CHAPTER

20

Antihypertensive Drugs

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ANGIOTENSIN-CONVERTING ENZYME INHIBITORS *[SED-15, 226; SEDA-33, 416; SEDA-34, 321; SEDA-35,364, SEDA-36, 282]*

General Information

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to possess chemoprotective properties in a majority of the studies. An elevated risk of cancer has been noted patients taking Angiotensin II Receptor Blockers (ARBs) in meta-analysis of trials but these trials were not designed to assess cancer risk. A retrospective cohort study investigated the relationship between ACEIs, ARBs and cancer risk in patients with high drug compliance (over 80%). The results indicate that patients on ACEIs had an overall lower risk of developing cancer. ACEIs are thought to exert their protective effect by reducing the degradation of angiotensin I to angiotensin II. ARBs block type I angiotensin II receptor which is anti-carcinogenic [1c].

Cardiovascular

A 51-year-old female was admitted with swollen tongue from taking an ACEI to which she had a reaction of angioedema about 5 months prior. She was advised never to take an ACEI again but later resumed the medication despite medical advice. She was intubated due to vocal cord and arytenoid edema. Her temperature was 36.7 °C, pulse rate was 80 beats per minute, blood pressure was 171/84 mmHg and oxygen saturation was 98% in room air. Her electrocardiogram showed deep T-wave inversion in the anterolateral leads and had a peak troponin-I level of 0.24 ng/mL leading to the diagnosis of non-ST segment elevation myocardial infarction. Her past medical history included diabetes mellitus, hypertension and tobacco use. She did not have a history of coronary artery disease or cardiomyopathy. Allergic myocardial infarction (Kounis syndrome) was included in her differential diagnosis. She had normal coronaries in her cardiac catheterization. She recovered in 1 week, and was discharged. Many drugs have been implicated as culprits in Kounis syndrome, however, none reported an ACEI. The name of the ACEI was not identified in this report [2A].

Delapril

General Information

Delapril is an ACEI that has been around since late 1980s and is available in a number of European and Asian countries. It has an indanylglycine moiety, differentiating it from captopril or enalapril, making it more lipophilic and thus more effective on ACE inhibition. It has less of an effect on bradykinin potentiation. It is metabolized in the liver into active and inactive metabolites. It has an elimination half-life of up to 3.4 hours with active metabolites and is renally excreted. The incidence of cough with delapril was 5% in one study. The antihypertensive effect of delapril is similar that the obtained with other ACEIs and has reno-protective and cardioprotective actions, with the potential to increase insulin sensitivity in hypertensive type 2 diabetic patients [3R].

Lisinopril *[SED-15, 2071; SEDA-33, 418; SEDA-34,324; SEDA-35, 367, SEDA-36, 282]*

Mouth and Teeth

Lisinopril contains a thiol group which has been reported to be involved in drug-induced pemphigus. Previously reported cases include the skin changes without mucosal involvement. Oral bullous eruption was reported with lisinopril in a case report in which a 78-year-old female suffered blisters and ulcers in vestibular, buccal, upper and lower jaw mucosa 3 weeks after taking

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lisinopril. She had been taking amlodipine for a year without any complications. The oral lesions resolved in a month with topical therapy and withdrawal of lisinopril [4A].

Drug Interactions

A 58-year-old female suffered angioedema while undergoing treatment for metastatic clear-cell renal cell cancer with everolimus. She had also been on lisinopril for hypertension for a year prior to starting everolimus. With increasing use of everolimus in oncologic treatment, using alternative antihypertensives other than ACEI may be warranted [5A].

ANGIOTENSIN RECEPTOR BLOCKERS/ ANGIOTENSIN II RECEPTOR ANTAGONISTS [SEDA-15, 2071; SEDA-34, 324; SEDA-35; SEDA-36, 282]

General Information

Acute toxicity from exposure to ARBs was assessed in an observational case series. The ARBs reported in 206 cases included candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Out of the acute toxicities reported in 150 children, only one required intervention for a blood pressure of 60/40 mmHg for a 2.5 year old who ingested an 8.75-fold maximum daily dose based on weight. The authors reported that 16.7% of patients experienced mild symptoms including hypotension, fatigue, dizziness, nausea, vomiting and somnolence. Moderate to severe symptoms were reported in 8.9% of patients including syncope, coma and/or pronounced hypotension. There were no reports of acute toxicities of less than fivefold of the maximum daily dose based on weight. The study concluded that patients with accidental overdose must be evaluated thoroughly. Since ingestion of less than a fivefold of the maximum daily dose (MDD) yielded no severe symptoms, only symptomatic patients and those who have ingested a greater than fivefold of the MDD should be referred for medical assessment [6c].

