Antihypertensive Drugs

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ANGIOTENSIN-CONVERTING ENZYME INHIBITORS [SEDA 39: 183–187]

Enalapril

Mouth and Teeth

In an observational study utilizing the French PharmacoVigilance Database, several antihypertensive medications were reportedly associated with gingival bleeding. Though rarely fatal, gingival bleeding is often considered a serious adverse drug reaction and should prompt discontinuation of the causative agent. Five reports of gingival bleeding were linked to enalapril following a causality assessment that evaluated chronology and presence of other potential causes. Though enalapril has not previously been associated with gingival bleeding, this study may be an early signal of a rare adverse drug reaction [1c].

Ramipril

Mouth and Teeth

In an observational study utilizing the French PharmacoVigilance Database, several antihypertensive medications were reportedly associated with gingival bleeding. Though rarely fatal, gingival bleeding is often considered a serious adverse drug reaction and should prompt discontinuation of the causative agent. Five reports of gingival bleeding were linked to ramipril following a causality assessment that evaluated chronology and presence of other potential causes. Though ramipril has not previously been associated with gingival bleeding, this study may be an early signal of a rare adverse drug reaction [1c].

ANGIOTENSIN RECEPTOR BLOCKERS/ ANGIOTENSIN II RECEPTOR ANTAGONISTS

Telmisartan

Cardiovascular

Angiotensin receptor blockers (ARBs) have been used for the treatment of Raynaud phenomenon. However, in a French national pharmacovigilance database study investigating reports of Raynaud phenomenon related to drug exposures, two instances of Raynaud phenomenon were reported in patients using telmisartan. In these two patients, authors found no concomitant use of medications known to induce Raynaud phenomenon and no other history of or risk factor for this complication. Due to the nature of adverse event reporting, they note the association may have resulted from notification bias. The case/noncase methodology use in this study is typically only useful for generating signals of potential associations, so further studies are warranted to investigate the associations noted [2c].

Gastrointestinal

While olmesartan has been associated with sprue-like enteropathy, limited evidence exists linking this adverse effect related to other ARBs. In a case report by Negro et al., a 52-year-old man who had been taking telmisartan 40 mg daily for 3 years presented with signs symptoms of moderate sprue-like enteropathy. Symptoms resolved within 1 week of discontinuation of his telmisartan, and duodenal biopsies 3 months later showed progressive duodenal recovery. This case report suggests that olmesartan-associated sprue-like enteropathy may actually be a class effect of ARBs. Though this is only the third known report

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of telmisartan-related sprue-like enteropathy, authors recommend discontinuation of the medication in the setting of a sprue-like enteropathy due to the potentially life-threatening nature of this adverse effect [3A].

ANGIOTENSIN II RECEPTOR BLOCKER; ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

Valsartan/Sacubitril

General Information

In two separate studies of valsartan/sacubitril use in patients with systolic hypertension, peripheral edema was identified as an adverse effect, in addition to other previously described adverse effects. Results from the study by Izzo et al. revealed three patients (2.1%) with peripheral edema in the sacubitril 400 mg plus valsartan 320 mg group, compared to two patients (3.4%) in the placebo group; one patient (0.7%) on valsartan 320 mg monotherapy also experienced peripheral edema [4C]. In a second study by Williams et al., six patients (2.6%) on sacubitril 97 mg and valsartan 103 mg experienced peripheral edema, compared to two patients (0.9%) in the control group (olmesartan 20 mg) [5C]. Neither study commented on whether these differences were statistically significant [4C, 5C].

Drug–Drug Interaction

An open-label study in 28 healthy Chinese males investigated the potential drug–drug interaction between sacubitril/valsartan 97/103 mg and atorvastatin 80 mg. While atorvastatin did not significantly alter levels of sacubitril/valsartan or active metabolites, sacubitril/valsartan did result in a twofold increase in the C_{max} of atorvastatin and its metabolites. The AUC of atorvastatin was only marginally increased (less than 1.3-fold), suggesting limited effect on atorvastatin absorption and clearance. One patient experienced an increase in alanine aminotransferase (ALT) levels during the study, though this was mild (ALT 90 U/L). Overall, the combination was considered safe and well-tolerated over the 5 days of coadministration [6c]. A pharmacokinetic modeling study also described this mild drug–drug interaction between sacubitril/valsartan, as well as predicted interactions between sacubitril/valsartan and other statins. Interactions were deemed unlikely with rosuvastatin, fluvastatin, and lovastatin, and predicted interactions were less than 1.5-fold for pitavastatin and pravastatin. No interaction was found between sacubitril/valsartan and simvastatin [7E]. Many patients on sacubitril/valsartan are also likely indicated for statin use; based on the results of these studies, coadministration can likely be considered safe.

