ISMP Adverse Drug Reactions

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Medications with Anticholinergic Effects and Their Implications in the Elderly

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MEDWATCH program (800-FDA-1088). If you have reported an interesting, preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@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.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS DUE TO LABETALOL

A 31-year-old pregnant female in the third trimester of pregnancy was treated with labetalol for 18 days with the addition of hydralazine, methyldopa, and methimazole during the 3 days prior to her caesarean section. Approximately 8 hours prior to delivery, the patient developed erythematous micropapular lesions on her face and neck with a fever of 38.7°C (101.7°F). These lesions became generalized over 4 to 5 days, affecting flexures, the intermammary cleft,

chest, back, palms of the hands, and soles of the feet with multiple micropustules. The patient also experienced mild dermal itching and discomfort when swallowing. On the second day of the skin eruption, methyldopa, methimazole, and hydralazine were discontinued, however new lesions continued to appear. Labetalol was discontinued; on the fifth day after discontinuing labetalol, no new lesions appeared.

A complete blood count (CBC) revealed leukocytes $20.3 \times 10^3/\mu\text{L}$ (normal range, $4.1\text{--}10.9 \times 10^3/\mu\text{L}$), neutrophils 90% (normal value, 54%–62%), 5%

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lymphocytes (normal value, 25%-33%), 5% monocytes (normal value, 3%-7%), with all other values within normal limits. Liver function testing also revealed an aspartate aminotransferase (AST) 37 IU/L (normal value, <35 IU/L), alanine aminotransferase (ALT) 72 IU/L (normal value, 10-35 IU/L), gamma-glutamyl transferase (GGT) 125 IU/L (normal value, 7-51 IU/L), and alkaline phosphatase 234 IU/L (normal value, 44-147 IU/L). Pustule contents were cultured, however the results were negative.

One month after the onset of her rash, the patient underwent a patch test with labetalol, methimazole, hydralazine, and methyldopa; there was a positive reaction only with labetalol. She also exhibited pustules in the labetalol-tested area. She then received a challenge test with methyldopa, methimazole, and hydralazine, and she tolerated all of the medications as well. The patient was subsequently patch tested with atenolol to find an alternative beta blocker that she could tolerate. The atenolol patch testing was negative; the patient then received an oral dose of atenolol 25 mg. One hour after receiving the oral atenolol, the patient complained of generalized itching and micropapules on her back and palms that persisted for 48 hours. The patient received methylprednisolone for 48 hours as treatment.

The patient was diagnosed with acute generalized exanthematous pustulosis (AGEP) due to labetalol with cross-sensitivity to atenolol. AGEP is an uncommon skin eruption characterized by superficial pustules. Typically the AGEP rash starts on the face or in the armpits and groin and then becomes more widespread. It is characterized by the rapid appearance of areas of red skin studded with small blisters filled with white/yellow fluid. There tends to be more disease in skin folds, and facial swelling often arises. AGEP may be associated with a fever and malaise. The rash may last for 1 to 2 weeks, and then the skin peels off the affected areas as it resolves. Increased neutrophils are usually found on blood testing, with skin biopsy showing subcorneal pustules filled with neutrophils.

The authors point out that 90% of cases of AGEP are caused by drugs. Case reports for AGEP have been reported for beta lactam antibiotics, macrolide antibiotics, hydroxychloroquine, cotrimoxazole, terbinafine, metronidazole, nystatin, diltiazem, acetaminophen, celecoxib, carbamazepine, povidone-iodine, allopurinol, metformin, sildenafil, abacavir, and quinolone antibiotics. Nondrug causes of AGEP can be viral infections, exposure to mercury, or ingestion of food allergens.

The authors warn that even though AGEP generally has a good prognosis, it has a mortality rate of approximately 5%. In light of the fact that the patient had a negative patch test with atenolol, the authors warn that negative patch testing results do not rule out the involvement of a specific drug. It is best to perform intradermal tests with the suspected drug, and a late reading is recommended.

Torrijos G, Rodriguez G, Caminero S, et al. First case of acute generalized exanthematous pustulosis due to labetalol. *J Investig Allergol Clin Immunol*. 2015;25(2):148-149.