Drug–Drug Interactions

A French pharmacovigilance study assessed the reported adverse drug reactions (ADRs) associated with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) with antihypertensive agents. Of the 81 084 ADRs reviewed by the authors of the study, 517 reports involved NSAIDS and of those, 125 (24.2%) were related to a drug–drug interaction with an antihypertensive agent. Cardiovascular ADRs such as heart failure, stroke, myocardial infarction, or increased blood pressure were found in 15 (2.9%) of reports, whereas acute renal failure, hyponatremia, and hyperkalemia was reported in 116 (28.1%) of cases. Acute renal failure occurred in 105 cases (25.4%), and had increasing frequency when used in combination with ACEI/ARB/diuretics. Nearly half of the cases (43/105) could not be connected to another cause. No particular NSAID was associated more frequently in adverse events. Women were found to be more likely to be exposed to concomitant use of both NSAIDs and antihypertensive agents. The authors advise caution, especially in women, to limit the use of NSAIDs in combination with ACEI/ARB/diuretics due to an increased risk of renal failure [7c].

Fimasartan [SEDA-36, 283]

Comparative Study

The safety and efficacy of fimasartan were compared to valsartan in a Korean population. While both fimasartan and valsartan significantly decreased blood pressure, fimasartan 60 mg daily reduced diastolic blood pressure more significantly than valsartan 80 mg daily. Fimasartan was well tolerated with the most common side effect being headache in 5% of the patients. Other side effects included dizziness, insomnia, nasopharyngitis, chest pain, diarrhea and elevated alanine aminotransferase. At a higher dose of fimasartan, 120 mg daily, 6.7% of patients experienced a transient increase in alanine aminotransferase [8c].

Irbesartan [SED-15, 1908; SEDA-32, 386; SEDA-36, 371]

Skin

A 52-year-old female presented with asymptomatic diffuse purpuric eruption which had been present for 2 years. Affected areas included the intergluteal, axillary and inguinal folds. Irbesartan and hydrochlorothiazide combination product had been initiated 7 years prior to presentation. The product was discontinued with complete resolution in 9 weeks. The same medication combination was used in another patient, a 78-year-old female, who developed itching and a rash in the gluteal region, which cleared after stopping the drug. The drug was reinitiated 9 months after resolution with no relapse of the rash [9A].

Losartan [SED-15, 2168; SEDA-32, 387; SEDA-33, 419; SEDA-36, 371]

Genetic Factors

Most safety and efficacy studies conducted with losartan were in caucasian populations who may have distinct genetic variations from Asians. The effects of losartan in

several Asian populations were recently evaluated in multiple studies involving the use of losartan in various Asian populations. In one study, researchers reported mild adverse reactions (5.8% of cases) in Indian patients. In another study, 11% of Japanese patients developed adverse effects. Chinese patients on losartan exhibited a significant decrease in serum urate levels. That authors suggest that Asian patients may have a genetic predisposition to experience dry cough with ACEI and therefore ARBs may be safer alternative antihypertensive agents [10R].

Olmesartan

Gastrointestinal

Several recent case reports with enteropathy adverse events have been reported recently with olmesartan. In one, a 78-year-old female prescribed and taking olmesartan for 4 years for hypertension presented with severe watery diarrhea over the past 4 months. Her biopsies showed mild villous blunting in the proximal small intestine with intraepithelial lymphocytosis and lamina propria inflammation, thickening of the subepithelial basement membrane, intraepithelial lymphocytosis and lamina propria chronic inflammation with eosinophil infiltration in the terminal ileum. She was diagnosed with celiac-like enteropathy, collagenous ileitis and collagenous colitis. Olmesartan was discontinued as the likely culprit along with atorvastatin and the diarrhea subsequently resolved. Upon re-challenge with olmesartan only, diarrhea returned. Ramipril was then substituted for olmesartan, which provided resolution of diarrhea. A repeat colonoscopy 4 months after initial findings revealed complete resolution of enteropathy-like changes. Given the long time course on olmesartan before presentation, this suggests a cell-mediated reaction [11A].

