CHAPTER

20

Antihypertensive Drugs

Augustine N. Odili[*, §, 1], *Bolaji Abdullahi*[¶]

[*]Department of Internal Medicine, College of Health Sciences, University of Abuja, Abuja, Nigeria; [§]Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [¶]Department of Internal Medicine, University of Abuja Teaching Hospital, Gwagwalada, Abuja

[1]Corresponding author: E-mail odilimercy@yahoo.com

GENERAL

The recent publication of hypertension treatment guidelines issued by Joint National Committee [1[S]] and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) Joint Committee [2[S]] provides updated evidence-based guidance for the management of hypertension in adults. The JNC 8 recommendations on treatment thresholds, goals and medications in the management of hypertension in adults were based on evidence drawn from randomised controlled trials, which represent the gold standard for determining efficacy and effectiveness. Hypertensive persons aged 60 years or older should be treated to a blood pressure (BP) goal of less than 150/90 mmHg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mmHg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mmHg for those groups based on expert opinion. For persons who have diabetes or nondiabetes chronic kidney disease, the recommended thresholds and goals are as for the general hypertensive population younger than 60 years. In the nonblack hypertensive population including those with diabetes, it is recommended that drug treatment can be initiated with an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker, calcium channel blocker (CCB) or thiazide-type diuretic while in blacks, a CCB or thiazide-type diuretic is recommended as initial therapy.

Although the JNC 8 recommendation of a therapeutic target of <150 mmHg in those ≥60 years of age was based on strict available evidence, more recent report from the subanalysis of INVEST trial [3[C]] has challenged that position in patients with coronary artery disease (CAD). The INVEST investigators concluded that in hypertensive patients with CAD who are ≥60 years of age, achieving a BP target of 140 to <150 mmHg as recommended by the JNC 8 panel was associated with less benefit than the previously recommended target of <140 mmHg. The implication of the INVEST report is that the threshold and target BP recommended by the JNC 8 panel may not be applicable to all patient groups. It is expected that the hypertensive management guidelines should only provide a guide to clinicians, however, they should feel free to use their own judgement for management of individual patients.

Electrolyte Balance

The risk associated with hypokalemia and hyperkalemia on treated hypertensive patients in the practice-based Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has been published [4[C]].

Side Effects of Drugs Annual, Volume 36
ISSN: 0378-6080
http://dx.doi.org/10.1016/B978-0-444-63407-8.00020-4

The study cohort was derived from 33,357 ALLHAT participants, who were aged 55 years or older, had hypertension and at least one additional cardiovascular disease risk factor. The participants who were normokalemic at baseline were randomised to chlorthalidone versus amlodipine or lisinopril and were stratified by level of potassium at year 1 into hypokalemia (<3.5 mmol/L) normokalemia (3.5–5.4 mmol/L) and hyperkalemia (>5.4 mmol/L). Incidence of hypokalemia in chlorthalidone was 12.9% and this differed significantly from amlodipine (2.1%, $p < 0.001$) and lisinopril (1.0%, $p < 0.01$). Incidence of hyperkalemia was greatest in lisinopril arm (3.6%) than in chlorthalidone arm (1.2%, $p < 0.01$) or amlodipine (1.9%, $p < 0.01$). Coronary heart disease occurred in 8.1%, 8.0% and 11% in patients with hypokalemia, normokalemia and hyperkalemia, respectively.

℞ Angioedema and Drugs that Target the Renin–Angiotensin–Aldosterone System

Angioedema has been linked with the use of medications that target renin–angiotensin–aldosterone system *[SEDA-33, 417; SEDA-34, 322; SEDA-35,364]*. The EIDOS and DoTS descriptions of angioedema using ACEI are shown in Figure 1. Absolute and relative risk of angioedema resulting from the use of these agents in the real-world clinical settings has been reviewed [5C]. The article provided an insight into the absolute and relative risk of angioedema by various agents that target renin–angiotensin system. Inception cohort design was used to identify patients who are18 years or older with an outpatient dispensing of an oral formulation of the following medications as a single ingredient or as a combination product with nonstudy drugs over a 10-year period: ACEI (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril or trandolapril); an ARB (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan or valsartan); direct renin inhibitors (aliskiren) and β-blockers (BBs) (acebutolol, atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, pindolol, propranolol or timolol) served as a common reference group.

