe metabolic and lactic acidosis with a pH of 6.9 (normal range, 7.35–7.45) and a bicarbonate of 2.9 mEq/L (normal range, 21–28 mEq/L). The patient had recurrent episodes of hypoglycemia and arterial ammonia levels of 559 μ g/dL (normal range, 15–45 μ g/dL) on admission. An ultrasound showed an enlarged liver of 12.4 cm (mean liver size is 7 cm for women). Computerized tomography (CT) of the head was suggestive of cerebral edema. Additional lab tests including; hepatitis

B surface antigen, IgM hepatitis B core antibody, anti-hepatitis C virus antibody, serologies for hepatitis A and E, cytomegalovirus, Epstein bar virus and herpes simplex virus, autoimmune markers including antinuclear, antimitochondrial, anti-smooth muscle, and anti-liver kidney muscle antibodies were all found to be negative.

The patient's Model for End-Stage Liver Disease score (MELD) was 38 on admission and she was counseled on the need for an urgent liver transplant. The MELD score is a reliable measure of mortality risk in patients with end-stage liver disease, and it is used as a disease severity index to help prioritize allocation of organs for transplant. The patient refused transplantation and was conservatively managed in the intensive care unit. Her encephalopathy worsened to grade IV and she died 4 days after admission due to increased intracranial tension and multiple organ dysfunction. Due to the absence of other possible causes for acute liver failure and the recent initiation of etodolac along with a recent dose increase, the authors concluded the patient experienced etodolac-induced liver disease that lead to acute liver failure.

Patient 2 is an 80-year-old woman with a medical history of diabetes, hypertension, and bilateral knee osteoarthritis. She developed nausea and vomiting after taking 2 doses of etodolac 400 mg and acetaminophen 500 mg fixed-dose combination as an analgesic for knee osteoarthritis. The following day she became drowsy and exhibited jaundice. A medication history revealed her other chronic medications were metformin and amlodipine, which she had been stable on for several years. She denied the use of herbal or complementary remedies. Prior to the start of etodolac, multiple liver function tests and imaging studies were found to be within normal limits.

On presentation, the patient was found to have jaundice, drowsiness, and flapping tremors suggestive of grade 2 hepatic encephalopathy. Her liver function tests revealed total bilirubin of 4.4 mg/dL, conjugated bilirubin 2.8 mg/dL, AST 6510 U/L, ALT 6896 U/L, alkaline phosphatase (ALP) 78 IU/L, and a blood urea nitrogen of 28 mg/dL (normal range, 8-23 mg/dL). Her creatinine was 1.3 mg/dL and she had an INR of 4.0. The patient's arterial ammonia on admission was 511 µg/dL and a CT of the head suggested cerebral edema. The ultrasound of the liver and etiological studies, as used with patient 1, were unremarkable. Over the next 2 days, her encephalopathy increased to Grade IV, she was anuric, and her serum creatinine increased to 7 mg/dL. She was conservatively managed in the liver intensive care unit and developed pneumonia and candidemia during her hospital stay. These were successfully treated with broad-spectrum antibiotics and antifungals. She was hospitalized for a total of 45 days and diagnosed with etodolac-induced DILI (drug-induced liver injury) leading to acute liver failure because she had no other etiologies for acute hepatic failure and recent new use of etodolac.

The authors noted that idiosyncratic DILI commonly causes acute liver failure. The most common drug class causing DILI is antibiotics, followed by herbal supplements, antiepileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Etodolac is a cyclooxygenase-2 (COX-2) selective NSAID that is commonly used as an analgesic and anti-inflammatory agent in musculoskeletal disease. Severe hepatic impairment is extremely rare with this drug; however, if it occurs it can present within a few days of initiation. Etodolac-induced hepatotoxicity, though extremely rare, may lead to severe hepatic failure. Health care professionals should keep this potential adverse reaction in mind when prescribing this drug and should closely monitor any patients that develop symptoms of hepatotoxicity.