DRUG FEVER AND LEUKOCYTOSIS CAUSED BY TIGECYCLINE

A 62-year-old male presented with aspiration pneumonia and received broad-spectrum antibiotics at another hospital until transfer. After transfer, the patient had a positive sputum culture with *Klebsiella pneumoniae* (multi-drug resistant, sensitive to tetracycline), and chest CT scan revealed bilateral lower lobe effusions and bilateral pleural effusions. His condition rapidly progressed, and he developed type I respiratory failure. The patient was weak and unconscious with a fever of 38.7°C (101.7°F), blood pressure of 149/75 mm Hg, and tachypnea of 30 breaths per minute. His antibiotic therapy was changed to tigecycline (*Tygacil*) 50 mg and vancomycin 1 g, both every 12 hours. Voriconazole 200 mg every 12 hours was added as empiric antifungal therapy. The patient gradually responded to therapy and his temperature normalized. He returned to consciousness and his signs and symptoms of pneumonia improved. After 2 week of therapy, the patient's voriconazole and vancomycin were discontinued, but his tigecycline was continued as his condition continued to stabilize.

During the patient's third week of tigecycline therapy, he developed a scattered rash on both legs and his temperature rose to 39°C (102.2°F), however the signs and symptoms of pneumonia did not worsen. The patient's leukocytes increased to $38.25 \times 10^3/\mu\text{L}$ from $13.34 \times 10^3/\mu\text{L}$ (normal range, $4.1\text{--}10.9 \times 10^3/\mu\text{L}$), with neutrophils of 83.2% (normal value, 54%-62%), 9.8% lymphocytes (normal value, 25%-33%), and 0.2% eosinophils (normal value, 1%-3%). Inflammatory markers were elevated with an erythrocyte sedimentation rate (ESR) of 58 mm/h (normal value, <17 mm/h) and C-reactive protein (CRP) of 108 mg/L (normal value, <10 mg/L). Repeat blood cultures and rapid TB testing were negative. Testing for T-cell subsets revealed that CD8+T cells were abnormally activated. Since the patient's fever

and leukocytosis could not be explained by infection or other causes and tigecycline was the only medication the patient was receiving, it was likely that tigecycline had induced the fever and leukocytosis.

Tigecycline was discontinued 2 days after the fever and leukocytosis occurred. Over the next 48 hours, the patient's fever, leukocytosis, and lower extremity rash gradually decreased. This time frame is consistent with the half-life of tigecycline of 42.4 hours. Four days later, the patient was given dexamethasone 2 mg daily for 3 days and his temperature, white blood cell (WBC) count, and inflammatory markers continued to decrease. A chest CT scan showed significantly improved pleural effusion on the right side and the absence of pleural effusion on the left side. The patient continued to recover and was discharged from the hospital 18 days later. He continued to be asymptomatic at his 3-month follow-up appointment.

The authors analyzed the possibility of tigecycline-induced leukocytosis and fever in their patient. Tigecycline is a tetracycline antimicrobial agent and minocycline has been reported to cause fever and leukocytosis. Case reports have reported that minocycline serves as a cytokine, which induces neutrophil movement from bone marrow into the circulation and results in leukocytosis. The authors theorize that since tigecycline and minocycline are both tetracycline derivatives, it is reasonable to conclude that they have the potential to induce similar hypersensitivities. The authors recommend that monitoring of T-cell subsets may help to recognize hypersensitivity in the early stage and facilitate early identification of hypersensitivity.

Shao QQ, Qin L, Ruan GR, et al. Tigecycline-induced drug fever and leukemoid reaction, a case report. *Medicine*. 2015;45:1-3.