The primary outcome of interest was angioedema and the secondary outcome was serious angioedema (resulting in airway obstruction requiring inpatient care). The follow-up period began on the index date and ended at the earliest occurrence of the following: first angioedema diagnosis, death, disenrollment, 365 follow-up days, December 31, 2010, cessation of use of study drug or initiation of another study drug of a different class (except for individual ARB analyses for which censoring also occurred with initiation of a different ARB). Cessation of use occurred when the days' supplies were exhausted for longer than 14 days without a subsequent dispensing.

A total of 3,909,596 subjects comprising of 1 845 138 ACEI initiators, 467 313 ARB initiators, 4867 aliskiren initiators and 1 592 278 initiators of BBs were enrolled for the study The mean follow-up durations were 149 days for ACEI initiators, 136 days for ARB initiators, 112 days for aliskiren initiators and 126 days for BBs. A total of 3301 angioedema events were associated with the use of ACEIs, 288 events with ARBs, 7 events with aliskiren and 915 events with BBs. Compared with the use of BBs, the adjusted hazard ratio and 95% confidence interval for angioedema were 3.04 (2.81–3.27) for ACEIs, 1.16 (1.0–1.0) for ARBs and 2.85 (1.34–6.04) for aliskiren. In summary, the risk of angioedema following the use of ACEIs and aliskiren is three times higher than the risk associated with the use of BBs. The risk seems to be 16% greater for ARBs as compared with BBs and losartan seems to have the greatest risk among the ARBs.

While angioedema commonly affects the mucus membrane and skin of the lip, tongue, face and peripheral parts of the body, the intestine can be affected very rarely. A case of intestinal angioedema has been reported [6A].

- A 49-year-old woman presented with acute abdominal pain and nausea. Abdominal CT scan revealed oedematous small bowel and ascites. She was thought to have intestinal ischaemia and was then subjected to a laparotomy which revealed that the intestine was vital with no perforation. ACEI-induced angioedema was suspected when a history of ingestion of lisinopril, 3 days prior to presentation was obtained. Lisinopril was replaced with amlodipine and the pain disappeared after 3 days.

Delayed-onset angioedema: In majority of the cases reported, angioedema occurs within 1 week of commencement of the therapy but in few cases, the delayed onset type can occur in patients who have had the therapy for many years or even after the drug has been stopped. Angioedema has been reported in two patients in their 70s who had been on ACEI for 7 years and more than 10 years, respectively [7A]. In both cases, swelling started in the tongue and progressed to involve the soft tissues of the oropharynx necessitating intubation. They both had intravenous antihistamine and corticosteroids and were successfully extubated after 72 h. An isolated genital swelling (an uncommon site for angioedema) has also been reported in a 71-year-old man who had been on ACEI for 3 years [8A]. Withdrawal of the lisinopril in addition to other supportive care resulted in resolution of the symptoms.