Nervous System

Based on the mechanism of sacubitril in inhibiting the enzyme neprilysin, theoretical concern existed regarding long-term effects on dementia formation though amyloid-β peptide accumulation. Cannon et al. described cognitive outcomes from several large-scale trials studying sacubitril/valsartan. Investigators identified 27 dementia-related adverse effects in the PARADIGM-HF trial, 12 of which occurred in the sacubitril/valsartan groups and 15 of which occurred in the comparator groups (enalapril) [hazard ratio 0.73, 95% confidence interval 0.33–1.59]. Similar rates of dementia-related adverse effects were also found in three other trials, with no evidence of increased concerns for dementia in patients taking sacubitril/valsartan vs enalapril. Further studies with longer durations and more sensitive methods to detect dementia are necessary to confirm this conclusion [8R].

BETA BLOCKERS

Atenolol

Mouth and Teeth

In an observational study utilizing the French PharmacoVigilance Database, several antihypertensive medications were reportedly associated with gingival bleeding. Though rarely fatal, gingival bleeding is often considered a serious adverse drug reaction and should prompt discontinuation of the causative agent. Four reports of gingival bleeding were linked to atenolol following a causality assessment that evaluated chronology and presence of other potential causes. Though atenolol has not previously been associated with gingival bleeding, this study may be an early signal of a rare adverse drug reaction [1c].

Carvedilol

Cardiovascular

Carvedilol has recently been used in the management of portal hypertension as prophylaxis of gastroesophageal varices. This beta blocker has been evaluated in a number of studies involving patients with cirrhosis, with doses ranging from 3.125 to 50 mg daily. Maharaj et al. describe a 56-year-old male with cirrhosis (Child-Pugh score of 7) who suffered cardiogenic shock following administration of two doses of carvedilol 12.5 mg (i.e., total dose of 25 mg). The authors note that only two other reports of carvedilol toxicity have been published, and both were in the setting of overdose. While carvedilol is contraindicated in severe hepatic impairment, there are

no suggested dose adjustments for mild to moderate hepatic impairment. Based on this case, authors suggest low starting doses of carvedilol (e.g., 3.125 mg twice daily) in patients with hepatic impairment, followed by slow up-titration of the dose and close monitoring for signs of toxicity [9A].

Propranolol

Drug–Drug Interaction

A case report by Rouabhia et al. described a 77-year-old man treated with propranolol and sofosbuvir who suffered from ventricular extrasystoles. The manufacturer of sofosbuvir has warned against co-administration with amiodarone due to risk of bradycardia, stating that this risk may be increased in patients who are also taking beta blockers; however, they did not warn against co-administration of sofosbuvir and beta blockers in the absence of amiodarone use. The patient in this case report had never taken amiodarone and was not on any other medications reported to interact with sofosbuvir. Three hours after his first sofosbuvir dose, the patient complained of palpitations and electrocardiogram revealed numerous monomorphic ventricular extrasystoles accompanied by bradycardia. No further doses of sofosbuvir were given, and symptoms resolved after 24 hours. Authors of the case report suggest that patients taking sofosbuvir and propranolol and should undergo cardiac rhythm monitoring during the first several hours of co-administration to identify this potential drug–drug interaction [10A].

Nervous System

In a case report, propranolol was suspected as the cause of temperature instability in an infant with infantile hemangioma. The patient, a 25 1/7-week premature twin girl, was started on propranolol at 36 5/7 weeks corrected gestational age. After 3 days on propranolol, her average axillary temperature had declined from 36.7°C to 36.4°C, requiring the patient to be returned to a heated incubator. The oral propranolol dose was increased from 0.7 mg every 8 hours to 1.4 mg every 8 hours, leading to further temperature decline. Despite returning to the lower dose, the infant was unable to wean from the incubator until the propranolol was discontinued on day 19 of treatment. Though cold extremities have been noted in infants receiving propranolol for infantile hemangioma, this type of temperature instability has only been reported with use of topical timolol. Authors of this case report suggest that the high lipophilicity and nonselective nature of propranolol may contribute to this adverse effect and suggest further consideration for preferential use of β_1-selective, low lipophilicity beta blockers such as atenolol in this treatment setting [11A].