A 70-year-old female taking olmesartan for 2 years presented with worsening diarrhea, epigastric pain, and a 30 pound weight loss. Celiac tests were negative, computed tomography showed diffuse wall edema and thickening of the jejunum and ileum. After discontinuation of the drug, symptoms improved. Previous cases suggest sprue-like enteropathy with a likely cell-mediated immune response. This is the first case report to describe villous atrophy on push enteroscopy and capsule endoscopy due to olmesartan-induced enteropathy [12A].

A 62-year-old female presented with similar symptoms including abdominal pain, weight loss, and nausea despite following a gluten-free diet. The patient's biopsy findings revealed persistent villous blunting with epithelial lymphocytosis. Olmesartan was discontinued and within 2 months, the patient's symptoms resolved. Olmesartan may have been the reason for development of collagenous sprue [13A].

Sprue-like enteropathy associated with olmesartan use was subsequently found in a 57-year-old woman who initially presented with 3 weeks of nausea, vomiting, and diarrhea. Histological findings of diffuse villous blunting and increased intraepithelial lymphocytes determined this to be consistent with celiac disease or another sprue-like process. The patient's symptoms improved significantly after not receiving olmesartan due to formulary restrictions at a care facility. The symptoms completely resolved within 2 weeks of discharge [14A].

Drug Interactions

Recombinant tissue plasminogen activator (rt-PA) is known to increase the risk of angioedema especially in those using ACEIs. ARBs are generally not thought to carry the same risk of angioedema, however, several cases have been reported. One recent case is the first known case of its kind to showcase angioedema from use of an ARB and rt-PA therapy. A 80-year-old Asian female presented with left-sided weakness and was given rt-PA with improvement in symptoms. The patient started developing difficulty breathing, throat pain, dysarthria and an odd sensation in her mouth 6 minutes after the end of infusion. Angioedema of the tongue, uvula, and lips was diagnosed and steroids started for treatment with presentation attributed to rt-PA. Olmesartan was initiated at 20 mg daily for hypertension after angioedema developed. Angioedema did not fully recover until olmesartan was also discontinued, suggesting potentiation by olmesartan in persistent angioedema symptoms [15A].

Valsartan [SEDA-36, 383]

Dermatological

A 58-year-old woman treated with valsartan and hydrochlorothiazide combination for 7 days presented with asymptomatic purpuric eruption of the palms spreading to the forearms. After discontinuation of the drug, the rash resolved in 2 months. In a case with a 64-year-old male, a cutaneous eruption on the lower limbs and buttocks present for 3 months, started 3 months after a dose increase of valsartan 160 mg from 40 mg which was initially started 2 years prior. The rash completely resolved within 2 months of discontinuation of therapy. A possible mechanism for this type of cutaneous reaction could be due to reduction of collagen content in the arterial intima through inhibition of AT-receptors [11A].

Observational Study

The safety and efficacy of valsartan were studied in a population with ages ranging from 6 months to 5 years in a randomized, double-blind study for 8 weeks followed by an 18-week open label continuation. The dosing of

valsartan was low: 0.25 mg/kg ($n=30$), medium: 1 mg/kg ($n=15$) or high: 4 mg/kg ($n=30$) once daily. No differences in adverse events were noted between the three different dosing strategies. Upper respiratory tract infections (8.1%) and abdominal pain (6.8%) were the most common adverse reactions reported. In regards to electrolytes and renal function, there were four patients who developed potassium levels >5.5 mmol/L all within the high dose regimen, although all had a history of renal conditions. One case resulted in discontinuation of therapy, but none were deemed serious by the researchers. Creatinine increases of more than 50% from baseline were observed in three patients in medium and high dose groups, however, there were no increases of more than 100% from baseline. A few patients had a decrease of more than 25% in glomerular filtration rate. In the extension study, the most reported adverse reactions by 57.6% of patients were fever (16.7%) and nasopharyngitis (10.6%). The adverse effects thought to be drug related were reported in 4.5% of patients included anorexia ($n=1$), hyperkalemia ($n=1$) and erythema ($n=1$). Adverse reactions of valsartan are generally mild to moderate in children aged 6 months to 5 years [16c].

