CHAPTER

18

Antihypertensives

Teresa DeLellis[*], *Sipan Keshishyan*[†], *Vladlena Kovalevskaya*[†], *Kalee Swanson*[†], *Kaitlin Montagano*[†], *Sidhartha D. Ray*[†,1]

[*]Department of Pharmacy Practice, College of Pharmacy, Natural and Health Sciences, Manchester University, Fort Wayne, IN, USA

[†]Department of Pharmaceutical Sciences, Manchester University College of Pharmacy, Natural and Health Sciences, Fort Wayne, IN, USA

[1]Corresponding author: sdray@manchester.edu

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Captopril

Mouth

A 39-year-old female with a history of angioedema at age 9 was started on sublingual captopril for arterial hypertension. Later she presented with complaints of oral lesions for 4 months, which were diagnosed as pemphigus vulgaris. Captopril was discontinued and the lesions treated with doxycycline, niacinamide, cetirizine, and cyclosporine mouth wash. While the direct mechanism of this established adverse reaction is unknown, given the patient's history of angioedema, the authors hypothesized this case to have an autoimmune component [1A].

Enalapril

Cardiovascular

Upper-airway angioedema is a well known complication of angiotensin-converting enzyme inhibitor (ACEI) therapy; visceral angioedema is less common and frequently unrecognized. A 60-year-old female on enalapril for hypertension was diagnosed with visceral angioedema after presenting with a 2-day history of abdominal pain and diarrhea. She was found to be hypotensive with elevated serum creatinine, leukocytosis, and small bowel wall thickening by computed tomography (CT) scan. Forty-eight hours after enalapril withdrawal and supportive care, the patient's symptoms improved. CT appearance improved within 72 hours. One year later she remained symptom free [2A].

Fosinopril

Immunologic

A 51-year-old male on fosinopril and combination metoprolol/hydrochlorothiazide presented with erythroderma and palmoplantar keratoderma. He was diagnosed with Pseudo-Sezary syndrome based on skin biopsy and flow cytometry. Flow Cytometry was performed which showed a population of 2500 "Sezary-like" CD4726 T-cells/μL in the blood. All antihypertensive medications were discontinued and the condition resolved completely [3A].

Lisinopril

Alopecia

A 53-year-old male on lisinopril for heart failure presented with new alopecia. Alopecia is a known adverse effect of ACEIs, causality was determined by Naranjo Adverse Drug Reaction Probability Scale-a total score of 6 was achieved and thus identified the adverse drug reaction as probable. Lisinopril was discontinued and changed to the angiotensin receptor blocker losartan. Four weeks later the alopecia resolved [4A].

Respiratory/Mouth

ACEI-induced upper-airway angioedema can recur months after discontinuation of ACEI therapy. A 67-year-old Caucasian male on lisinopril for several years presented with three angioedema episodes recurring over several months. His past medical history was significant for type II diabetes, hypertension, hyperlipidemia, and obesity. His daily medications included

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aspirin, amlodipine, metoprolol, metformin, glipizide, insulin glargine, and cholecalciferol. The first episode of moderate tongue angioedema without urticarial or pruritis was attributed to amoxicillin therapy and resolved with intravenous diphenhydramine and corticosteroid treatment. The next month he presented with the same symptoms, was no longer taking amoxicillin, and the episode was attributed to lisinopril. His symptoms resolved after overnight observation in an intensive care unit, and lisinopril was permanently discontinued. Two months later the symptoms recurred with less severity shortly after initiating niacin and resolved several hours after taking two diphenhydramine tablets. Niacin was discontinued. Later, based on negative penicillin skin test and oral graded niacin challenge performed at an allergy clinic, all three episodes were attributed to the lisinopril. Niacin was resumed, and at 2-year follow-up no further episodes had occurred [5A].

Two cases have been reported of ACEI therapy likely worsening symptoms of Pollen Food Allergy Syndrome (PFAS) reactions involving angioedema. The first was a 65-year-old male with a history of seasonal allergic rhinoconjunctivitis on lisinopril for 10 years for hypertension. He presented with two episodes of tongue and lip angioedema and mouth itching within 10 minutes of apple consumption. The second episode required treatment with antihistamine, epinephrine, and corticosteroids. Lisinopril therapy was changed to losartan. At 3-year follow-up, no further episodes had occurred [6A].

