Antihypertensive Drugs

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ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Benazepril

Hematology

Medications are common causes of drug-induced agranulocytosis. Among angiotensin-converting enzyme inhibitors (ACEIs), captopril has been described as a cause of agranulocytosis. Hashmini et al. described a case report of drug-induced agranulocytosis following treatment with benazepril, the first such report published in a patient treated with benazepril. White blood cell counts quickly recovered after benazepril was discontinued. Authors recommend prompt discontinuation of benazepril following recognition of agranulocytosis [1A].

Lisinopril

Endocrinology

Kataria et al. described a case report of a heart failure patient with lisinopril-induced alopecia. While others have previously reported alopecia induced by other ACEIs (enalapril and captopril), this was the first such report with lisinopril in particular. Alopecia improved 4 weeks after discontinuation of lisinopril in this case report. Clinicians should consider lisinopril as a causative factor for unexplained alopecia [2A].

Ramipril

Transplant

Mandelbrot et al. described the effects of ramipril on urinary protein excretion in maintenance renal transplant patients converted from a calcineurin inhibitor to sirolimus. After 1 year, ramipril was effective at preventing urinary protein excretion and did not increase adverse events associated with sirolimus. Statistically significant treatment-emergent adverse events included increased serum creatinine (16.1% vs 8.6%) and leukopenia (12.3% vs 4.3%) when comparing ramipril ($n=155$) to placebo ($n=140$), though these are known side effects associated with ACE inhibitor use [3C].

ANGIOTENSIN RECEPTOR BLOCKERS/ ANGIOTENSIN II RECEPTOR ANTAGONISTS

Azilsartan

General Information

The efficacy and safety of azilsartan, a new angiotension II receptor blocker (ARB), was compared to olmesartan and valsartan in patients with prediabetes or type 2 diabetes. All medications were similar in terms of efficacy and safety outcome. Authors conclude that this new, well-tolerated ARB is an option for patients with hypertension in the setting of type 2 diabetes [4M].

Fimasartan

General Information

Fimasartan is a new angiotensin II type 1 receptor blocker recently approved in Korea. A derivative of losartan, fimasartan has a longer duration and higher potency than losartan. Lee et al. conducted a candesartan-controlled parallel group trial of fimasartan in Korean patients with hypertension. Efficacy and safety outcomes

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of fimasartan 60 or 120 mg and candesartan 8 mg were similar [5C]. Youn et al. conducted a Phase III clinical trial comparing fimasartan 30 mg vs valsartan 80 mg and also found no statistically significant differences in efficacy or safety of the two ARBs [6C]. Authors of both articles concluded that fimasartan appears safe with comparable clinical outcomes to other available ARBs [5C, 6C].

Losartan

Urinary Tract

The PREVER-treatment randomized trial compared chlorthalidone/amiloride vs losartan for blood pressure control in patients with stage I hypertension ($n=655$). While rates of reported adverse events in this trial did not differ significantly between study groups, authors noted a trend towards increased incidence of microalbuminuria in the losartan group (15.5 mg/L vs 16.2 mg/L, $P=0.822$). Significant findings included lower serum cholesterol, LDL-cholesterol, triglycerides, and serum uric acid in the losartan group ($P\leq0.001$). Authors note that increased lipid levels have previously been associated with amiloride, but that this adverse effect is unlikely to outweigh the beneficial lowering of blood pressure seen with the medication [7C].

Olmesartan

Gastrointestinal

Several cases of olmesartan-induced sprue-like enteropathy have been reported since 2012, although the potential mechanism of this rare adverse effect is not understood. Patients with suspected olmesartan-induced enteropathy usually have severe diarrhea, dehydration, or renal failure and have been taking olmesartan for several months or years [8A]. Testing for celiac disease is usually negative, and gluten-free diets are ineffective, but symptoms resolve with discontinuation of olmesartan [9A]. Basson et al. conducted an observational cohort study in the French National Health Insurance database to evaluate whether olmesartan compared to other ARBs or ACEIs increased the likelihood of enteropathy. Two hundred and eighteen events were observed in this observational study ($n=4\,546\,680$; or 9 010 303 person-years), and olmesartan was associated with an increased risk of hospitalization for intestinal malabsorption ($P<0.0001$) and hospitalization for enteropathy ($P<0.0001$). No association with this adverse effect was found for other ARBs [10MC]. Healthcare providers should consider olmestartan as a cause of enteropathy, even after months or years of use.

Telmisartan

Drug–Drug Interaction

ARBs and statins are medications commonly co-administered to reduce the risk of cardiovascular events and death. Hu et al. described a drug–drug interaction between telmisartan and rosuvastatin. Co-administration of telmisartan and rosuvastatin to healthy subjects for 14 days significantly increased the maximum plasma concentration (Cmax) of rosuvastatin by 71% and the area under the plasma concentration time curve (AUC) of rosuvastatin by 26%. The mechanism of interaction was demonstrated to be inhibition of ATP-binding cassette transporter G2 (ABCG2)-mediated efflux of rosuvastatin. While further studies are needed to characterize the extent of this interaction, authors suggest considering a reduced dose of rosuvastatin in Chinese patients also taking telmisartan, which may help to avoid side effects of increased rosuvastatin plasma concentration [11c].