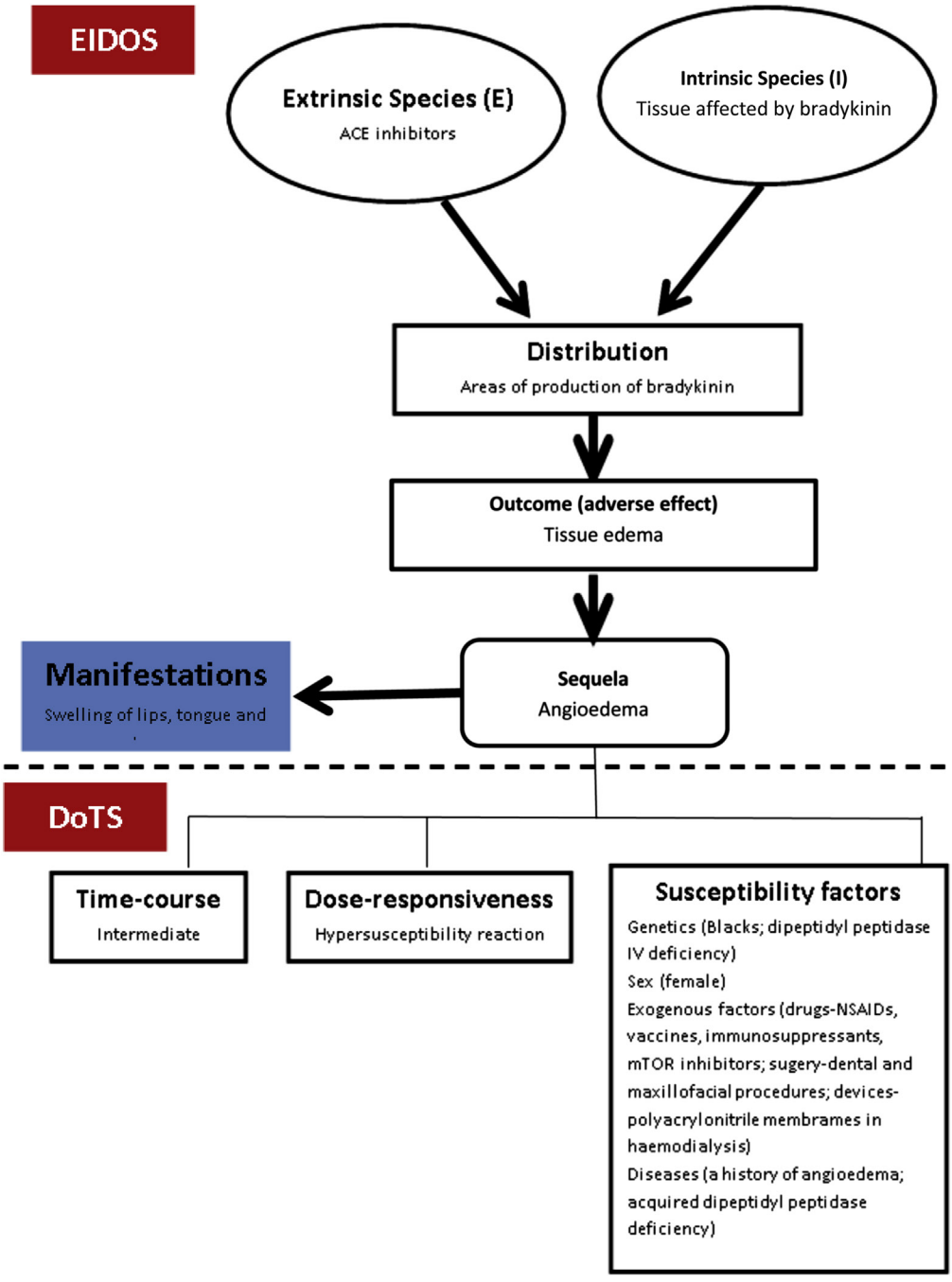

FIGURE 1 The EIDOS and DOTs descriptions of angioedema due to ACE inhibitors.

There has been interest in the use of icatibant, a bradykinin antagonist approved for use in the treatment of hereditary angioedema and ACEI-induced angioedema. A 76-year-old man who was having recurrent lisinopril-induced angioedema had a 10-h resolution of symptoms after injection of 30 mg of icatibant. Resolution of symptoms for previous attacks in the man took 48 h for recovery [9[A]]. Although a well-designed randomised controlled trial is essential, this case report is an improvement in the earlier case series *[SEDA-34, 323]* in which historical controls were used for comparison.

Fresh frozen plasma (FFP) contains kininase II, which resembles ACE and catalyses the degradation of excessive bradykinin. In a case series involving seven patients who had recalcitrant angioedema, administration of FFP resulted in resolution of symptoms within hours [10[A]]. The concern associated with the use of FFP stems from the transmission of viral agents like hepatitis and HIV as well as fluid overload from patients with congestive cardiac failure.

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

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

Nervous system: Visual hallucination has been reported in four elderly patients on lisinopril. Visual hallucination stopped when lisinopril was withdrawn in all the four cases and reappeared in two of them who had a re-challenge [11[A]]. The authors reasoned that older age particularly those with dementia or mild cognitive impairment may predispose to a higher risk.

Drug overdose (paediatric) A 13-year retrospective study of lisinopril ingestion in children within the age range of 9 months to 5 years has been published [12[R]]. Of the 296 patients, 8 (2.7%) developed hypotension (BP ranged from 55–74 mmHg systolic to 22–48 mmHg diastolic). The lowest dose of lisinopril that caused hypotension was 50 mg or 3.9 mg/kg.

Ramipril *[SEDA-15, 3022; SEDA-34 324, SEDA-35]*

Liver Ramipril-induced hepatotoxicity has been reported.