The second case was a 45-year-old male, also with a history of seasonal allergic rhinoconjunctivitis, on lisinopril for 1 year for hypertension. He experienced three episodes of tongue angioedema and mouth itching several minutes after jackfruit and cashew nut consumption; the third episode required antihistamine and prednisone treatment. Lisinopril was changed to losartan, and at 1-year follow-up no further episodes had occurred [6A].

Immunologic

One case report exists for lisinopril-induced eosinophilic pleural effusions. The effusions resolved after lisinopril was discontinued and reoccurred after lisinopril re-challenge [7A].

ANGIOTENSIN RECEPTOR BLOCKERS

Eprosartan

Gastrointestinal

An 83-year-old female taking eprosartan for 10 years for hypertension presented with sudden-onset diarrhea 6 months after her daily dose was doubled to 600 mg. Celiac serology was negative despite celiac disease-like biopsy results. Symptoms resolved after changing eprosartan to amlodipine. Control biopsies at three and 6 months after the diagnosis yielded slightly improved mucosal layer, thus indicating a delayed regeneration of the duodenal mucosa after treatment with eprosartan. While similar reactions have been reported with other angiotensin receptor blockers (ARBs), this is the first case study involving eposartan [8A].

Losartan

Gastrointestinal

A 31-year-old African American female on losartan for 1 year for hypertension and end-stage renal disease on dialysis presented to the emergency department with severe abdominal pain, diarrhea, nausea, and vomiting. She had a 6-year history of abdominal pain coinciding with the start of lisinopril. One year prior to arrival in the emergency department, lisinopril was changed to losartan for resolution of a cough. All laboratory studies were normal, while CT scans revealed perihepatic fluid and small bowel wall edema. Symptoms resolved after discontinuation of losartan. After 1 year without ACEI or ARB therapy, no further symptoms had occurred [9A].

Hyponatremia

A 73-year-old type 2 diabetic male was initiated on losartan 50 mg daily for newly diagnosed moderate hypertension. After taking losartan for 3½ months, he presented to the emergency department in a drowsy state, with weakness and occasional palpitations. The patient was diagnosed with type 2 diabetes 3 years ago and was well controlled only by oral metformin 500 mg twice daily. Other than being a diabetic, patient was well. Laboratory examinations revealed that his serum sodium level was 123 mEq/L. His pulse was 90 bpm, and his blood pressure 134/88 mmHg. No evidence was found that might have indicated any metabolic, infective, organic or other pathologic causes of the current symptoms, other than the use of losartan. Losartan was discontinued. The patient was managed with sodium repletion and dietary water restriction. Water loss was promoted with furosemide 40 mg twice daily given intravenously for 5 days. Patient was discharged 1 week later in a stable condition. He was prescribed hydrochlorothiazide 25 mg daily for blood pressure control [10A].

Olmesartan

Gastrointestinal

An 84-year-old Asian female on olmesartan suffered from severe, chronic, diarrhea for 15 months despite multiple empiric treatments. After an extensive work-up, she was diagnosed with ARB-induced sprue-like

enteropathy. Both her symptoms and histological findings improved after olmesartan was discontinued [11A].

Two females, 82 and 76 years old, on 2 consecutive days were admitted with severe diarrhea lasting approximately 8 months. Both women presented with significant weight loss of 16 and 20 kg, respectively. Patient work-up revealed identical results for both patients and led to identical diagnosis of refractory seronegative sprue. Subtotal villous atrophy with an increased number of intraepithelial lymphocytes was the result of duodenal biopsy. Human leukocyte antigen DQ2+ and DQ8− genotyping was consistent with celiac disease. Trial of antibiotic and strict gluten free diet was ineffective. Oral budesonide was initiated which brought some relief. All of the possible causes of villous atrophy were evaluated. Both patients had been taking olmesartan 40 mg daily for 6 and 4 months, respectively. Olmesartan was discontinued which lead to complete cessation of diarrhea within a 2-week period period. Biopsy 8 weeks later showed complete recovery of villous atrophy [12A].