℞ ANGIOTENSIN II RECEPTOR BLOCKER; ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

Valsartan/Sacubitril

General Information

Valsartan/sacubitril is a novel cardiovascular therapy, combining an ARB with an angiotensin receptor neprilysin inhibitor (ARNI). The PARIDIGM-HF trial found an exciting reduction in heart failure deaths and hospitalizations in patients with reduced ejection fraction treated with valsartan/sacubitil compared to enalapril [12MC]. The TITRATION trial published by Senna et al. evaluated the safety of two up-titration strategies, one condensed and the other more conservative, for starting valsartan/sacubitril in patients with heart failure ($n=498$) and titrating to a target dose of 200 mg twice daily used in the PARIDIGM-HF trial. No significant differences in safety outcomes (serum creatinine, hypotension, hyperkalemia) were observed between the two titration regimens. Increased tolerability of optimized doses (200 mg twice daily) was reported among patients on lower doses of ACEI/ARB at baseline in the more conservation titration arm [13C].

BETA BLOCKERS

Atenolol

Skin

Several medication classes have been known to cause pityriasis rosea-like reactions; however, atenolol has not

been generally thought of as a causative agent. One case study describes a 56-year-old female who presented to an outpatient clinical setting with itchy, scaly, bright red/violet skin patches on her neck, abdomen, axilla and upper limbs over the course of 1 week. Three weeks prior to the eruption, this patient had started atenolol for treatment of hypertension. In clinic, she had negative blood tests but a biopsy was consistent with the diagnosis of pityriasis rosea-like reaction. This appears to be the first case of this reaction related to atenolol use. Clinicians should consider atenolol as a potential cause of pityriasis rosea-like reactions [14A].

Propranolol

Mouth and Teeth

One case report identified a 32-year-old woman who presented to an oral specialty center with a 2-year duration of abnormal growth of her upper and lower gums. Her comorbid conditions included 6 years of hypertension and a congenital cardiac condition for which propranolol was prescribed as treatment. Given her clinical presentation of specific musculoskeletal, dermal, facial and developmental abnormalities, she was diagnosed with Nager syndrome. The medical team concluded that the abnormal gum development, not necessarily seen in Nager syndrome, was propranolol-induced gingival hyperplasia, a rare occurrence in beta blockers that is more closely associated with calcium channel blockers [15A].

Cardiovascular

In a case report, a 35-year-old male with a history of smoking who was otherwise healthy reportedly suffered from cardiac arrest due to Torsades de pointes without QT prolongation manifesting on his EKG following a medication combination of chlorpheniramine (prescribed for upper respiratory tract infection symptoms) and propranolol (prescribed for essential tremor and anxiety). He displayed no other abnormal findings on laboratory evaluations. The authors suggest that although both chlorpheniramine and propranolol have been known to cause arrhythmias, this is the first known case of a combination of these medications leading to cardiac arrest without electrical changes [16A].

Propranolol is considered first-line treatment for infantile hemangiomas and has demonstrated relative safety in populations including preterm neonates and those with congenital heart disease; however, adverse effects including bradycardia, hypotension, and hypoglycemia have been known to occur with this treatment. Tran et al. performed a novel case series to study the safety and efficacy of propranolol in nine patients with genital infantile hemangiomas. At doses increased to 2 mg/kg daily, no abnormal changes in blood pressure, heart rate, or blood glucose were noted. One patient was taken off propranolol treatment due to exacerbated peripheral cyanosis, though the effects were deemed neither harmful nor painful to the patient [17A].

CALCIUM CHANNEL BLOCKERS

Amlodipine

Respiratory

Hu et al. published a study comparing perindopril arginine 4 mg plus amlodipine 5 mg and monotherapy of each of these two medications. One treatment-emergent adverse event occurred in the perindopril/amlodipine group when a patient experienced diaphragmatic eventration requiring surgical intervention. After successful recovery, the patient finished the study [18C].

Drug Formulations

In a study comparing amlodipine besylate and amlodipine orotate, researchers investigated safety, efficacy and bioequivalence of the two different amlodipine salt forms paired with olmesartan. There was no significant difference in mild or moderate adverse effects with no severe effects reported. The study concluded that these two salt forms of amlodipine appear to be similar in both safety and bioequivalence and authors suggest that this new formulation could be utilized as an effective amlodipine salt [19c].