- A 40-year-old male patient presented with acute onset of jaundice and a 20-fold increase in the level of alanine transaminase. Viral and autoimmune hepatitis as well as bilious aetiology of the jaundice were ruled out. Withdrawal of several of his medications including ramipril resulted in reduction of serum alanine transaminase, while reintroduction of ramipril resulted in a 35-fold increase in alanine transaminase. ACE-associated hepatic toxicity is more commonly linked with enalapril. Ramipril-associated hepatic toxicity is rather rare [13[A]].

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

General

Fetotoxicity: The pregnancy outcome and foetal renal prognosis in 21 pregnancies exposed to blockers of renin–angiotensin system; 20 of which were ARBs and 1 ACEI has been reviewed [14[c]]. The median duration of exposure was 28 weeks (range 22–37 weeks). Foetal serum β2-microglobulin was measured in 15 (71%) patients and was under the threshold (5 mg/L) in five cases (33%). Amniotic fluid volume got restored after the withdrawal of antihypertensive therapy in 7 out of 17 patients but a persistent oligohydramnios was observed in the remaining 10 cases, as in the 4 cases with persistent exposure.

Out of the 21 pregnancies, 11 resulted in live births and 10 either got terminated (8 pregnancies) or culminated in intrauterine foetal death (IUFD). Among these 10 cases, renal histological examination was normal in 2, and tubular dysgenesis was observed in 7 cases. In one of the two IUFD cases, renal histology was not feasible because of the macerated state of the foetus. Only 1 of the babies born alive had normal renal function; the rest had renal failure.

Renin–angiotensin system blockage results in the hypoperfusion of the foetal kidney during nephrogenesis and will thus culminate in tubular dysgenesis. The renin–angiotensin system may also play an important role in the development of the foetal kidney. Angiotensin II is a growth factor for kidney development and as such its blockage can explain the presence of renal histological lesions in the foetus.

In a systematic review [15[M]] of published case reports and case series dealing with intrauterine exposure to agents that block the renin–angiotensin system, 52% of exposure to ACEI and 13% to ARBs resulted in no complications ($p < 0.0001$). Neonatal complications including renal failure, oligohydramnios, death, arterial hypotension, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent patent ductus arteriosus or cerebral complications were more frequent following exposure to ARBs. The long-term outcome was described as positive in only 50% of the exposed children.

Haematologic: Thrombocytopenia has been reported in a 61-year-old Caucasian hypertensive man who had his losartan increased from 50 to 100 mg per day [16[A]]. Platelet count dropped from the baseline value of 280×10^9cells/L to 15×10^9cells/L. Following prednisone taper, his platelet count returned to $>200 \times 10^9$cells/L and losartan was replaced with valsartan. Forty-seven days after commencement of valsartan, the platelet count dropped again to 37×10^9cells/L. Valsartan was withheld and prednisolone taper recommenced and the platelet count improved to 214×10^9 cells/L. The authors suggested the possibility of antibody cross-reactivity between losartan and valsartan due to similarity in their molecules.

Fimasartan

A new nonpeptide angiotensin II receptor blocker with a selective AT1 receptor blocking effect has been compared with losartan in a double-blind randomised dose escalation trial [17[c]]. At the end of 12 weeks, 60/120 mg of fimasartan was found to be noninferior in the improvement of sitting diastolic BP as compared with losartan 50/100 mg. Incidences of adverse drug reaction were 7.84% and 10.40% in the fimasartan and losartan groups, respectively. The common adverse effects that had a suggestive causal relationship with the use of the drug in the fimasartan group were dizziness in 2.75% and headaches in 2.35% of patients while in the losartan group headaches were reported in 4.4% and dizziness in 2.8% of patients.

Telmisartan

Drug–Drug Interaction: Lithium. Telmisartan 40 mg per day was added into the antihypertensive regimen of a 52-year-old schizophrenic woman who had been on lithium 900 mg and haloperidol 20 mg per day. Her lithium level increased to 2.6 meq/L from a range of between 0.83 meq/L and 1.02 meq/L prior to the introduction of telmisartan; urea and creatinine increased from normal baseline values to 76 mg/dL and 4.6 mg/dL, respectively, and potassium level was 7.0 mmol/L. Following haemodialysis, her laboratory results returned to normal, symptoms abated and lithium was replaced with valproic acid [18[A]]. The exact mechanism of this interaction is not known; however, it is thought that activation of AT1 results in increasing sodium reabsorption at the proximal convoluted tubules which subsequently results in reduction in aldosterone secretion. This ultimately causes hyperkalemia and hyponatraemia. Sodium depletion may cause increase in lithium reabsorption from the proximal convoluted tubules.