Telmisartan

Skin

A 53-year-old male on telmisartan and hydrochlorothiazide combination for 2 weeks for hypertension presented to the hospital with cutaneous urticarial vasculitis. Red ecchymotic lesions of variable size and shape were spread over abdomen, flanks, groin, buttocks, and extremities. Emogram showed mild leukocytosis (total leukocyte count—12,800/cmm) and neutrophilia; all other laboratory tests were normal. Symptoms resolved after treatment with prednisolone and cetirizine. Despite medical advice to the contrary, the patient resumed telmisartan and hydrochlorothiazide, resulting in lesion recurrence. The lesions responded to treatment as with the first occurrence. Later, re-challenge with similar doses of telmisartan monotherapy and hydrochlorothiazide monotherapy resulted in recurrence with telmisartan but not with hydrochlorothiazide [13A].

BETA-BLOCKERS

Carvedilol

Hyperkalemia

A 69-year-old male with chronic kidney disease stage III on carvedilol 3.125 mg twice daily was hospitalized for abdominal pain, nausea, and vomiting. During the hospitalization his serum potassium increased from 4.8 to 6.7 mEq/L when carvedilol dose was increased to 6.25 mg twice daily. Patient's hyperkalemia was unresponsive to sodium polystyrene sulfonate but normalized to 4.4 mEq/L following adjustment of carvedilol back to 3.125 mg twice daily. Although a rare, known effect of beta-blockers, this is the first case report specifically with carvedilol [14A].

Labetalol

Skin

A 31-year old patient in her third trimester with twins was treated with labetalol for 18 days and hydralazine, alpha-methyldopa, and metamizole for 3 days prior to admission for cesarean section. Before the operation she developed acute generalized exanthematous pustulosis (AGEP) on her face and neck, which became more generalized over the next 4–5 days despite withdrawal of hydralazine, alpha-methyldopa, and metamizole on day 2. No new lesions appeared after labetalol discontinuation on day 5. Patch tests performed 1 month later were negative for hydralazine, alpha-methyldopa, metamizole, and atenolol but positive for labetolol. However, she did develop recurrence 1 hour after taking atenolol 25 mg, which persisted for 48 hours despite methylprednisolone treatment [15A].

Metoprolol

Drug–Drug Interaction

A 63-year-old Caucasian male on metoprolol 200 mg daily, for stable coronary artery disease presented to the emergency room with symptomatic bradycardia (confusion and falls; heart rate 37 beats per minute). The patient was on terbinafine 250 mg daily for onychomycosis but unfortunately developed bradycardia on 49th day of a 90-day treatment regimen. The bradycardia was hypothesized to be a result of terbinafine inhibition of cytochrome P450 2D6, decreasing metoprolol clearance. A score of 7 on the Naranjo adverse drug reaction probability scale suggested a probable relationship between the patient's sinus bradycardia and the drug interaction between metoprolol and terbinafine. Heart rate increased with a decrease in metoprolol dose and returned to normal when metoprolol was changed to bisoprolol, a beta blocker that does not interact with terbinafine [16A].

Psychological

A 44-year-old Caucasian male on metoprolol 50 mg daily was admitted to a psychiatric ward due to psychotic symptoms. Metoprolol was initiated 2 weeks earlier by his general practitioner for primary hypertension. After starting metoprolol he felt confused, restless and had difficulty falling asleep. He stopped

taking metoprolol and all symptoms diminished. Upon re-initiation of metoprolol, he reported chaotic thinking and delusional thoughts. His general practitioner prescribed oxazepam 10 mg three times daily and mirtazapine 15 mg daily. All physical and laboratory tests were normal. Upon admission, he was confused with vivid visual hallucinations. Patient had no medical or psychiatric history, no history of substance abuse, and other than metoprolol, he was not on any other medications. Psychiatric examination revealed delusional content of his thoughts without any signs of cognitive impairment. I was deemed that his psychotic symptoms were caused by metoprolol. Olanzapine 10 mg twice daily was initiated and metoprolol was discontinued. A few days later, his psychosis gradually disappeared. He was initiated on nifidepine 30 mg for primary hypertension. Patient was discharged 2 weeks later free of any psychiatric symptoms. Olanzapine was tapered off over the following 3 weeks [17A].