CALCIUM CHANNEL BLOCKERS

Tumorigenicity

A population based study enrolled 880 women with invasive ductal breast cancer (IDC), 1027 with invasive lobular breast cancer (ILC) and 856 controls assessed the potential link between antihypertensive medication use and diagnosis of breast cancer. Patient interviews, past medical histories of hypertension, heart disease, use of antihypertensive agents such as: ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, diuretics, and combination therapies were collected at the time of use. There were no differences found between the three groups at baseline and 44% of the women in each group had a history of hypertension. While current, former, and short-term use of antihypertensive agents were not associated with risk of IDC or ILC, an increased risk was found in current users of calcium channel blockers for at least 10 years. This trend was found for both IDC (OR, 2.4; 95% CI, 1.2–4.9) ($P=0.04$ trend) and for ILC (OR 2.6; 95% CI, 1.3–5.3) ($P=0.01$ trend). Current use of short-acting formulations had a 3.7-fold increased risk for IDC (95% CI, 1.2–11.8) and 3.6-fold increased risk for ILC (95% CI, 1.2–11.4). Long-acting formulations did not have the same risk, however, use greater than 10 years did have increased risk (IDC: OR, 2.7; 95% CI, 1.2–5.7; ILC: OR, 2.5; 95% CI, 1.2–5.5). Current use of dihydropyridines for greater than 10 years also had an elevated risk of both ILC and IDC. The associations did not vary based on the ER status of the breast cancer. This is the first study to examine duration of therapy for greater than 5 years. All associations with an increased risk of ILC and IDC occurred at more than 10 years. This was a population observational study and thus results must be validated in clinical trials before discontinuation of calcium channel blockers can be recommended [17C].

DIRECT RENIN INHIBITORS [SEDA-33, 420; SEDA-34, 328; SEDA-35, 373; SEDA-36, 283]

Aliskiren

Liver

A 61-year-old woman undergoing routine liver function monitoring in conjunction with long-term antiepileptic therapy was noted to have a drug-induced liver injury manifested as an asymptomatic acute hepatic cytolysis 1 month after the initiation of aliskiren therapy. Upon discontinuation of aliskiren use, the patient experienced rapid biological improvement, including normalization of serum AST and a sharp decline in serum ALT within 1 week [18A].

Kidney

A prospective, open-label study of 67 patients with CKD who were already being treated with other antihypertensives was conducted to assess the reno-protective effects of Aliskiren. Significant decreases in eGFR after 4 weeks of aliskiren treatment were noted and patients returned to a pretreatment level within 12 weeks of treatment initiation [19c].

A case reported of patient developed acute renal failure after the addition of aliskiren to the patient's regimen including a: diuretic, angiotensin-converting enzyme inhibitor and aldosterone antagonist. This case highlights the point that acute renal failure can occur as an adverse effect of aliskiren. Little to no conclusive evidence exists about the safety of aliskiren when used in combination with multiple drugs that inhibit renin angiotensin aldosterone system, therefore caution should be exercised [20A].

Drug–Drug Interaction

The authors review the most relevant information available, reported from the last 5 years, pertaining to the most important clinical trials on renin–angiotensin system blockers. Data reviewed include the trials of aliskiren, telmisartan, olmesartan and azilsartan and the possible risk of cancer associated with ARBs. The results of ASPIRE and ALTITUDE trials suggest that concomitant use of aliskiren with either ARBs or angiotensin

converting enzyme inhibitors should be avoided. Olmesartan is an effective and safe antihypertensive agent but high-risk patients, such as those with coronary disease, should be carefully monitored for adverse events to avoid an excessive reduction in blood pressure [21R].

ACT-077825 (MK8151)

General Information

A study was conducted in healthy male subjects to evaluate the multiple-dose tolerability, pharmacokinetics, and pharmacodynamics of ACT-077825, a novel direct renin inhibitor [22c].

In this single-center, double-blind, placebo-controlled, active-controlled with 20 mg of enalapril, randomized multiple-ascending dose study, researchers found: adverse events, diarrhea, headache, and postural dizziness to be the most frequently cited side effects. The incidence of diarrhea was greater in the 1000 mg group and a dose of 500 mg of ACT-077825 was identified as the maximum tolerated dose [19c].

DIRECT VASODILATORS [SEDA-36, 284]

Hydralazine [SEDA-33, 427; SEDA-34, 331; SEDA-35, 379; SEDA-36, 284]

Immunologic

A 48-year-old woman with end-stage renal disease receiving continuous ambulatory peritoneal dialysis presented with polyarthritis. Painless cloudy peritoneal dialysis effluent was also noted. Analyses of the effluent dialysate showed an increased leukocyte count with a predominance of lymphocytes. The turbidity of effluent dialysate was still increased after 1 week of antibiotic treatment. Laboratory tests showed significant antinuclear antibody positivity. The patient had been taking hydralazine for 3 months prior to the event. Because drug-induced lupus was suspected, hydralazine was discontinued and low-dose steroids were initiated. Clinical symptoms and cloudy dialysate rapidly abated afterwards [23A].

