CHAPTER

18

Antihypertensive drugs

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ANGIOTENSIN CONVERTING ENZYME INHIBITORS [SEDA-39, 183–187; SEDA-40, 263; SEDA-41, 219–220]

Drug class

Hematologic

A retrospective cohort study by Guirguis evaluated the prevalence of anemia in patients with heart failure. The goal of the study was to attempt to categorize risk factors for anemia development in this patient population, particularly ACE inhibitor and aspirin use [1c]. This study included 96 patients with heart failure seen in an outpatient heart failure clinic in a major metropolitan hospital in Melbourne, Australia. Use of an ACE inhibitor was associated with a relative risk of 17.4 for development of anemia compared to no ACE inhibitor use ($P=0.013$). Patients who were taking an ACE inhibitor had significantly lower hemoglobin levels, by an average of almost 17 g/L than patients who were not taking an ACE inhibitor ($P<0.0001$). Interestingly, the results from this study suggest the risk of anemia development from ACE inhibitor use may not be homogenous for all ACE inhibitors. Perindopril was associated with a statistically significant relative risk of anemia of 20.7 ($P=0.02$), whereas ramipril was associated with a non-statistically significant relative risk of 14.18 ($P=0.05$). The author concluded that anemia is common among patients with heart failure, and this anemia may be exacerbated by concurrent ACE inhibitor use. The risk of anemia is variable among drugs in this class, and so patients taking these agents, especially those taking perindopril, should be monitored closely for hematologic abnormalities.

Autacoids

ACE inhibitor use is the most frequent cause of angioedema, with an incidence as high as 0.7% among patients who take ACE inhibitors [2R]. Most ACE-inhibitor associated angioedema cases are mild and resolve within 48–72 h after discontinuing the offending agent. ACE inhibitor-related angioedema is characterized by non-pruritic swelling of the dermis and subcutaneous tissues caused by rapid extravasation from post-capillary venules. Angioedema may occur hours after taking the first dose of an ACE inhibitor, or may occur years later. The mechanism by which ACE inhibitors potentiate angioedema is not well-characterized; however, it is known that genetic deficiencies of C1-inhibitor (C1-INH) cause hereditary angioedema, a rare autosomal dominant disorder. A pharmacokinetics study by Hahn et al. evaluated the effect of ACE inhibitor treatment on C1-INH levels of 5 patients given 5 or 25 mg of captopril for the first time, and 17 patients receiving an ACE inhibitor for the first time [3E]. Researchers found decreases in C1-INH levels in patients given captopril; however, the magnitude of this effect was variable among participants in the study. Authors concluded that more research is needed to determine the exact cause of ACE inhibitor-related angioedema.

Respiratory

Chronic, dry cough is a well-documented potential side effect of ACE inhibitor therapy [4R]. A cough may occur within hours of the first dose but may not appear until weeks or months after beginning therapy with an ACE inhibitor. A review by Yılmaz notes that there are several possible mechanisms by which ACE inhibitors cause this dry, hacking cough [5R]. These mechanisms include a bradykinin degradation deficit, genetic polymorphisms, and increased sensitivity of bradykinin-dependent airway sensory nerve fibers. A review by Shim and colleagues discussed the first of these theories, and hypothesized that ACE inhibitors potentiate a dry cough due to accumulation of bradykinin or substance P, both of which are degraded by ACE [6R]. The presence

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of an ACE inhibitor suppresses turnover of bradykinin and substance P, causing their accumulation and ultimately, a chronic cough. Patients who develop ACE inhibitor-induced cough after exposure to one agent in this class often report the same adverse effect when therapy is switched to an alternative ACE inhibitor, illustrating chronic cough as a class-wide adverse effect. Providers should note that in patients who experience intolerable ACE inhibitor-induced chronic cough, discontinuing ACE inhibitor therapy is currently the only known effective mitigation strategy.

Captopril

Autacoids

A case report from Gorsane et al. describes a rare case of a 36-year-old woman with angioedema and pancreatitis which developed hours after beginning an ACE inhibitor. The described patient presented to a hospital in Tunisia with headache associated with paresthesia of the right upper limb, vomiting, and aphasia [7A]. Physical exam revealed mucocutaneous pallor and oliguria. Objective findings showed the patient was hypertensive at 220/100 mmHg. Urinalysis showed proteinuria and hematuria, and blood testing showed a serum creatinine of 1125 μmol/L (12.72 mg/dL). Hematology testing showed anemia with a hemoglobin of 6.1 g/L and thrombocytopenia with platelets of 61 000/mm^3. The patient's baseline laboratory markers were either unknown or not documented by authors. A renal ultrasound ruled out prerenal etiology; renal histology revealed lesions of thrombotic microangiopathy. Clinicians evaluated the patient for hemolytic uremic syndrome. She was placed on peritoneal dialysis, and her HTN was initially treated with nicardipine, methyldopa, and furosemide, with the later addition of captopril. Twelve hours after initiating captopril, the patient developed severe epigastric pain with cramping. She vomited twice and was unable to eat. A serum lipase was evaluated at 560 IU/L, and abdominal computed tomography (CT) showed a pancreas with mild inflammation and edema. The patient was diagnosed with stage B pancreatitis. Twenty-four hours later, the patient developed edema of the neck with no associated dyspnea or dysphonia. Cervical ultrasound was performed and showed infiltration of the subcutaneous space. Captopril was discontinued and the edema resolved. The patient's serum lipase was within normal limits by the patient's fourth day of admission. Authors of this case report note that angioedema and pancreatitis are known adverse effects of ACE inhibitors, although the pathophysiology of these effects remains controversial. They recommend discontinuation of ACE inhibitor therapy immediately upon suspicion of ACE inhibitor-related angioedema or pancreatitis, and initiating supportive measures including fluids, airway management, and close vital sign monitoring.