CALCIUM CHANNEL BLOCKERS

Amlodipine

Mouth and Teeth

Drug-induced gingival overgrowth (DIGO) is a well-established effect of calcium channel blockers (CCB), most commonly with nifedipine and less frequently with amlodipine. In Dublin, a 63-year-old male on amlodipine 10 mg daily for hypertension presented to a dental clinic with 2-year history DIGO that had recently become severe. The DIGO was attributed to both amlodipine and poor plaque control based on histopathological analysis. The patient was treated successfully with oral hygiene education and local debridement [18A].

Liver

A 34-year-old Caucasian male presented to the emergency department 100 days post allogenic stem cell transplant for gastrointestinal graft versus host disease (GVHD) and was treated with high-dose steroids. Three days later amlodipine 5 mg daily was started for steroid-induced hypertension. On day 3 of amlodipine therapy alanine aminotransferase (ALT) levels doubled and continued to rise, peaking on day 11 at 630 IU/L. Aspartate aminotransferase (AST) also peaked on day 11, at 421 IU/L; total bilirubin and alkaline phosphatase remained normal throughout. Amlodipine was changed to carvedilol based on results of a liver biopsy, resulting in an ALT and AST drop which trended down to normal within 2 weeks [19A].

Diltiazem

Mouth and Teeth

A 48-year-old male on diltiazem for hypertension presented with drug-induced gingival hyperplasia. Rather than starting with periodontal treatment, the patient's physician was asked to change antihypertensive therapy. With this change to a non-calcium channel blocker antihypertensive, the gingival hyperplasia improved significantly over the next 3 months without periodontal intervention [20A].

DIRECT VASODILATORS

Doxazosin

Urinary

A 70-year-old male status-post radical prostatectomy followed by salvage radiotherapy 3 years later, on doxazosin for hypertension, developed urinary incontinence after radiotherapy. While being considered for artificial urinary sphincter placement, doxazosin was discontinued. After discontinuation, his urinary symptoms resolved and did not require further intervention. This was attributed to the relaxant effects of doxazosin on the internal sphincter [21A].

Terazosin

Cardiovascular

A 71-year-old male on terazosin 5 mg daily for benign prostatic hyperplasia presented to the emergency department with acute myocardial infarction (MI). Earlier that day, he had self-medicated with an additional 5 mg terazosin dose for a blood pressure of 220/110 mmHg. An hour later he experienced angina following a syncopal episode and presented to the emergency department. Workup revealed chronic occlusion of the left anterior descending artery, as well as terazosin-induced obstruction of the left ventricular outflow tract resulting in a hemodynamically produced MI. Intravenous atenolol resulted in clinical and symptomatic improvement within minutes [22A].

Clonidine

Cardiovascular

A 30-year-old male presenting with status epilepticus being treated in the intensive care unit developed withdrawal syndrome associated with substance misuse and was treated with a clonidine infusion. Two hours after clonidine was stopped abruptly, he developed severe hypertension, tachycardia, high-grade fever,

profound sweating and lacrimation, and acute pulmonary edema resulting in respiratory distress syndrome. A low-dose clonidine infusion resolved symptoms; clonidine was then slowly discontinued by slow dose taper of intravenous followed by oral clonidine. This slow discontinuation did not result in further complications, and the patient was discharged from the intensive care unit [23A].

DIURETICS

Diazoxide

Hematologic

A 24-year-old female admitted for hypoglycemia was diagnosed with an insulinoma and started on diazoxide 250 mg daily for hypoglycemia prevention. On day 5 diazoxide was increased to 500 mg daily, and to 600 mg daily on day 6. On day 10 she developed chills, a temperature of 38.0 °C, and a 4.6 kg weight gain from edema. By day 13 her platelet count had decreased from 186000/μL to 28000/μL, and she developed epistaxis and purpura in her lower extremities. When platelets fell to 12000/μL the next day, diazoxide was discontinued, prednisolone was started at 30 mg/day, and she received 2 days of consecutive platelet transfusions. Thrombocytopenia and weight gain reversed within 8 days of diazoxide discontinuation [24A].