TOXIC HEPATITIS INDUCED BY METHYLPREDNISOLONE INTRAVENOUS PULSE DOSING

The authors report 4 cases of liver injury after receiving intravenous methylprednisolone for the first time in doses of 1 g to 5 g for the treatment of multiple sclerosis relapse. Patient 1 was a 50-year-old female whose transaminases began to increase 4 days after treatment. Her transaminases peaked on day 8 with an AST 136 IU/L (normal value, < 35 IU/L), ALT 355 IU/L (normal value, 10-35 IU/L), and GGT 346 IU/L (normal value, 7-51 IU/L), and they normalized on day 24. Patient 2 was a 30-year-old female whose transaminases began increasing on day 3 and peaked on day 6 with an AST 157 IU/L

and ALT 627 IU/L, which normalized within 2 weeks. Patient number 3 was a 38-year-old female whose transaminases peaked after 2 months with an AST 109 IU/L, ALT 260 IU/L, and GGT 54 IU/L. Her elevated values normalized in another month. The fourth patient was a 24-year-old female who received intravenous methylprednisolone in February followed by a 1-month oral methylprednisolone taper. Before the patient's next dose in July, her transaminases were elevated with an AST 211 IU/L and ALT 494 IU/L. After receiving her July dose of methylprednisolone, her transaminases were elevated in September with an AST 315 IU/L, ALT 671 IU/L, and GGT 89 IU/L. The patient had an abdominal ultrasound that revealed liver steatosis, and her transaminases returned to normal by November. In December, the patient received a rechallenge dose of intravenous methylprednisolone, and her transaminases increased over 1 week to an AST 37 IU/L and ALT 104 IU/L. Patients 3 and 4 received liver biopsies that both showed inflammatory infiltrates, necrosis, fibrosis, and numerous macrophages.

The authors suggest that the hepatitis in their patients was probably related to an idiosyncratic reaction to intravenous methylprednisolone treatment. They suggest that glucocorticoid-induced liver toxicity is probably more frequent than it may appear. As a consequence, treatment of multiple sclerosis relapses becomes challenging if intravenous steroids are not a safe choice, considering that only approximately one-third of patients respond to treatment. The authors call for further studies on current second-line and third-line treatments such as plasma exchange and intravenous immunoglobulins and other possible alternative regimens to offer alternatives to patients who experience liver toxicity with pulse dose methylprednisolone.

Ferraro D, Mirante VG, Losi L, et al. Methylprednisolone-induced toxic hepatitis after intravenous pulsed therapy for multiple sclerosis. *Neurologist*. 2015;19(6):153-154.

MITOXANTRONE-RELATED OSTEONECROSIS OF THE JAW

A 58-year-old female with a history of infiltrating ductal carcinoma of the right breast, which had been treated with radical mastectomy, doxorubicin, cyclophosphamide, radiation therapy, and tamoxifen, was disease free for 13 years. The patient then developed pleural metastases and was treated with letrozole. Her disease progressed to her bones and liver, and she was initiated on zoledronic acid 4 mg as a 15-minute

intravenous infusion every 3 to 4 weeks for 24 cycles. The patient had no oral problems during zoledronic acid treatment.

Due to the patient's worsening metastases, she was started on mitoxantrone (*Novantrone*) 10 mg/m²/day. The patient developed oral mucositis and severe diarrhea, and the second cycle of mitoxantrone was discontinued. The patient developed multiple ulcers on her lower and upper gingiva, which were managed with chlorhexidine 0.12% mouthwashes. Her gingival ulcers persisted and extensive bone was exposed in both jaws. The ulcers were painful and were accompanied by generalized diffuse gingivitis. The patient's ulcerations persisted and the underlying bone became exposed and finally necrotic after 2 months. The patient was diagnosed with medication-related osteonecrosis of the jaws (MRONJ).

The patient had dental x-rays, gingival biopsy samples, and direct immunofluorescence to rule out mucocutaneous diseases as a cause for her condition. Histopathological study of the bone revealed areas with bony structures showing wide acellular necrotic sequestra and large, scalloped Haversian canals containing inflammatory cells. All of the findings confirmed the diagnosis of MRONJ. The patient continued to receive basic periodontal treatment to eliminate dental plaque. She was maintained on chlorhexidine mouthwashes; after 4 months, there was improvement in the patient's gingivitis. The patient's multiple bones exposures increased and were still present 6 months after their first appearance. The patient's cancer progressed, and she died from her cancer with MRONJ lesions still present.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is more evident with intravenous bisphosphonate use; the most significant risk factor is the duration of bisphosphonate therapy. The risk increases if corticosteroids and antiandrogenic drugs are also administered. Bisphosphonates cause BRONJ since they inhibit cell migration necessary for bone healing thus inhibiting wound healing. Zoledronic acid delays healing from tooth extraction socket wounds and inhibits oral epithelial cell migration. The authors point out that mitoxantrone causes nausea, vomiting, leukopenia, stomatitis, diarrhea, and anorexia.