Valsartan

Cardiovascular: A 67-year-old obese female diabetic patient developed hypotension (BP of 66/40 mmHg as against baseline value of 110/60 mmHg) on the morning of surgery for laparascopic gastric bypass following an inadvertent ingestion of 160 mg of valsartan. Hypotension was unresponsive to fluids and phenylalanine administration. Methylene blue (0.8 mg/kg) restored the BP to 115/65 mmHg paving way for the proposed surgery to proceed [19[A]]. In addition to reducing vasoconstriction by locking the angiotensin receptors, ARBs also increase nitric oxide-mediated vasorelaxation. The authors reasoned that the patient developed hypotension at 160 mg of valsartan because the bioavailability of valsartan nearly doubles when it is taken without meals. Methylene blue was preferred against other vasoconstrictors because it prevents nitric oxide-mediated vasoconstriction but does not constrict normal vessels.

DUAL ANGIOTENSIN II RECEPTOR ANTAGONISTS/NEPRILYSIN ANTAGONISTS

LCZ696 *[SEDA-34, 327; SEDA-35, 372]*

LCZ696 is an angiotensin II receptor antagonist and an inhibitor of an endopetidase. The safety and efficacy of LCZ696 has been tried in heart failure patients with preserved systolic function [20][C]. LCZ696 titrated to 200 mg twice daily was compared with valsartan titrated up to 160 mg once daily in a double-blind parallel group trial over a 36-week treatment period. After 12 weeks, the NT-proBNP, a maker of left ventricular wall stress, was significantly lower in the LCZ696 group as compared to the valsartan group. The adverse effect of interest including symptomatic hypotension, renal dysfunction and hyperkalemia was similar in both arms.

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

Nonpeptide Inhibitors

Aliskiren [SEDA-33, 420; SEDA-34, 328; SEDA-35, 373]

Combination studies: There is a growing interest in combining aliskiren with other antihypertensives. The safety and efficacy of a triple combination of aliskiren, amlodipine and hydrochlorothiazide were evaluated in patients with moderate to severe hypertension [21[c]]. Patients received aliskiren/hydrochlorothiazide 300/12.5 mg followed by add-on amlodipine 5 mg for 1 week. Thereafter the doses of amlodipine and hydrochlorothiazide were doubled. There were significant reductions in mean systolic BP of 34 and 37 mmHg at 28 and 54 weeks, respectively while

corresponding reductions in diastolic BP were 20.3 and 21.8 mmHg, respectively within the same period. The common side effects recorded were peripheral oedema (9.4%), headache (3.7%), nasopharyngitis (4.1%) and bronchiolitis (3.7%). Pain in the extremity was recorded as serious adverse effect on 2.7% of patients and about the same number had a potassium level greater than 5.5 mmol/L. On the whole, the triple combination was well tolerated.

The effect of combination treatment of aliskiren and blockers of renin–angiotensin system on hyperkalemia and acute renal injury has been reviewed [22R]. Combination therapy with aliskiren and ACEIs or angiotensin receptor blockers significantly increased the risk of hyperkalemia compared with monotherapy using ACEs or angiotensin receptor blockers (RR 1.58, 95% CI, 1.24–2.02) or aliskiren alone (1.67, RR, 95% CI, 1.0–2.79). The risk of acute kidney injury did not differ significantly between the combined therapy and monotherapy groups (RR, 1.14, 95% CI, 0.68–1.89).

DIRECT VASODILATORS

Hydralazine *[SED-15, 1701; SEDA-33, 427; SEDA-34, 331; SEDA-35, 379]*

Immunologic: ANCA-positive vasculitis involving the lungs and the kidneys (pulmonary-renal syndrome) has been reported in an elderly Caucasian woman [23A] and in a 48-year-old Caucasian man [24A]. Both has had hydralazine for >2 years and were both treated with corticosteroids and immunosuppressive therapy. While the woman was reported to have improved on this treatment, the case of the man ended in death.

Minoxidil *[SED-15, 2354; SEDA-33, 428; SEDA-34, 332, SEDA-35, 379]*

Skin: A case of pseudofolliculitis barbae resulting from oral minoxidil use has been reported.