Furosemide

Survival

A retrospective study was performed on 173 clinically stable heart failure patients comparing 3-year composite endpoint-free survival rates (all-cause mortality, heart transplantation, and mechanical-assist device implantation) among patients on high-dose furosemide (>80 mg daily; $n=70$) to low dose furosemide ($\leq$80 mg daily; $n=103$). Baseline characteristics did not differ between groups with the exception of a higher estimated glomerular filtration rate in low-dose group (72.9 ± 19.4 vs 60.8 ± 22.0 mL/min/m^2, $p<0.001$). Rates of 3-year survival free from the composite endpoint were significantly higher in the low-dose group (93.1% vs 60.0%, $p<0.001$). The high-dose furosemide group also had higher rates of renal function decline and hypokalemia (73.2% vs 48.3%, $p=0.003$, and 43.1% vs 6.5%, $p=0.001$, respectively) [25c].

Hydrochlorothiazide

Hyponatremia

A 69-year-old male on hydrochlorothiazide for 2 weeks presented to the emergency department complaining of generalized weakness for the past week, which coincided with a hydrochlorothiazide dose increase from 12.5 mg daily to 25 mg daily. Upon workup he was found to have serum sodium 120 mmol/L. Hydrochlorothiazide was discontinued, and free water restriction initiated. By day 2, symptoms considerably improved; serum sodium level showed 128 mmol/L, and the patient was ready for discharge. Hyponatremia and symptoms were completely resolved 3 days later at outpatient follow-up, and he was started on hydralazine for hypertension and instructed to discontinue further hydrochlorothiazide use [26A].

Eye

A 67-year-old female on hydrochlorothiazide presented with acute bilateral angle closure glaucoma associated with profound hyponatremia and bilateral ciliary effusions. Both the effusions and hyponatremia resolved with discontinuation of hydrochlorothiazide and free water restriction [27A].

Skin

A 32-year-old male presented 24 days after his antihypertensive was changed from losartan 50 mg daily to losartan–hydrochlorothiazide 50/12.5 mg combination, complaining of flu-like symptoms. He returned 3 days later with wide-spread bullous and vesicular lesions with an erythematous base and was sent to the emergency department for further diagnosis and treatment. A punch biopsy of a prebullous lesion demonstrated spongiotic dermatitis with clefting at the dermo-epidermal junction. Inflammatory infiltrate, eosinophils and neutrophils were found in the papillary dermis. He was eventually diagnosed with bullous pemphigoid and treated with prednisone and mycophenolate mofetil. With this treatment and discontinuation of hydrochlorothiazide, the rash resolved; prednisone and mycophenolate were tapered off over 8 and 20 weeks, respectively, without recurrence of symptoms [28A].

Pancreatitis

A 31-year-old female presented to the hospital with a 2-day history of epigastric pain radiating to the back associated with nausea and vomiting. Her medical history included hypertension for which she was started on hydrochlorothiazide 25 mg 5 days prior to presentation. Her other medications included metformin for polycystic ovarian syndrome and omeprazole for heartburn. She appeared to be in moderate pain and afebrile with a heart rate of 105 bpm. Her body mass index was 39. Physical examination showed epigastric tenderness. Laboratory findings yielded leukocytosis of 18600/μL. Liver chemistry was normal; amylase and lipase levels were 35 and 35 U/L, respectively. The patient was treated supportively with bowel rest, opiate analgesia, and intravenous

fluids. She improved without complications and was discharged the next day. Hydrochlorothiazide was discontinued [29A].

Eplerenone

A single-center, prospective, open-label study evaluated 31 kidney transplant patients with impaired renal function (30 and 50 mL/min/1.73 m^2). All patients received eplerenone 25 mg/day for 8 weeks. Patients were closely monitored for changes in renal function and serum potassium.

Eight patients experienced mild hyperkalemia (>5 mmol/L), one moderate hyperkalemia (>5.5 mmol/L) and had to receive potassium-exchange resin. No instances of sever hyperkalemia (>6 mmol/L) were reported. One case of acute kidney injury occurred, after further analysis it was deemed secondary to diarrhea. It was determined that basal serum potassium and bicarbonate were independently associated with a significantly higher risk of developing mild hyperkalemia while being treated with eplerenone (OR 6.5, $p = 0.003$ and 0.7, $p = 0.007$, respectively). Furthermore, a value of 4.35 mmol/L for basal serum potassium was the best factor to predict the risk of developing hyperkalemia [30c].

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