The author's interpretation of the patient's adverse reaction is she experienced epithelial breakdown with mitoxantrone. This epithelial breakdown provided an entry point for infection to the bone in a patient who was receiving intravenous bisphosphonates.

The authors point out that this mechanism adds a new factor to be considered in the development of BRONJ/MRONJ.

Bagan JV, Bagan L, Poveda C, et al. Mitoxantrone as a contributing factor in medication-related osteonecrosis of the jaws. *Int J Oral Maxillofac Surg*. 2016;45(3):377-379.

MEDICATIONS WITH ANTICHOLINERGIC EFFECTS AND THEIR IMPLICATIONS IN THE ELDERLY

Researchers conducted systematic reviews and a meta-analyses to assess the association between drugs with anticholinergic effects (DACEs) on cognitive impairment, falls, and all-cause mortality in older adults. The researchers included randomized controlled trials, prospective and retrospective cohort studies, and case-control studies to look at the effect of DACEs in adults 65 years and older. They searched the medical literature utilizing multiple methods and reviewed 35,341 studies; they found 18 studies that included 124,286 patients who fit their research criteria.

DACEs may impair cognitive performance as well as physical function in older adults. For example, normal age-related declines in memory could increase with susceptibility to the potential side effects of DACEs. Comorbid conditions in older adults, including Parkinson's disease and type 2 diabetes, can also predispose patients to a decline in cognition and amplify the effects of DACEs on cognitive function. Other characteristics of DACEs such as the daily dose, binding affinity to the muscarinic receptor, permeability of the blood-brain barrier, and serum and tissue concentrations influence the risk of anticholinergic effects. The researchers utilized the Anticholinergic Cognitive Burden Scale (ACB), Anticholinergic Drug Scale (ADS), Anticholinergic Risk Scale (ARS), and the Drug Burden Index (DBI) anticholinergic component to assess anticholinergic effects.

The systematic review revealed no significant association between DACEs and cognitive impairment. The association between specific DACEs and falls revealed that imipramine, mirtazapine, amitriptyline, paroxetine, and olanzapine were associated with an increased fall risk. The studies assessed for the association between DACEs and all-cause mortality did not reveal an increased risk. When all-cause mortality was evaluated based on gender, it showed that women did not have a risk of all-cause mortality but men did have an increased risk. When evaluating all-cause mortality and specific DACE medications, the

analysis revealed amitriptyline, mirtazapine, olanzapine, paroxetine, trazodone, and quetiapine were associated with an increased risk of all-cause mortality.

The meta-analysis revealed that DACE use is associated with an increased risk of cognitive impairment. With regard to falls, olanzapine and trazadone were associated with increased odds of falling. When evaluating all-cause mortality, the ACB scale revealed an increase in mortality whereas the DBI and ARS scales did not.

The researchers evaluated the complete study results of the systematic reviews and meta-analyses that revealed evidence of increased risk for each of the 3 outcomes. Exposure to DACEs as a class was associated with a 45% increase in the odds of cognitive impairment. Olanzapine and trazadone were associated with an approximate doubling in the risk of falls, and an increase in the ACB scale was associated with an approximate doubling in the odds of all-cause mortality. The meta-analyses results for falls showed a 116% and 79% increase in odds of a fall

occurring with the use of olanzapine and trazadone, respectively. Amitriptyline, paroxetine, and risperidone showed no significant associations with falls, whereas olanzapine and trazadone did. There was also a trend toward an increased fall risk with amitriptyline, paroxetine, and risperidone. Results from the meta-analyses for all-cause mortality showed that exposure to DACEs was associated with a 106% increase in mortality rates for each additional point scored on the ACB scale, but there was no observed association with the ARS.

The researchers point out that their findings raise concerns about the risks of utilizing DACEs and the potential clinical implications. Health professionals prescribing DACEs should be aware and carefully weigh the potential adverse effects associated with these drugs with their potential benefits in the older population.

Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2015;80(2):209-220. ■