A 68-year-old female presented with dyspnea on exertion and pleuritic chest pain of 1 week duration. Associated symptoms included low grade fever but no joint pain or rash. She had been maintained on warfarin for her paroxysmal atrial fibrillation and hypertension was managed with hydralazine 100 mg three times daily. Serology revealed anti-nuclear antibody anti-chromatin antibodies and anti-histone antibodies. A diagnosis of hydralazine-induced lupus syndrome was established, and the patient was started on high-dose prednisone after stopping hydralazine. The patient recovered with resolution of effusion on repeat echocardiograms [24A].

A case series reported four caucasian female patients who presented to a large, mid-western academic medical center on chronic hydralazine therapy with acute kidney injury, nephritic urine sediment on urine microscopy and had evidence of pauci-immune glomerulonephritis on kidney biopsy. This case series is of particular interest to rheumatologists due to the possibility of pauci-immune glomerulonephritis in patients taking hydralazine. It also highlights the presence of multiple antibodies in such cases and questions the long-term use of hydralazine especially in the elderly female population [25c].

DOPAMINE BETA-HYDROXYLASE INHIBITOR

Etamicastat

General Information

Etamicastat (also known as BIA 5–453) is a new generation, reversible, dopamine beta-hydroxylase inhibitor for hypertension. In a phase II study of males aged 18–65 years with mild to moderate hypertension, etamicastat 50, 100 and 200 mg daily showed dose-dependent decreases in both systolic and diastolic blood pressure after 10 days. However, the dose-dependent blood pressure effects were not clearly seen between doses 100 and 200 mg. The most common side effects experienced were dermatological, specifically maculopapular rash, pruritus, eczema and dry skin. This is could be a promising novel drug therapy that works by reducing the synthesis of norepinephrine [26C].

DRUGS THAT ACT ON THE SYMPATHETIC NERVOUS SYSTEM [SEDA-33, 424; SEDA-34, 329; SEDA-35, 376; SEDA-36, 286]

Guanfacine

Drug Overdose

A 12-year-old boy with attention-deficit/hyperactivity disorder and Tourette syndrome, presented 18 hours after ingesting three times his usual dose of extended-release guanfacine. On presentation, he was lethargic, bradycardic, and hypertensive with an otherwise nonfocal neurological examination. He remained hypertensive due to paradoxical initial stimulation of post synaptic receptors causing vasoconstriction, until administration of an intravenous antihypertensive agent, nicardipine, 24 hours after ingestion. Bradycardia may be a reflex response to hypertension. After cessation of the calcium-channel blocker, he continued to have intermittent episodes of symptomatic hypotension for the next 2.5 days. This

hypotensive effect is due to stimulation of central nervous system alpha two receptors. This particular case report is unique in that hypertension followed by prolonged symptomatic hypotension is rare with ingestions of centrally acting α2-adrenergic agonists [27A].

Methyldopa [SED-15, 2291; SEDA-33, 424; SEDA-34, 330; SEDA-35, 377; SEDA-36, 286]

Drug Overdose

A 50-year-old woman developed sinus bradycardia, prolonged profound hypotension, and drowsiness after ingesting over 300 tablets (>75 g) of methyldopa. Upon presentation, her blood pressure was 59/27 mmHg, heart rate 49 beats/minute, and Glasgow Coma Scale Score of 14. Severe methyldopa overdose can be complicated by prolonged profound hypotension. The management of these patients should include close monitoring of vital functions and administration of intravenous fluids, colloids, and vasopressor agents [28A].

DIURETICS

Chlorthalidone

Renal Disease

Adverse events were assessed following chlorthalidone administration in moderate to advanced chronic kidney disease. An interventional pilot study evaluated adding chlorthalidone to existing medications in a dose of 25 mg/day, and the dose doubled every 4 weeks if the blood pressure remained elevated. The following adverse events were reported in seven subjects. Hypokalemia, hyperuricemia, hyponatremia, transient creatinine changes, dizziness, hyperglycemia, and constipation. One subject reportedly had an ischemic stroke during the study. Chlorthalidone may significantly reduce BP via volume contraction in moderate to advanced CKD with poorly controlled hypertension. The authors conclude that adverse events may take weeks to appear after initiation of therapy and patients should be carefully monitored [29c].