ANGIOTENSIN RECEPTOR BLOCKERS [SEDA-40, 263–264; SEDA-41, 220–221]

Drug class

A systematic review of hypertensive patients in East and Southeast Asia by Lee et al. evaluated efficacy and safety of combination ARB and amlodipine therapy compared to amlodipine monotherapy [8M]. This meta-analysis included 6 studies and 678 patients to evaluate for short-term treatment-emergent adverse effects. The trials evaluated patients taking amlodipine with azilsartan, candesartan, fimasartan, olmesartan, telmisartan, or losartan. The data in the included studies indicated that ARBs were well-tolerated and no more likely to potentiate adverse effects than amlodipine. Furthermore, patients taking telmisartan and amlodipine had a statistically significant reduction in risk of treatment-emergent adverse effects compared to patients taking amlodipine monotherapy. Authors of this meta-analysis concluded that all studied combinations of ARB's with amlodipine showed comparable and favorable safety profiles. They recommend further study with longitudinal cohorts, and head-to-head trials to give further evidence supporting these findings.

Azilsartan

Cardiovascular

A multicenter, randomized, open-label, parallel-group, exploratory study was conducted at 27 centers in Japan between June 2014 and April 2016 by Naruse and colleagues [9c]. The trial randomized 33 adult patients with HTN and diabetes mellitus to either azilsartan 20 mg per day or telmisartan 40 mg per day. Investigators evaluated the safety and efficacy of these two regimens at the end of the treatment period (12 weeks). The incidence of treatment-emergent adverse effects in the azilsartan group was 35.3% (6/17) and 50.0% (8/16) in the telmisartan group. Only one treatment-emergent adverse effect was determined to be caused by azilsartan, which was a mild decrease in blood pressure leading to discontinuation of study medication. Authors concluded that azilsartan and telmisartan were both effective and safe in treating HTN in their patient population, and they did not identify any novel safety signals.

Candesartan

Nervous system

Data from a multicenter, randomized, double-blind, parallel, phase III clinical study were published by Cho and colleagues [10C]. This 12-week trial randomized 219 patients with HTN and hypercholesterolemia 1:1:1 to candesartan 32 mg, candesartan 32 mg/rosuvastatin 20 mg, or rosuvastatin 20 mg daily. The primary outcome of the study was changes in the mean SBP and mean DBP and the percentage changes of LDL-C from baseline to drug treatment at 8 weeks. Authors also reported safety data of the monotherapy regimens was compared to combination therapy. Of the four patients who discontinued their participation in the study due to adverse effects, one patient was in the candesartan/rosuvastatin group, one patient was in the candesartan group, and two patients were in the combination therapy group. The proportion of patients who experienced a treatment-emergent adverse effect was statistically similar in all three groups (19.7% in the combination group, 15.1% in the rosuvastatin group, and 21.9% in the candesartan group; $P = 0.745$). The most common adverse effect was headache in all groups. Authors concluded that most treatment-emergent adverse effects were likely unrelated to the study drugs, and that candesartan was well-tolerated. The authors also note that the short duration of the study is a limitation in extrapolating the data to patients taking these agents in the long-term. The study included Korean patients only; therefore, the results may not be generalizable in patients of other racial groups who have different risk factors and lifestyle characteristics.

Losartan

Musculoskeletal

A case report published by Fishman et al. describes a 56-year-old man in the United States who experienced tremors and dysarthria requiring hospitalization [11A]. The patient had a medical history of gastroesophageal reflux disease (GERD) and hypertension. He presented to the hospital 3 days after beginning antihypertensive therapy with losartan 50 mg per day. The patient was experiencing upper extremity tremors that worsened on intention and later affected his lower extremities, limiting his freedom of movement. Acute stroke was ruled out, and the patient was treated with fluids and lorazepam. His losartan was discontinued and switched to amlodipine and lisinopril. He was discharged from the hospital within 24 h, at which time the tremors and dysarthria had completely resolved. The authors of this case report concluded that due to the resolution of the patient's symptoms following discontinuation of losartan and supportive care only, the patient's tremors and dysarthria were likely a side effect of losartan therapy. They noted that this is the first published report of this adverse event related to losartan, and as such, more data are required before making conclusions regarding a causal link between losartan and tremor development.

Olmesartan

Gastrointestinal

A case report published in Australia by Sher et al. details a 72-year-old woman who experienced nonceliac sprue-like enteropathy [12A]. The patient had a medical history of HTN long-treated with olmesartan and metoprolol. On presentation, she complained of three to four daily episodes of profuse watery diarrhea for 6 weeks, 1 month of vomiting, and an 8 kg (17.6 lb) weight loss. She was prescribed loperamide by her primary care provider which did not ameliorate her symptoms. A CT scan showed fluid-filled distension of the colon and cholelithiasis without cholecystitis. The patient's olmesartan and metoprolol were discontinued, and the patient's symptoms improved. Approximately 1 year later, olmesartan was reinitiated and the patient presented to the hospital with similar symptoms: watery diarrhea, vomiting, and 9 kg (19.8 lb) weight loss. Olmesartan was discontinued, and the patient's symptoms improved. The patient's care team concluded that olmesartan was the likely cause of this patient's symptoms and olmesartan therapy was discontinued and the patient was initiated on the calcium channel blocker lercanipine without a return of the patient's symptoms. Authors of the report recommend consideration for nonceliac sprue-like enteropathy as a rare side effect of olmesartan, and to consider uncommon side effects of medications when evaluating patients for etiology of new symptoms.

In contrast, a Korean retrospective, observational, cohort study performed by You et al. did not find a correlation between olmesartan use and intestinal malabsorption or weight loss [13C]. This study evaluated 108 559 patients who were initiated on various RAAS inhibitors. Of the included patients, 23 610 were taking olmesartan; this subgroup demonstrated an enteropathy incidence of 0.18 per 1000 persons. The odds ratio (OR) of intestinal malabsorption in the olmesartan group was lower than that of the other ARBs studied (olmesartan odds ratio, 0.26; 95% confidential interval [CI], 0.08–0.80; $P = 0.020$, combination of all other ARB's OR, 0.30; 95% CI, 0.13–0.72; $P = 0.007$). From this data, authors concluded that olmesartan was not associated with a higher incidence of intestinal malabsorption or weight loss than ACE inhibitors or other ARBs in Koreans.