Drug Overdose

Hopkins et al. presented the first case of a propranolol drug bezoar in a case report of a 21-year-old female. The patient presented to the hospital following attempted suicide by medication overdose. Suspected ingested tablets included propranolol 40 mg sustained-release, amlodipine 10 mg, and olanzapine 10 mg. Despite fluid resuscitation, intubation, and treatment with glucagon, adrenaline, insulin, and intravenous fat emulsion, the patient remained hypotensive. Endoscopy revealed a large pharmacobezoar, estimated at 200 mL in total of tablets. Though rare, this type of bezoar may form due to delayed gastric absorption in the setting of persistent low cardiac output. Though endoscopy and gastric washout are not routinely recommended or performed in drug overdose, authors concluded that these interventions may be considered as a means to limit further drug absorption in patients who are refractory to standard treatments [12A].

CALCIUM CHANNEL BLOCKERS

Amlodipine

General Information

Chen et al. compared initiation of *S*-(−)-amlodipine 5 mg (high dose) vs 2.5 mg (low dose) among patients with mild–moderate hypertension. At 8 weeks, the incidence of adverse events was low in both arms with similar tolerability. The rate of adverse events was similar between high dose (20.0%, $n=70$) and low dose (17.7%, $n=62$) arms ($P=0.50$) [13c].

Nicardipine

Respiratory/Hematologic

Monaco et al. described findings from an Italian pharmacovigilance database which collects real-world reports of suspected adverse drug reactions. Among several cardiovascular agents reviewed within the database, a potential correlation was observed between nicardipine and acute pulmonary edema (off-label use as tocolytic during pregnancy) and between nicardipine and thrombocytopenia. The authors noted the benefit of pharmacovigilance databases which allow for continuous evaluation of the risk and benefit of medications, particularly in special populations such as pregnancy which are rarely studied in clinical trials [14c].

DRUGS THAT ACT ON THE SYMPATHETIC NERVOUS SYSTEM

Urapidil

Mouth and Teeth

In an observational study utilizing the French PharmacoVigilance Database, several antihypertensive medications were reportedly associated with gingival bleeding. Though rarely fatal, gingival bleeding is often considered a serious adverse drug reaction and should prompt discontinuation of the causative agent. Three reports of gingival bleeding were linked to the alpha-1 agonist urapidil following a causality assessment that evaluated chronology and presence of other potential causes. Though urapidil has not previously been associated with gingival bleeding, this study may be an early signal of a rare adverse drug reaction [1c].

FIXED-DOSE ANTIHYPERTENSIVE COMBINATION THERAPIES

Indapamide/Perindopril

General Information

An analysis of the ADVANCE and PROGRESS trial data was conducted by Atkins et al. to evaluate the side effects and tolerability of dual fixed-dose combination antihypertensive therapy. The analysis included more than 14 000 patients with hypertension who were randomized to treatment with perindopril and indapamide vs placebo. Patients were stratified into five subgroups by baseline systolic blood pressure (mmHg): less than 120, 120–129, 130–139, 140–159, and 160 mmHg or greater. Discontinuation rates due to hypotension or dizziness ranged from 1.3% to 3.6% depending on the degree of baseline blood pressure elevation. Overall side effects with combination antihypertensives, including renal adverse effects, were similar across all subgroups stratified by baseline systolic blood pressure [15R].

Triple-Combination Therapy

General Information

Hypertension practice guidelines emphasize that many patients will require the use of combination therapies to achieve adequate blood pressure control. As many as one-third of patients may require three or more antihypertensive agents. Düsing et al. reviewed four randomized control trials evaluating the efficacy and safety of triple vs dual combination antihypertensive therapy in a single pill. Combinations were made up of amlodipine, angiotensin receptor blockers, and hydrochlorothiazide. While more efficacious at blood pressure reduction, triple combination therapy was associated with similar rates of adverse effects as dual combination therapy. The most common adverse effects with triple combination therapy were dizziness, peripheral edema, and headache [16R].

Additional case study reports can be found in these reviews [17R, 18R].

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