Drug–Drug Interactions

An 85-year-old African-American female with atrial arrhythmias, maintained on dofetilide therapy, presented to an ambulatory cardiology clinic with hypotension. A pharmacist identified a potential major drug–drug interaction between dofetilide and chlorthalidone causing increased risk for hypotension. After discontinuation of chlorthalidone, the patient's systolic BP was maintained between 140 and 145 mmHg with low-dose amlodipine and lisinopril. This case highlights the importance of proper prescribing and monitoring of patients on dofetilide [30A].

Hydrochlorothiazide

Eyes

A case of hydrochlorothiazide (HCTZ)-induced retinal detachment has been reported in a 48-year-old man that presented with a 3-week history of a painless loss of peripheral vision in his left eye. An afferent pupillary defect was present; the patient had recently started a combination medication for his hypertension that included hydrochlorothiazide. The use of HCTZ, a sulfa-derivative, in this patient predisposed to uveal effusion (short eye, thick sclera) caused ciliochoroidal effusion syndrome, severe exudative phenomena of peripheral serous pigment epithelial detachment (SPED), and serous retinal detachment (SRD). A positive challenge test was withheld due to ethical reasons, however, the patient improved with atropine eye drops twice daily and discontinuation of HCTZ [31A].

Electrolyte Balance

A cohort study evaluated risk and predictors of adverse events in older adults with multiple morbidities. The primary outcome was a composite of metabolic adverse events (AE) defined as sodium less than 135 mEq/L, potassium less than 3.5 mEq/L, or a decrease in the estimated glomerular filtration rate (eGFR) of more than 25% from the baseline rate. Secondary outcomes included severe AEs (sodium <130 mEq/L, potassium <3.0 mEq/L, or a decrease in eGFR of more than 50%). Over the course of 9 months of follow-up, low-to-normal and unmeasured baseline sodium and potassium values were among the strongest predictors of hyponatremia and hypokalemia, respectively. Of the patients treated with thiazides, 42% had laboratory monitoring within 90 days after treatment had begun. Greater attention should be paid to potential complications and closer laboratory monitoring before and after initiation of thiazides [32C].

A longitudinal retrospective cohort study in kidney transplant patients assessed safety and efficacy of thiazides in kidney transplantation. Safety and efficacy comparisons were measured using changes in blood pressure between thiazide recipients and control patients. After controlling for baseline differences, safety analysis revealed thiazide recipients were at higher risk to develop hyperkalemia or hypokalemia. Based on long-term outcomes, thiazides appear to be safe and effective antihypertensives; however, in the short-term, thiazides may increase the risk of developing potassium disturbances [33c].

Skin

While bullous pemphigoid, a common subepidermal blistering disorder, typically occurs in the elderly without any obvious inciting event, a recent episode involving a

32-year-old male was reported. A case study documents a patient's experience of generalized bullous pemphigoid induced by HCTZ [34A].

Tumerogenicity

Hydrochlorothiazide was examined as a putative chronic antigen in a cohort of prospectively staged patients after patients were observed with HCTZ-associated common cutaneous T cell lymphomas (CTCL). Patients with hypertensive CTCL were divided into two groups based on whether they were treated with HCTZ or not. Association between HCTZ use and CTCL was analyzed and about 30% of patients experienced complete remission after discontinuing HCTZ. Three patients were rechallenged and developed lesions that resolved or improved with discontinuation of the medication. HCTZ is commonly prescribed and may be a putative antigen in a small subset of patients with mycosis fungoides [35c].

Genetic Factors

A study finds a novel mechanism HCTZ-induced adverse metabolic effect in African-American population. A genome-wide association study and meta-analysis of the change in fasting plasma glucose and triglycerides were reported in response to HCTZ in two separate clinical trials. Two single-nucleotide polymorphisms achieved genome-wide significance for association with a change in fasting plasma triglycerides in African Americans, whereby each variant allele was associated with a marked increase in triglyceride levels. Two single-nucleotide polymorphisms (rs 12279250 and rs 4319515 9r(2) = 0.730) located at 11p15.1in the NELL1 encodes a cytoplasmic protein that contains epidermal growth factor-like repeats and has been shown to repress adipogenic differentiation. A novel mechanism underlying adverse, HCTZ-induced, metabolic effects can be inferred from these findings [36M].