Skin

Charfi et al. describe a case of a 57-year-old Tunisian woman who experienced non-pruritic erythematous scaly plaques and associated fissuring on the soles of both feet [14A]. She had been taking olmesartan 20 mg per day for hypertension for 4 years. A physical exam revealed a well-defined erythematous and hyperkeratotic keratoderma with fissures extending to over 50% of the plantar surfaces of her feet. She was diagnosed with plantar psoriasis and prescribed topical clobetasol. Her olmesartan was continued, and her condition continued to worsen. Three months later, olmesartan was replaced with a combination of amlodipine and perindopril, and ultraviolet A (UVA) phototherapy was initiated 1 month later. The hyperkeratosis and pain resolved quickly after UVA treatment, and she remained symptom-free at a 2-year follow-up. Clinicians evaluated the probability of this reaction occurring as a result of olmesartan therapy using the Naranjo Scale, and determined a total score of 3 (possible). Authors remarked that this is the first reported case of olmesartan-induced plantar psoriasis published in available literature. They conclude the case is of clinical interest because of the long delay in appearance of the reaction after initiation of olmesartan therapy. Authors recommended that prescribers be aware of this rare cutaneous side effect.

Valsartan

Adverse effects in children

There are very few studies evaluating the treatment of hypertension in children. A trial by Lou-Meda et al. was published to address this dearth of data [15C]. This was an 18-month, open-label, multicenter, prospective evaluation of 150 children aged 6–17 years taking valsartan for hypertension with or without chronic kidney disease (CKD). Researchers found that children with CKD were more likely to experience an adverse effect compared to children without CKD (85.3% vs 73.3%, respectively, no *P*-value reported). Most of the adverse events were mild (50.7%) or moderate (18.7%) in severity. Lupus nephritis (2.7%) and pneumonia (1.3%) were the most commonly reported serious adverse effects. Authors concluded that valsartan was safe and effective in patients aged 6–17 years, including in those with CKD.

BETA BLOCKERS [SEDA-40, 264–265; SEDA-41, 221–222]

Atenolol

Drug overdose

Tale and colleagues described a case report of a 66-year-old male in India who developed severe cardiovascular depression after ingesting 25 tablets of fixed dose amlodipine and atenolol (total 125 mg amlodipine and 1250 mg of atenolol) [16A]. The patient presented with refractory bradycardia, hypotension, and acute kidney injury. He suffered a cardiac arrest and was revived after 5 min of cardio-pulmonary resuscitation. The patient received supportive care consisting of fluids, gastric lavage, inotropes, atropine, calcium gluconate, insulin euglycemia therapy, and lipid emulsion therapy. The patient improved and on the eighth hospital day he was discharged in stable condition. Authors of this case report concluded that individually, amlodipine or atenolol overdose can result in severe bradycardia and hypotension, but the combination of the two agents can cause cardiac arrest. Authors highlight that timely and aggressive management of overdoses such as these with a multifaceted approach can overcome this effect.

Bisoprolol

Cardiovascular

Beta blockers are a component of guideline-recommended therapy for the management of patients who experience an acute coronary syndrome (ACS) event. A case report of a 69-year-old man in Japan was published by Sawai et al. and describes a patient who experienced multiple life-threatening coronary artery spasms after ACS due in part to bisoprolol administration [17A]. The patient first presented to the emergency room with an ST-elevation myocardial infarction. He received a drug-eluting stent in the LMCA/LAD and was started on aspirin, prasugrel, rosuvastatin, eplerenone, lisinopril, and 2.5 mg of bisoprolol. On the second day of admission, the patient experienced sudden-onset chest pain followed by loss of consciousness. An EKG showed bradycardic atrial fibrillation with ST-elevation. CPR was started and the patient received an urgent coronary angiogram to confirm a suspected subacute stent thrombosis; however, no significant stenosis was noted. The patient experienced another episode of sudden chest pain with ST-elevation noted on EKG. An angiogram of the RCA showed severe spasms in the middle and distal portions of the RCA. Isosorbide dinitrate intracoronary injection temporarily relieved the spastic changes and chest pain. After the angiogram bisoprolol was discontinued, and therapy with low-dose amlodipine (2.5 mg/day) was initiated. The patient did not experience any additional episodes of coronary spastic angina during admission or after discharge. The authors note that Japanese patients post-ACS are more likely to experience coronary vasospasm compared to Caucasian patients. Additionally, this patient's risk of coronary artery spasm was compounded by the administration of bisoprolol. The authors recommend that beta blocker therapy in post-ACS Japanese patients should be used cautiously.

Carteolol

Respiratory

Wu et al. describe an interesting case of a 24-year-old woman in Taiwan with a history of allergic rhinitis, urticaria, and eczema who developed asthma 1 week after starting carteolol solution for ocular hypertension [18A]. The patient noticed progressive upper chest tightness without radiation accompanied by a non-productive cough. Two months after starting the carteolol eye drops, at a pulmonology clinic appointment, of the patient reported increased breathing difficulty with a feeling of airway restriction. She was diagnosed with sudden asthma onset. When the patient revealed that she had recently started carteolol eye drops, the pulmonologist discontinued carteolol eye drops and initiated an inhaled bronchodilator for as-needed usage. After 5 days, the patient experienced significant improvement in her respiratory status. She did not require use of her bronchodilator, and experienced no episodes of chest tightness. Repeat pulmonary function tests were conducted 1 month after discontinuing the carteolol drops. The patient's forced vital capacity and forced expiratory volume were similar to her last examination, and a methacholine test was negative. The pulmonologist determined that the patient's baseline status should be considered non-asthmatic, and the clinical incident should be considered an episode of reversible asthma induced by ophthalmic beta blocker usage. Authors recommend that clinicians be aware that non-selective beta blocking eye drops can induce symptoms of asthma even in non-asthmatic patients. They emphasize the importance of counseling patients with atopy that beta blocker eye drops can cause respiratory symptoms.