- A 61-year-old Afro-Caribbean man presented with a 5-year history of tender and inflamed papules and pustules associated with keloid scarring in the beard area extending to the cheeks and posterior scalp. His medical history included hypertension, glaucoma and gout for which he was being treated with amlodipine, oral minoxidil, doxasozin and allopurinol. Microbiological swabs of the lesion grew *proteus mirabilis*, *Enterococcus faecalis* and mixed anaerobes. Histology of biopsied lesion revealed intrafollicular and perifollicular multifocal chronic inflammatory infiltrates composed mainly of lymphocytes, plasma cells and neutrophils. The infiltrates resulted in destruction of the hair follicles causing giant cell reaction and fibrosis. Treatment with topical and oral antibiotics and steroids provided only temporary relief. Surgical removal was undertaken due to the recalcitrant nature of the lesion. Although the wound healed well without keloidal scarring, the pseudofolliculitis persisted. Within 6 weeks of cessation of oral minoxidil, the oedema, erythema and pustular exudates reduced drastically [25A].

ENDOTHELIN RECEPTOR ANTAGONISTS *[SED-15, 1215; SEDA-33, 421; SEDA-34, 328; SEDA-35, 374]*

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

Susceptibility factor *Age*: The efficacy and safety of ambrisentan in children with pulmonary hypertension have been studied in a retrospective cohort study [26C]. A total of 38 patients received ambrisentan either as an add-on therapy to bosentan (23 children) or transition from bosentan (15 children). Five patients (13%) discontinued ambrisentan due to severe headache, lack of clinical efficacy or near syncope. Ten patients (26%) had side effects associated with ambrisentan treatment, including nasal congestion, headache and flushing. However, no patients had aminotransferase abnormalities and there were no deaths after initiation of ambrisentan during follow-up.

Drug–Drug Interactions

Different drug interaction studies have been conducted with ambrisentan in healthy volunteers. Clearance of ambrisentan is determined by the uridine diphosphate glucoronyl transferase. Only 20% of the drug undergoes oxidative metabolism mainly by cytochrome P450 (CYP450 3A4) and to a lesser extent by CYPs 3A5 and 2C19. Hepatic uptake of ambrisentan is partly mediated by the polymorphic organic anion-transporting polypeptide (OATP).

Clarithromycin: Clarithromycin is an inhibitor of CYP3A4 and OATP1B1. Administration of a combination of clarithromycin and amrisentan increased the area under the curve of ambrisentan by 41% and peak concentration by 27%. Different haplotypes of SLCOB1 (the gene that encodes OATP1B1) did not affect this interaction [27[c]]. This suggests that clarithromycin can be administered safely with ambrisentan.

Liver: In a posttrial surveillance for hepatotoxicity, only 76 out of 10927 patients had cases of clinically significant hepatic events. Following this discovery, the FDA removed the requirement for mandatory monthly monitoring of LFT with ambrisentan therapy [28[c]].

Bosentan *[SED-15, 549; SEDA-33, 422; SEDA-34, 329; SEDA-35, 375]*

Drug–Drug Interaction Telaprevir: This is an NS3-4A serine protease inhibitor that inhibits CYP3A4 and P glycoprotein; both of which are involved in the metabolism of bosentan. Both bosentan and telaprevir were coadministered in a 57-year-old Caucasian man with pulmonary hypertension and HCV/HBV/HIV coinfection [29[A]] and it resulted in a fourfold increase in the level of bosentan thus resulting in serious neuropsychiatric adverse effects. The adverse effects abated within 2 days of stopping both bosentan and telaprevir. Telaprevir was recommenced latter but ambrisentan was used to replace bosentan and both agents were both tolerated with stabilisation of HCV and PAH conditions.

Sitaxsentan *[SEDA-33, 423; SEDA-34, 329; SEDA-35,376]*

Sitaxsentan was withdrawn from the worldwide market in December 2010 (SEDA-35) on account of hepatic damage that did not resolve on withdrawal of the drug but eventually proved fatal. A double-blind randomised controlled trial [30[C]] was conducted prior to the withdrawal to assess the efficacy and safety of lower dose range of sitaxsentan (50 or 100 mg) compared to placebo. Most adverse events documented by the authors including headaches, peripheral oedema, dizziness, nausea, extremity pain were said to be mild/moderate. Increased liver transaminases greater than three times of the upper limit was reported for one patient in each treatment arm, but reversed back to normal on discontinuation of the drug.