A genome-wide association study evaluated uric acid (UA) and hyperuricemia associated with HCTZ therapy. Single-nucleotide polymorphisms (SNP) were replicated in caucasians and African Americans treated with HCTZ add-on therapy in the PEAR study [8c]. Replicated regions were followed up through expression and pathway analysis. Five unique gene regions were identified in African Americans and one region was identified in caucasians. Increases in UA were observed following HCTZ therapy in individuals homozygous for risk alleles. Several risk alleles were also associated with an increased risk of HCTZ-induced clinical hyperuricemia. Several novel gene regions were associated with HCTZ-induced UA elevations in African Americans and one such region was associated with in caucasians [37c].

Indapamide

Eyes

A case is reported of indapamide-induced, transient myopia with ciliary body edema and supraciliary effusion. A 39-year-old caucasian female patient presented with a chief complaint of headache and sudden bilateral loss of distant vision. Neurological assessment and cranial CT scans were unremarkable. For the patient's hypertension, twice a day bisoprolol 2.5 mg and once a day indapamide 1.5 mg tablets were prescribed several days before. Two days after the patient stopped taking indapamide, the ciliary body edema and detachment disappeared [38A].

Triamterene

Kidney

Triamterene crystalline nephropathy has rarely been reported and its histologic characteristics are not well characterized. The authors of the article describe two cases of triamterene crystalline nephropathy, one of which initially was misdiagnosed as 2,8-dihydroxyadenine crystalline nephropathy [39A].

ENDOTHELIAN RECEPTOR ANTAGONISTS

Ambrisentan [SEDA-33, 421; SEDA-34, 328; SEDA-35, 374; SEDA-36, 284]

Eyes

A 29-year-old woman presented with bilateral painless blurred vision with a duration of 1 week and began after initial treatment of daily ambrisentan 5 mg for her recently diagnosed idiopathic pulmonary arterial hypertension. Her past medical history was notable for hypertension for which her medication regimen consisted of aspirin 81 mg daily, amlodipine 5 mg daily, and lisinopril 40 mg daily. On the day of presentation, her blood pressure was 132/90 mmHg. On dilated fundus examination, multiple cotton wool spots were noted in both eyes, along with several small nerve fiber layer hemorrhages. No early perfusion defect was found, but fluorescein angiography demonstrated focal areas of late hyperfluorescence and leakage in the cotton wool spots. A laboratory workup was unremarkable and ambrisentan was discontinued due to the correlation between initiation of therapy and symptoms. At a 2-week follow-up appointment, resolution of cotton wool spots were observed on dilated fundus examination and blood pressure remained stable at 140/85 mmHg. Tadalafil 40 mg daily was initiated as an alternative therapy for the

patient and she experienced no further visual changes or cotton wool spots [40A].

PROSTACYCLIN ANALOG

Treprostinil Diolamine

Hepatic Disease

The pharmacokinetics and safety of oral treprostinil diolamine was studied following a single-dose administration in 30 patients with mild, moderate, and severe hepatic impairment based on Child-Pugh classification. Mean plasma concentrations increased and clearance decreased by 89% with increasing severity of hepatic disease. The most frequently cited side effects were headache, nausea, diarrhea, and dizziness; 36 adverse events were reported in 12 (40%) of the 30 patients. The study ended enrollment for the severe group (Child-Pugh score >10) due to the severity of headache caused by treprostinil diolamine. Based on the results of this study, the authors suggest dose adjustments for Child-Pugh Class A with initial dose 0.125 mg twice daily and dose escalation every 3–4 days. Child-Pugh Class-B patients should start 0.125 mg twice daily with dose titration every 5 days. Treprostinil diolamine is contraindicated in patients with severe hepatic impairment [41c].

Infection Risk

A 14-year-old boy diagnosed with World Health Organization Group I idiopathic pulmonary arterial hypertension with an estimated ejection fraction of 30% was being treated with furosemide and bosentan when he began intravenous treprostinil continuous infusion. Two years later the patient presented with fatigue, muscle cramping, and fever and was subsequently treated for sepsis caused by a Gram-negative bacilli, Chryseomonas luteola, which was susceptible to ceftriaxone. The patient was treated with meropenem, amikacin, and ultimately ceftriaxone and was discharged with a 14-day course of ceftriaxone. Other studies have demonstrated a decrease in bacterial infections when treprostinil is prepared using epoprostenol diluent due to the more alkaline pH. The patient was later changed to the epoprostenol diluent without further infections. The authors advise consideration of this more alkaline diluent to prevent bacterial infections in patients on continuous intravenous treprostinil therapy [42A].