Carvedilol

Psychological

Hallucinations are rarely reported side effects of beta blockers and to date, this adverse effect has solely been reported in patients taking propranolol or metoprolol. A case report by Aikoye et al. describes the first case of hallucinations reported in a patient taking carvedilol [19A]. The patient was a 67-year old male with a history of diabetes mellitus, hypertension, hyperlipidemia, mild cognitive impairment, prostate cancer and myocardial infarction. The patient's hypertension was sub-optimally managed on amlodipine and benazepril; therefore, carvedilol was started for additional blood pressure control. Within days, the patient reported seeing people and animals at his bedside at night. The patient continued to experience visual and auditory hallucinations for over 10 months. He was started on quetiapine at bedtime, which did not eliminate the visual hallucinations. Carvedilol therapy was tapered down and finally discontinued, with resolution of the patient's visual hallucinations 3 weeks later. Authors concluded that beta blockers, including carvedilol, have central nervous system-related side effects, including auditory and visual hallucinations. They hypothesized that visual hallucinations induced by beta blockers may be due to serotonergic blockade or from an exacerbation of beta blocker-related delirium.

Liver

An 83-year-old woman was admitted to an acute care facility in Portugal for asymptomatic hyperkalemia (7.1 mmol/L) identified in routine blood testing [20A]. An abdominal examination was negative. A cholestatic pattern of liver injury was reported (AST 67 U/L, ALT 110 U/L, alkaline phosphatase 430 U/L). Lactate dehydrogenase, total bilirubin, and C-reactive protein were within normal limits. Ultrasonography ruled out biliary obstruction and showed a liver with regular contours and slightly heterogeneous texture with increased reflectivity probably due to steatosis. Syphilis and viral causes of hepatitis (hepatitis A, B, C, and E, cytomegalovirus, adenovirus, Epstein–Barr, and HIV) were all excluded. Suspecting drug-induced toxic hepatitis, clinicians discontinued allopurinol, atorvastatin, carvedilol, sitagliptin, diazepam, and venlafaxine. On hospital day 5 through 13, the patient's ALP increased to 453 U/L, g-GT increased to 1098 U/L, AST increased to 230 UL, and ALT increased to 316 U/L, which corresponded to reintroduction of carvedilol, furosemide, losartan, and insulin at the time of the patient's transfer within the facility. A liver biopsy showed normal portal tracts with mild inflammation of mononuclear cells without interface damage and with periportal ductular reaction. A liver histology assessment showed discrete anisocytosis, anisocariosis, and some mitoses. Acinar inflammatory foci with hepatocyte necrosis was noted, but no steatosis. Iron deposits in Kupffer cells were discrete. This is similar to the pattern of liver injury in the only previously published incidence of carvedilol-induced liver disease. Carvedilol was thus discontinued as the most likely agent in this patient's liver damage, and the patient improved. At 9 months post-discharge, the patient's liver function tests were within normal range. Authors concluded that this was a rare case of carvedilol-induced toxic hepatitis. They recommend to avoid re-challenge with carvedilol as there is potential for an anamnestic response and acute liver failure, associated with a 15% risk of mortality. In this case, re-challenge with carvedilol was unintentional and due to an error in medication reconciliation. This case illustrates the importance of medication reconciliation, particularly during transitions of care.

Labetalol

Cardiovascular

A case report from Avila-Vega et al. describes a 30-year-old American woman who experienced Raynaud's phenomenon of the nipple as a side-effect of antihypertensive therapy with labetalol [21A]. The patient was diagnosed with gestational hypertension during a routine antenatal care visit at pregnancy week 32. She was started on nifedipine XL 30 mg daily. At week 34, her blood pressure remained elevated so the nifedipine dose was increased to 60 mg daily. The next day, in addition to continued hypertension, she experienced headache. Urinalysis revealed an elevated protein to creatinine ratio of 0.56. She was transferred to an acute care facility for evaluation of pre-eclampsia. Her blood pressure on admission was 168/69 mmHg, and she was initiated on labetalol 100 mg intravenously, with betamethasone, intravenous penicillin, and magnesium sulfate. The patient was transferred to an institution equipped to manage high-risk pregnancies. After transfer, she was asymptomatic and normotensive. Clinicians discontinued the nifedipine, which they believed was masking pre-eclampsia-related hypertension. Three days after nifedipine was discontinued, she had severe hypertension, for which she received 20 mg of intravenous labetalol, followed by an additional 40 mg. Approximately 20 min after each dose of labetalol, she experienced intense areolar burning. The patient states she previously experienced this burning phenomenon when she was exposed to cold weather. Each episode of areolar burning lasted approximately 15–20 min. The burning sensation completely resolved within 1 h of labetalol administration. Clinicians began scheduled oral nifedipine with intravenous nifedipine and labetalol for breakthrough hypertension. The patient denied further areolar pain, even after six doses of labetalol. The patient had an uncomplicated cesarean section and gave birth to a healthy baby. Authors concluded that this was among the first documented cases of Raynaud's phenomenon of the nipple secondary to labetalol use. They recommend that clinicians be aware of this possible side effect of labetalol as patients may not report this side effect due to discomfort or embarrassment. The authors additional emphasize the importance of patient education to report any nipple pain that occurs after starting therapy with labetalol.