Nimodipine

Cardiovascular

Hanggi et al. compared enteral nimodipine and a sustained-release intraventricular form of the medication in patients suffering an aneurism-induced subarachnoid hemorrhage. This new dosage form is thought to reduce hypotensive effects of enteral dosing and increase cerebral spinal fluid concentrations, leading to increased efficacy. In this study, it lead to similar rates of overall adverse effects and fewer serious side effects in the intraventricular group. There were 3 cases of hypotension related to the study medication in the enteral nimodipine group ($n=18$) and none in the intraventricular group ($n=54$). The authors suggest that this new formulation may reduce the potential for adverse effects [20c].

Verapamil

Drug–Drug Interaction

In a case report, a 68-year-old man who was being treated with ibrutinib for relapsed mantle cell lymphoma was

seen in the emergency department after losing consciousness with comorbid dizziness, nausea, severe diarrhea and malaise. After intensive review of his condition and his medication regimen from a clinical pharmacist, the team determined that his verapamil, in a combination product with trandolapril, resulted in CYP3A4 inhibition leading to ibrutinib toxicity. While other antihypertensive medications had been prescribed to this patient, including an ARB, the clinical effects were thought to be due to the verapamil drug interaction. Prescribers must take caution when utilizing ibrutinib in the presence of CYP3A4 inhibitors. In this case the patient was subsequently prescribed another calcium channel blocker that did not undergo metabolism through this pathway. Clinicians should consider avoiding verapamil in patients being treated with ibrutinib [21A].

DRUGS THAT ACT ON THE SYMPATHETIC NERVOUS SYSTEM

Clonidine

Respiratory

Clonidine was studied by El-Ebiary et al. as an adjuvant in the management of acute anticholinesterase pesticide poisoning. In 60 adult patients, moderate doses of clonidine did not significantly impact clinical outcomes following anticholinesterase pesticide poisoning, but did significantly impact patients' vital signs. In addition to lowering pulse rate ($P=0.0002$), clonidine was shown to decrease oxygen saturation ($P=0.0262$) and increase time to normalization of vital signs ($P=0.0067$) compared to placebo. Authors suggest that clonidine may not improve clinical outcomes significantly when used in the setting of anticholinesterase pesticide poisoning. Caution must be taken with this treatment due to high incidence of hypotension, though this may be beneficial for patients presenting with hypertension and tachycardia following these poisoning events [22c].

A case report described a clonidine overdose in a 22-month-old girl as a result of an unintentional oral exposure to a compounded topical cream containing clonidine, camphor, gabapentin, ketoprofen, and lidocaine. Serum analyses revealed undetectable levels of all ingredients except clonidine, which was slightly elevated at 2.6 ng/mL (reference range 0.2–2 ng/mL at steady state). Results of this overdose, as noted in the emergency department approximately 1 hour after ingestion, included intermittent excitation, altered consciousness, miosis, apnea requiring endotracheal intubation, hypothermia, bradycardia, first-degree heart block, and hypotension. After approximately 14 hours of supportive care, the patient was successfully extubated. The authors of this case report urge healthcare providers and parents to be alert to the potential dangers associated with pediatric ingestion of compounded medications [23A].

Ketanserin

Drug–Drug Interactions

Valle et al. performed a placebo-controlled trial to explore the relationship between the psychotropic plant ayahuasca and the serotonergic 5-HT2A receptor. Ketanserin was utilized for the study based on its known mechanism as an antagonist of this receptor. Analysis of 12 healthy study participants confirmed that ketanserin attenuated the neurophysiological and psychotropic effects of ayahuasca; however, authors noted it was unexpected to see only partial blockade of these effects. Authors offered a possible explanation for this partial blockade regarding ayahuasca agonism at other serotonergic receptors, particularly the 5-HT1A receptor, implicating this receptor for the marked sedation displayed in participants who received the ketanserin/ayahuasca combination [24c].

Reserpine

Death

A case report from Gicquel et al. described the death of a 30-year-old woman related to consumption of a mislabeled powder supplement found to contain reserpine. In this case, a powder intended to treat opiate withdrawal was analyzed, along with autopsy findings. The powder, which was sold online as *Tabernatnthe iboga*, did not contain the labeled ibogaine, but rather contained several toxic alkaloids—ajmaline, yohimbine, and reserpine; of these three alkaloids found in *Rauvolfia* plant species, reserpine is described as the most potent. Blood and bile analyses revealed amounts of reserpine below therapeutic concentrations, in combination with therapeutic concentrations of ajmaline and yohimbine, as well as low concentrations of cannabinoids and oxazepam. The patient's death was deemed a consequence of exposure to a combination of substantial *Rauvolfia* concentrations (including reserpine) and concomitant drug withdrawal. While cases regarding *Rauvolfia* alkaloids have been described separately, the authors of this case note this is the first report of death related to the simultaneous consumption of all three. The authors also call attention to safety concerns surrounding counterfeit medications and supplements purchased over the Internet [25A].

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