PULMONARY VASODILATORS [SEDA-33, 421; SEDA-34, 328; SEDA-35, 374; SEDA-36, 284]

Observational Study

A retrospective observational study was conducted to evaluate the safety and tolerability of treatment options for pulmonary hypertensive vascular disease (PVHD) in 63 children and to analyze the incidence and type of ADRs. As many as 90 different treatments were used between all the patients in the study, both monotherapy and combination therapy, with any of the following agents: sildenafil, bosentan, iloprost, treprostinil, epoprostenol, ambrisentan, and sitaxentan. The median age at therapy initiation was 3.4 years. NYHA functional class I–IV was 1.6%, 22.2%, 39.7%, and 36.5%, respectively. 39 patients (61.9%) were categorized as Group I pulmonary arterial hypertension, followed by 33 patients (52.4%) categorized as having congenital heart disease. Over the 12-month study period, a total of 90 episodes were recorded including 34 patients (54%) having ADRs and 37 events occurred with monotherapy, while 53 events occurred with combination therapy to give an incidence rate of 1.02 ADRs/patient/year. Most common events included gastrointestinal symptoms and spontaneous erection in male patients. The majority of reported events were considered mild (42, 46.7%) or moderate (39, 43.4%) versus severe (9, 10%). Headaches were found to have increased with patients greater than 8 years old, and gastrointestinal symptoms were more common for patients less than 2 years old. Gastrointestinal symptoms occurred in patients on sildenafil, which is likely due to relaxation of the esophageal sphincter and smooth muscle relaxant effect in patients who lack developed muscle tone. The ADR frequency was different than that of adults treated with these agents. More erections were noted in the pediatric population (12% versus unknown); however, less pediatric patients reported limb pain as compared to the reported adult ADR rate (2% versus ≥10%) while on sildenafil therapy. Pediatric patients also experienced higher rates of flushing and hypotension while on bosentan compared to reported adult rates (20% versus 1–10%). Increased transaminases are found in ≥10% of adult patients on bosentan, but the pediatric patients reported a lower rate of 4%. Patients receiving inhaled iloprost experienced higher frequencies of respiratory ADRs such as coughing, secretions, and bronchospasms as well as an increase in hypotension and vasodilation when compared to the adult population. This may be due to the developing airways of the pediatric patients which as more reactive and smaller in size. Treprostinil continuous infusion was well tolerated with 10% of the pediatric patients having local reactions causing discontinuation [43c].

In the United States, the Food and Drug Administration (FDA) recommends against the use of sildenafil in children. This is based on the results of the STARTS-2 trial which demonstrated decreased survival of children receiving high doses of sildenafil monotherapy. The STARTS-2 study followed the European Medicines Agency recommendations of 10 mg/8 h for patient

<20 kg, and 20 mg/8 h for patients >20 kg. Mean ADRs per treatment were higher for patients exceeding recommended dosing (1.47, IQR 0.78–2.16) compared to those receiving the recommended dosing regimen (0.68, IQR 0.36–1). Therefore, dosing in pediatric patients should not exceed the recommended dosing. This study was the largest report of ADRs for the pediatric population and demonstrated that these treatment options can be safely used in pediatric patients with PVHD [43c].

ANTIHYPERTENSIVES IN PREGNANCY

Observational Study

A cohort study found that women with chronic hypertension who were prescribed labetalol had infants that were more likely to require hospitalization for respiratory distress syndrome, seizures and sepsis than infants born to women who were prescribed methyldopa. More neonatal adverse effects have been reported in literature with beta-blockers than methyldopa and are most likely due to effects of fetal circulation. Another population based cohort study revealed the increased risk for low birth weight in infants was more likely in pregnant women who used vasodilators for hypertension. Beta-blockers and calcium channel blockers were, however, found to be relatively safe as antihypertensive agents [44c].

Genetic Factors

The bioavailability of several antihypertensive agents is lower in pregnant women than in non-pregnant women. There has been considerable research devoted to applying pharmacogenetics to assisting in individualized dosing in pregnancy. Polymorphisms in the eNOS gene are associated with variations in the pharmacological response to atenolol. Patients with a G498A polymorphism in the eNOS gene have a better blood pressure response to atenolol. A NAT enzyme associated with a polymorphism can lead to reduced enzymatic activity of hydralazine resulting in higher concentrations of hydralazine hence pronounced side effects such as hypotension. Nifedipine is metabolized by CYP3A family and polymorphisms in CYP3A5 can affect the maternal blood concentration of nifedipine [45R].

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