Metoprolol

Skin

Pemphigus vulgaris (PV) is a rare, potentially life-threatening autoimmune disorder that frequently occurs without an identifiable etiology [22A]. A case report by Patel and colleagues describe a 79-year-old American female who was referred to an oral medicine clinic for evaluation of sloughing and bleeding of the gingiva. Although the oral lesions were painless, she had also experienced painful scalp lesions for the last 3-months. Biopsy confirmed the diagnosis of pemphigus-like reaction in her oral mucosa and scalp. The patient's medication history included metoprolol 100 mg twice daily for atrial fibrillation. Clinicians noted that metoprolol-induced PV has been published in medical literature; therefore, the patient was switched to diltiazem by her cardiologist. She remained symptom-free at 1 and 4 months after metoprolol discontinuation. Authors concluded that this patient experienced metoprolol-induced PV. Authors recommend considering metoprolol as a causative agent in PV-like lesions.

Timolol

Cardiovascular

A case report by Wang and colleagues describe a case of a 62-year-old Chinese male who was taking timolol eye drops for a 13-year history of glaucoma [23A]. The patient presented to the emergency room for intermittent shortness of breath, dizziness, and amaurosis. He was hypertensive (BP 190/100 mmHg) with a heart rate of 29 beats per minute on presentation. He had been taking hydrochlorothiazide for the past year, and timolol eye drops for the last 13 years. A 12-lead EKG showed bradycardia with third-degree AV block. Isoprenaline was administered and up-titrated to 3 μg/min. During the course of the hospitalization, clinicians noted the patient experienced bradycardia to 35 BPM correlating with administration of timolol eye drops. Timolol was discontinued in favor of travaprost therapy after an ophthalmology consultation. About 48 h after timolol was discontinued, the patient's heart rate increased to 65 beats per minute without the isoprenaline drip and an EKG showed intermittent first-degree AV block. One week after admission, a Holter monitor showed first-degree AV block with intermittent second-degree type II AV block. Authors determined that timolol was likely the causative agent transforming the patient's existing first-degree A-V block into third degree A-V block. At the time of the case's publication the patient remained asymptomatic under continued monitoring. Authors concluded that topical timolol can induce severe systemic side effects. They recommended that health care providers should be mindful of the potential for cardiovascular side effects.

Skin

Koumaki and Orton describe a case of allergic contact dermatitis in a 17-year-old adolescent male in the United Kingdom. The patient was using timolol 0.25% eye drops

(which contained the preservative benzalkonium chloride 0.01%) for glaucoma caused by radiotherapy for a diffuse choroidal hemangioma resulting from Sturge–Weber syndrome [24A]. The patient presented with a 1-month history of persistent left-sided periorbital dermatitis, edema, and infections. The patient was initially prescribed tacrolimus 0.1% twice daily for dermatitis, but this was not well-tolerated and was discontinued. He was prescribed miconazole 2% and hydrocortisone 1% cream to be applied topically twice daily for 7 days. The patient underwent allergy patch testing, including tests for the prescribed timolol eye drops and benzalkonium 0.1% aqueous solution. The patch test readings were positive for the timolol eye drops and not to the benzalkonium chloride solution. Clinicians determined that the patient's adverse reaction to timolol was due to allergic contact dermatitis. The timolol eye drops were discontinued, and the patient experienced complete remission within 2 weeks. Authors concluded that although some allergic reactions to topical beta blockers may be due to preservatives or excipients in medicinal therapies, this case demonstrates a true allergy to timolol. Authors recommend to perform allergy patch testing in the case of possible allergic contact dermatitis.

Musculoskeletal

Oliphant and Gouws describe a 55-year-old male patient in the United Kingdom, being treated for ocular hypertension with topical timolol 0.25% to each eye [25A]. The patient developed both Peyronie's disease and Dupuytren's contracture within 3 months of starting the timolol solution. Both the Dupuytren's contracture and Peyronie's disease were interfering significantly with the patient's quality of life. The patient's timolol eye drops were switched to a prostaglandin analogue and a carbonic anhydrase inhibitor. After discontinuation of timolol, the patient experienced no worsening of his symptoms, however, neither improved. Authors concluded that beta blockers can be implicated in causing fibrotic conditions. Authors recommend that clinicians be aware of this uncommon but possible side effect of topical beta blockers.

CALCIUM CHANNEL BLOCKERS [SEDA-40, 265; SEDA-41, 222–223]

Amlodipine

Drug–drug interaction

Morgenthau and Kim described an interesting case of lisinopril-induced angioedema which seemed to be exacerbated by amlodipine [26A]. The patient was a 50-year-old man with polycystic kidney disease who awoke from sleep with unilateral jaw swelling. Home medications included amlodipine, lisinopril, allopurinol, venlafaxine, and talvaptan. This swelling progressed over 6 h to involve his lips and tongue. He presented to the emergency room where he required emergency intubation for airway management. On physical exam, the patient was found to have edema of the jaw, lips, tongue, and eyelids. The patient reported that he had been experiencing similar unexplained jaw swelling which would resolve within hours to days. The patient could not recall when the jaw swelling had begun but did note that the frequency of episodes had increased over the last 4–6 months, which correlated with initiation of amlodipine. The patient's lisinopril and amlodipine was discontinued, and the patient improved over the next 4 days. The patient expired from unrelated causes 2 months after discharge. There had been no re-occurrence of angioedema. Authors concluded that ACE inhibitor-induced angioedema can be exacerbated by amlodipine, although the mechanism of this interaction is unknown. They concluded that drug-induced angioedema can occur months to years after starting the inciting agents and can present with progressive and recurrent symptoms. Patients who present with suspected drug-induced angioedema should receive aggressive airway management, including intubation if severe.