Severe Cognitive Impairment Due to High Free Valproic Acid Levels⁵

A 66-year-old woman with an 18-year history of bipolar disorder was initiated on valproic acid (VPA) after she experienced lithium encephalopathy. She had been stable on lithium for 15 years prior but nephrotic syndrome may have precipitated the patient's lithium encephalopathy. She was hypomanic and was started on VPA 300 mg/day (day 1) and referred to the outpatient psychiatric clinic. On day 13 of VPA therapy, the patient had no cognitive impairment with a Montreal cognitive assessment (MoCA) score of 24/30 (normal range ≥ 26) during hypomania. On day 18, multiple blood tests were drawn and the results are as follows: total VPA concentration (tVPAC) 21 mg/L (normal range, 40-120 mg/L), erythrocyte sedimentation rate 108 mm/h (normal range, 1-30 mm/h), glomerular filtration rate (GFR) 53 mL/min/1.73 m² (normal, ≥ 90 mL/min/1.73 m²) and albumin 23 g/L (normal range, 35-55 g/L). The patient's VPA dosage was gradually increased to a maximum recommended dose of 2500 mg/day. On day 49, a tVPAC level was drawn and revealed a level of 30 mg/L (normal range, 40-120 mg/L). Concomitantly, her liver function tests were all within normal range and no drug interactions were noted that could have induced a low tVPAC level.

At this time, the patient shifted from hypomania to mania which resulted in reintroduction of lithium and the VPA was continued. Reintroduction of lithium failed twice, first on day 66 due to concurrent deliria and on day 80 due to urinary retention. As mania worsened, on day 77, VPA was increased to 4000 mg/day exceeding the approved maximum dose by 700 mg based on patient weight (maximum dose 60 mg/kg). On day 81, a tVPAC was 59 mg/L and the patient was disoriented and was sometimes able to answer questions. The patient had moderate cognitive impairment based on Global Deterioration Scale (GDS) 4 of 7 (normal, 1 of 7). On day 90, lithium 400 mg was started and on day 94, it was increased to 800 mg/d. On day 96, the patient started to experience hypotension, disorientation, and somnolence. Day 98, the

patient was transferred to the internal medicine service as she experienced pancytopenia which resulted in the discontinuation of her cyclophosphamide. On day 99, a lithium level was drawn of 1.3 mmol/L (normal range, 0.4-0.8 mmol/L) which resulted in lithium being held. On day 109, patient's MoCA score declined to 15/30 (normal range, ≥ 26) and Mini mental examination was 20/30 (normal range, 27-30). The patient's cognitive function further deteriorated post lithium cessation. As a precaution, on day 118, the patient's VPA dose was reduced from 4000 mg/day to 3000 mg/day. On day 124, the patient's albumin level had dropped to 1.4 g/dL (normal range, 3.5-5.5 g/dL) and GDS score was 6 (normal, 1 of 7). The patient became disinterested, lost motivation to continue living, lost motivation to eat, drink, and needed a wheelchair. On day 126, VPA was stopped immediately after a free VPA concentration of 15.8 mg/L (reference range, 4-12 mg/L) and tVPAC of 24 mg/L (normal range, 40-120 mg/L). It was retrospectively determined that on day 113, the free concentration of VPA was 37.8 mg/L with tVPAC of 68 mg/L. On day 130, patient went into VPA withdrawal and switched from hyperactive delirium to having a seizure. Olanzapine 5 mg was started and the patient regained cognitive, will to live, and physical functioning within days while regaining the ability to complete activities of daily living. On day 154, patient was transferred to the psychiatric medicine unit for further recovery. Her liver function tests were within normal range except for AST 58 U/L (normal range, 10-40 U/L) and ALT 127 U/L (normal range, 7-56 U/L). The patient's Mini mental status examination 27/30 (normal range, 27-30), MoCA 27/30 (normal range, ≥ 26) and GDS 1 (normal range, 1 of 7). On day 197, patient was discharged and later that year lithium was reintroduced without problems.

The authors point out the difficulty in diagnosing VPA causing dementia and cognitive impairment. The difficulty is that dementia and cognitive impairment can be symptoms of the disease VPA is trying to treat, particularly bipolar depression and mania, resulting in misinterpretation. It becomes even more difficult to recognize that the symptoms are caused by VPA when the total VPA serum levels are within reference range. In this patient, VPA was neglected as a casual factor because tVPAC was below or within the reference range. However, not until the free concentration of VPA was

measured which indicated that the VPA levels were far above the reference range and more likely the cause of severe cognitive impairment. The free concentration of VPA was considered because VPA is 80% to 95% protein bound to albumin.

The authors conclude that this case report suggests that it is necessary to monitor the free concentration of VPA in hypoalbuminemic patients to prevent misinterpretation of adverse effects or toxicity particularly in the elderly as there is evidence that VPA affinity for serum proteins decreases with age resulting in an increase in free fraction of VPA. They also note that research has shown that there may be a link with VPA-induced encephalopathy due to hyperammonemia as there have been other case studies published on VPA-induced encephalopathy due to hyperammonemia. However, in this case study ammonia was not measured and could have contributed to the patient's symptoms.

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