Mouth and teeth

Cyclosporine A is one of the most frequently used immunosuppressants used to prevent organ rejection after kidney transplantation. Patients taking cyclosporine may need additional antihypertensive therapy due to cyclosporine-induced vasoconstrictive hypertension. This is of particular concern for patients initiated on calcium channel blockers. Gingival overgrowth occurs in about 1.7%–3.3% of patients taking cyclosporine and amlodipine. A case report by Nanda et al. describes a 42-year-old man who presented to a periodontology clinic complaining of a 1-year history of swollen gums, particularly in the upper left side of the mouth [27A]. The patient also described bleeding while brushing, which resolved on rinsing of the mouth. He had been taking cyclosporine with amlodipine for 11 years post renal transplant. Supragingival scaling and polishing was performed, followed by subgingival scaling and root planing, followed by surgical treatment. One month after treatment, the patient's gingival overgrowth was resolved. Authors concluded that although the patient may have benefitted from a change in his anti-rejection or antihypertensive medications to ameliorate the noted side effect, a therapy change may have led to adverse post-transplant outcomes. In this instance, preventative treatment with scaling and root planning was of most benefit to a patient with drug-induced gingival overgrowth. Authors recommend that dentists should make

decisions about optimal dental interventions in conjunction with the medical providers treating the patient's medical problems.

Drug overdose

A case report by Haughey et al. describes a 47-year-old man who attempted suicide by ingesting 400 mg of amlodipine and 200 mg of lisinopril [28A]. The man was found unconscious and had several episodes of emesis during transportation to the hospital. On arrival, he was obtunded with a blood pressure of 60/40 mmHg. His serum creatinine was 2.3 mg/dL, and there was evidence of lactic acidosis (pH 7.24, lactate = 8.4 mmol/L). The patient received 6 L of crystalloid fluids and was started on epinephrine, norepinephrine, phenylephrine, dopamine, and vasopressin. He received a lipid emulsion, and hyperinsulinemia/euglycemia therapy was started. Despite utilization of various airway support measures, including ventilator support with volume control, pressure control, and BiLevel, the patient remained hypotensive with worsening hypoxemia and lactic acidosis. The patient was placed on venous extracorporeal membrane oxygenation (VV ECMO). Due to the large volume of dextrose being administered to achieve euglycemia with concomitant IV insulin administration, the patient became net positive 23.8 L by hospital day 2. Despite diuretic administration, satisfactory kidney function, and adequate urinary production, the patient remained net positive, and continuous renal replacement therapy was initiated. He gradually improved on VV ECMO and renal replacement therapy, and he was weaned off vasopressors and decannulated from ECMO by hospital day 7. The patient was extubated on hospital day 10 and was discharged to an acute rehabilitation facility on hospital day 18. Authors concluded that this was the first reported case of calcium channel blocker and ACE inhibitor overdose treated successfully with VV ECMO. Authors recommend consideration of VV ECMO as a viable treatment strategy for calcium channel blocker and ACE inhibitor overdose which results in refractory hypoxemic respiratory failure if cardiac function is preserved. If cardiac function deteriorates, authors recommend considering venoarterial ECMO instead.

Another case report from Khan and colleagues describes a 57-year-old male who attempted suicide by ingesting 30 tablets of amlodipine 10 mg [29A]. The patient was evaluated in the emergency room for lightheadedness. On exam he was bradycardic with a heart rate of 50 beats per minute and hypotensive with a systolic blood pressure of 70 mmHg. Clinicians administered 2 L of intravenous normal saline. On admission, his potassium was 3.2 mmol/L, bicarbonate was 19 mmol/L, creatinine of 6.3 mg/dL, and calcium of 8.2 mg/dL. He received 2 more liters of normal saline, then calcium gluconate in dextrose was started as recommended by the local poison control center and the patient's potassium was supplemented. He received 20 g of dextrose 5% at a rate of 100 mL/h. At that time, an EKG showed a QTc of 525 ms. Approximately 6 h after an infusion of calcium chloride was started, the patient's potassium increased from 2.7 to 3.6 mmol/L, bicarbonate increased slightly from 17 to 18 mmol/L, creatinine decreased from 9.3 to 2.7 mg/dL, and calcium increased from 9.3 to 22.7 mg/dL. The calcium was stopped, and an EKG at that time showed a QTc of 393 ms. Five hours later, the patient's calcium was 19.4 mg/dL. Three hours later the patient began complaining of abdominal pain. A CT showed peripancreatic stranding consistent with acute pancreatitis. Treatment was started with an isotonic solution, which improved the patient's symptoms. The authors concluded that management of calcium channel blocker overdose involves optimizing intravascular volume and restoring cardiac output. Administration of calcium is beneficial for hemodynamic stability, but the optimal dose is not well established. Authors recommend avoiding hypercalcemia-induced pancreatitis by measuring serum calcium levels frequently while administering intravenous calcium gluconate for amlodipine overdose.

Another case report of an amlodipine overdose describes a 73-year-old man evaluated in the emergency room of a Japanese hospital for altered awareness, decreased body temperature, and hypotension [30A]. The patient was found at home with empty pill packages of many prescription medications, including packages originally containing 200 tablets of metformin, 78 tablets of glimepiride, 2 tablets of alogliptin, 29 tablets of candesartan and 84 tablets of amlodipine; therefore, clinicians presumed the patient overdosed. A serum amlodipine level was measured at 90.2 ng/mL on the patient's arrival to the hospital. Normal amlodipine concentrations are around 8 ng/mL, giving further evidence that this patient experienced an amlodipine overdose. The patient was intubated and 100 mL of lipid emulsion was administered as an intravenous bolus, and continuous hemodialysis and hemodiafiltration.

(CHDF) were simultaneously initiated and continued for about 24 h. The patient rapidly improved in a few hours. The patient's amlodipine level immediately after lipid emulsion therapy was 49.9 ng/mL; however, towards the end of dialysis, the level increased to 70.8 ng/mL on admission day 2, followed by a drop to 26.2 ng/mL on day 3, and then 13.4 ng/mL on day 7. Authors concluded that amlodipine elimination half-life during the period following hemodialysis treatment was about 60 h, which was longer than the previously reported range (30–50 h). Based on the positive results of this trial, authors recommend to consider infusion of a lipid emulsion for amlodipine overdose.

Efonidipine

Skin

A 2019 case report from Davis et al. details an 84-year-old woman in India who experienced an exanthematic drug eruption 1 week after beginning therapy for hypertension and left anterior descending artery stenosis with aspirin, clopidogrel, atorvastatin, pantoprazole, nebivolol, aldactone, and efonidipine [31A]. The patient presented with generalized itching and erythema for the previous 4 days. All of the patient's medications were discontinued and she was given topical steroids and oral antihistamines for symptom management. To confirm the identity of the drug that had precipitated the adverse reaction, efonidipine 20 mg daily was re-initiated on the third day of admission. The patient developed itching 8 h after receiving the medication, and efonidipine was stopped and switched to nebivolol. She did not develop any additional adverse reactions after the remainder of her home medications were restarted. Using the World Health Organization Uppsala Monitoring Center causality assessment, authors concluded that the association between the patient's reaction and efonidipine was "certain." Authors recommend that health care professionals carefully monitor patients for development of skin reactions while administering calcium channel blockers.

Verapamil

Bradycardia

A case report by Drutel et al. described a 59-year-old American man who was found to be bradycardic during a routine physical exam by his primary care provider [32A]. He was referred to the hospital for evaluation. An EKG on presentation showed irregular bradycardia. The patient was taking verapamil, clonidine, and hydralazine for hypertension. At that time, verapamil was discontinued and the patient returned to normal sinus rhythm. The patient was discharged on the second hospital day. Authors concluded that verapamil caused a junctional escape rhythm due to sinus bradycardia.

DIURETICS [SEDA-41, 223–224]

Hydrochlorothiazide

Skin

A case report from Reap et al. describes an 80-year-old woman who developed severe acute generalized exanthematous pustulosis (AGEP), a severe cutaneous adverse reaction characterized by the appearance of erythematous plaques and papules with overlying non-follicular pinpoint pustules [33A]. The patient reported a 1-year history of a diffuse, erythematous rash located in her trunk, upper extremities, and face, and she presented to the hospital after 3 days of bilateral eye swelling. This swelling was severe enough to disrupt her regular social engagements. Prior to admission, she had been treated by a dermatologist, who previously prescribed multiple courses of low and medium potency topical and oral steroids. These steroid courses would temporarily improve the rash, but the symptoms would worsen after completion of the course. During hospitalization, a skin examination revealed a maculopapular rash on the face, trunk, upper extremities, and chest. A medication history was taken, which revealed the patient had previously taken atenolol which was switched to combination hydrochlorothiazide and losartan approximately 1 year prior to admission. She reported that the rash started about 2 weeks after initiation of this new blood pressure regimen. Clinicians discontinued the combination hydrochlorothiazide and losartan and administered topical mupirocin and steroids. The patient's rash improved extensively overnight, and she was discharged home. At a follow-up 2 weeks later, her rash had completely resolved, and her blood pressure was adequately controlled on metoprolol succinate monotherapy. Authors concluded that either the hydrochlorothiazide or losartan may have potentiated this skin reaction, and because both medications were co-administered, it is difficult to assign causality to either one agent. Authors did note that there are no case reports in medical literature describing losartan-induced AGEP. In contrast, hydrochlorothiazide carries a high risk of adverse drug reactions, 59% of which occur in the skin. Authors concluded that the most likely causative agent for this patient's drug related adverse effect was the hydrochlorothiazide. Authors recommend that a thorough medication review, including timing of medication initiation and discontinuation, is critical in evaluating novel rashes.

Respiratory

Kaabi and colleagues report a 53-year-old Tunisian woman who experienced acute dyspnea 4 days after starting a combination of olmesartan and hydrochlorothiazide once daily for hypertension [34A]. She was also taking tamoxifen for breast cancer that had been treated surgically 1 year prior. She presented to the emergency room and improved on oxygen therapy. The patient continued taking the olmesartan/hydrochlorothiazide combination tablet for 3 additional weeks, and mild dyspnea and breathlessness persisted. The patient experienced two more episodes of acute respiratory distress, which required emergency room evaluation. The olmesartan/hydrochlorothiazide was replaced with irbesartan. Three days after the change of therapy, the

patient's dyspnea had resolved completely. Authors of this case report concluded that the hydrochlorothiazide was the causative agent of this patient's dyspnea symptoms because olmesartan has not been associated in previous literature with dyspnea. Authors recommend in the case of persistent dyspnea without other causes, clinicians should evaluate for hydrochlorothiazide as a possible cause.

Spironolactone

Electrolyte balance

A randomized, placebo-controlled clinical trial published by Charytan and colleagues in the United States describes the safety and efficacy of spironolactone in patients who have end stage renal disease (ESRD) dependent on hemodialysis (HD) [35C]. Investigators randomized 129 patients on HD to placebo or spironolactone 12.5, 25 or 50 mg daily in a 2:1:1:1 ratio for 36 weeks. The primary safety endpoints were hyperkalemia (defined as $K > 6.5$ mEq/L) and hypotension requiring emergency department visit or hospitalization. Diastolic function was assessed by echocardiography. Researchers determined that hyperkalemia frequency was similar between all doses of spironolactone and placebo (0.49 vs 0.50 events per patient-year, $P = 0.9$); however, an increased rate of hyperkalemia was observed at the 50 mg spironolactone dose (0.89 events per patient-year, $P = 0.04$). Hypotension occurred infrequently and event rates were similar between spironolactone and placebo. Change in diastolic function was similar with spironolactone and placebo. Researchers concluded that spironolactone appears safe in carefully monitored maintenance hemodialysis patients; however, their data did not support a benefit to cardiovascular parameters as seen in landmark trials. Authors recommend that the results of this trial be used to inform decisions related to safety of spironolactone in patients who require hemodialysis. The data from this trial suggest that spironolactone is safer at a maximum of 25 mg dosage in patients on maintenance HD.

Endocrine

A case report of an 86-year-old man in Belgium was published by Dhondt et al. detailing progression of prostate cancer after starting spironolactone [36A]. The patient had been admitted for acute clot retention. He was diagnosed with a high-risk cT3b, Gleason 5+5, PSA 756.2 μg/L adenocarcinoma of the prostate. He was started on androgen deprivation therapy and responded well. His PSA nadir was 2.1 μg/L. The patient developed Metastatic Castration-Resistant Prostate Cancer (mCRPC) 25 months after initiation of androgen deprivation therapy (PSA 278.7 μg/L) with radiographic evidence of bone metastases. In response, the patient was started on systemic abiraterone and prednisone. Three months after initiating this regimen, his PSA had increased significantly to 792.7 μg/L and scans showed new, multifocal metastatic disease. Primary resistance to abiraterone was suspected until the patient revealed that his primary care provider had initiated spironolactone for treatment of edema and hypertension. The spironolactone was discontinued, and within 1 month the patient's PSA was 334.2 μg/L. Eight months after spironolactone was discontinued, the patient continued to show positive response to abiraterone. Authors concluded that spironolactone acts as a partial androgen receptor agonist in an androgen-depleted environment. Authors recommend against use of spironolactone for symptoms of glucocorticoid-refractory mineralocorticoid excess in mCRPC patients treated with CYP17 inhibitors. If low-dose glucocorticoid supplementation is not enough to control mineralocorticoid excess in patients treated with abiraterone, clinicians should consider amiloride with or without hydrochlorothiazide.

ALPHA-2 AGONISTS [SEDA-41, 224]

Clonidine

Drug overdose

An American case report of a 4-year-old who unintentionally ingested four 0.1 mg clonidine tablets showcased the development of altered mental status and bradycardia [37A]. He had been prescribed the clonidine for management of autism and associated attention-deficit/hyperactivity disorder. Shortly after ingestion, the patient became altered and limp. The patient was brought to a community hospital emergency department approximately 1 h after ingestion of the clonidine. On initial exam, the patient was found to have altered mental status and sinus bradycardia (heart rate 54 BPM). The patient's presentation mimicked signs of opiate overdose; therefore, naloxone hydrochloride was administered followed by isotonic crystalloid fluids. Throughout treatment, the patient exhibited progressively worse bradycardia and alteration. The patient began exhibiting agonal breathing and intermittent episodes of apnea. His Glasgow Coma Scale score was 4, with a heart rate of 63 BPM. His pupils were dilated, non-reactive and he had diminished lung sounds bilaterally. Three attempts were made prior to successful intubation, which was complicated by episodes of emesis. The local medical team transported the patient by helicopter to the closest children's hospital. On his arrival to the children's hospital, he was observed in the pediatric ICU for aspiration pneumonitis, but his condition improved and he was extubated the next day, and discharged that evening. Authors concluded

that management of clonidine overdose is largely supportive with a primary focus on cardiopulmonary support. The signs and symptoms of clonidine overdose can mimic that of opioid overdose, which led to naloxone administration in this case. Although naloxone can be safely used in children, it is not typically considered useful to use in clonidine poisoning. Authors recommend that clonidine overdose be managed with supportive care, activated charcoal depending on the patient's clinical status, and intubation in the presence of dyspnea or apnea. They also recommend bradycardia treatment with crystalloid bolus, although atropine can also be used.

VASODILATORS [SEDA-41, 224–225]

Hydralazine

Drug overdose

Vahabzadeh et al. described a 38-year-old Iranian woman who purposefully ingested 10 mg clonazepam and 750 mg hydralazine in a suicide attempt, and presented to the hospital 2 h after ingestion [38A]. On arrival to the emergency department the patient's blood pressure was 70/55 mmHg and heart rate was 90 BPM. The patient was lethargic but pupils were reactive to light. An EKG was positive for ST-elevation myocardial infarction and she was started on aspirin, clopidogrel, heparin infusion, nitroglycerin infusion, and oral atorvastatin. She underwent coronary angiography which showed no visible disease. Thirty-six hours after presentation to the hospital, her symptoms improved and 2 days later, she was discharged from the hospital in good condition. Authors concluded that this patient experienced hydralazine-induced EKG changes. They note that there is no specific antidote for hydralazine; therefore, patients should be managed with gastric lavage and activated charcoal slurry if the patient's condition permits. The authors also remarked that cardiopulmonary support is of the greatest importance while managing patients with hydralazine overdose.

Cardiovascular

A case report by Paley et al. describes a 45-year-old patient with hydralazine-induced anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) [39A]. The patient had a medical history of Marfan's syndrome and hypertension, who presented with a 3-week history of sharp chest pain, radiating to the back, left arm, and abdomen. She had been taking hydralazine 100 mg three times daily. Her blood pressure was 210/107 mmHg with a heart rate of 47 BPM. She received prochlorperazine for nausea, which lead to angioedema of the mouth and pharynx complicated by cardiac arrest with successful resuscitation. A CT angiogram showed a type B dissection of the entire descending aorta. The aorta was repaired surgically with stent placement. Postoperatively, the patient stopped producing urine and required emergent hemodialysis. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were positive at 1:320 and 1:1280, respectively. Renal histology showed pauci-immune diffuse necrotizing crescentic glomerulonephritis. She was diagnosed with hydralazine-induced AAV and treated with intravenous methylprednisolone for 3 days, then oral prednisone 1 mg/kg/day. On day 4 of prednisone, blood was noted in her endotracheal tube. She became hypoxic and was started on ECMO. A chest X-ray showed bilateral lung opacities consistent with diffuse alveolar hemorrhage. She underwent plasma exchange for six cycles and received two doses of rituximab. She remained on ECMO for 3 weeks. Her tracheostomy was decannulated after 6 weeks and dialysis was discontinued after 8 weeks. Her renal function improved and her creatinine stabilized at 1.1 mg/dL after 6 months. Authors concluded that this patient experienced hydralazine-induced AAV, and she was treated successfully with ECMO and intravenous rituximab. Authors recommend that clinicians utilize a high-degree of vigilance to treat this serious and rare complication of hydralazine.

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