Liver: A case of a 61-year-old female who developed acute severe hepatitis following a 16-week therapy of sitaxsentan at 100 mg daily has been reported [31[A]]. Despite withdrawal of therapy, her liver tests failed to improve after 6 weeks of follow-up. She however showed clinical and biochemical improvement when a high dose of corticosteroid was administered. The authors thus opined that an immune-mediated mechanism as opposed to an inhibition of the bile salt transport is the pathway through which sitaxsentan causes hepatotoxicity.

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

Presynaptic Alpha-Adrenoceptor Agonists

Clonidine [SED 15, 817; SEDA-33, 424; SEDA-34, 329; SEDA-35, 376]

Clonidine exerts analgesic effect when administered intrathecally. This action is said to be mediated through α_2 receptors located at the dorsal horn of the spinal cord. It is administered with opioid analgesics in cases of neuropathic pain. Erectile dysfunction has been reported in a man who had intrathecal administration of morphine and clonidine for intractable neuropathic pain [32[A]].

- A 54-year-old hypertensive and diabetic man presented with intractable neuropathic pain despite intrathecal morphine injection. His medical history included hypertension and diabetes mellitus which he has had for 30 years with complications including polyneuropathy with bladder dysfunction and erectile dysfunction. Good erectile function had been achieved in the past 5 years on testosterone treatment. He has had intrathecal administration of morphine for 9 years. Despite dose escalation, considerable pain relief had not been achieved. A trial of Ziconotide was stopped because it did not provide any pain relief but rather caused severe side effects. A combination of morphine and clonidine was delivered by a programmable pump. Considerable pain relief was achieved in 2 weeks at a clonidine dose of 0.04 mg per day. However, he developed erectile dysfunction and relative hypotension immediately he commenced clonidine because of which he opted to stop clonidine and revert back to morphine monotherapy. Thereafter, erectile dysfunction disappeared and BP reverted back to habitual high levels

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

Haematologic: A case of autoimmune haemolytic anaemia has been reported in a 36-year-old gravida 2 para 1 woman at 37^{+6} weeks gestation with a medical history of β-Mediterranean thalassaemia trait and gestational hypertension [33A]. She was on alpha methyldopa 500 mg twice daily since her 34th gestational week. She had microcytic, hypochromic anaemia which was evident with a strongly positive direct antiglobulin test.

Guanfacine

Metabolism: Guanfacine has been recently approved for the treatment of attention-deficit disorder in children aged 6–12 years. A case of excessive weight gain of 9.53 kg in 4 weeks has been reported in a 7-year-old boy treated with extended-release guanfacine for attention-deficit hyperkinetic disorder [34A].

POSTSYNAPTIC ALPHA-ADRENOCEPTOR ANTAGONISTS *[SEDA-33, 425; SEDA-34, 330; SEDA-35, 377]*

Tamsulosin *[SED-15, 3303; SEDA-33, 426, SEDA-34-331; SEDA-35, 378]*

Sensory systems Eyes: Tamsulosin and other alpha-1 antagonists have been associated with intraoperative floppy iris syndrome (IFIS). A recent review compared the incidence of IFIS in patients using tamsulosin and other chronic medications [35R]. In a review of 1530 subjects who underwent phacoemulsification, 80% of current tamsulosin users, 60% of previous tamsulosin users, 1% of patients on other chronic medications including antihypertensives, antipsychotics, antidiabetics and 1.7% of those on no medications at all had IFCS. The authors concluded that while IFCS was most likely associated with tamsulosin, it was also observed among patients on other chronic drugs like metformin, lisinopril and aspirin. The predisposing factors to IFCS for patients on these medications need to be elucidated.

Sexual function: The effect of tamsulosin on the ejaculatory function has been studied among healthy male volunteers [36C]. Anaejaculation occurred in all subjects after tamsulosin administration.

β-Blockers

Outcomes following unintentional and supratherapeutic ingestions of a patient's own BB or CCB have been reviewed [37R]. Out of 436 cases reviewed, symptoms developed in 44 (10.1%) and 32 (7.3%) cases were admitted due to the ingestion. Of those admitted, five (15.6%) received treatment (three intravenous fluids, one glucagon and one calcium). Only one death was recorded in a 90-year-old lady who ingested four doses of her daily medications: diltiazem 240 mg, atenolol 50 mg, glyburide 5 mg, warfarin 2 mg, frusemide 40 mg, lisinopril 5 mg, potassium chloride 20 mg, Zaroxyln 5 mg and hydralazine 25 mg. She was reported to have died of shock after the family initiated a do-not-resuscitate directive.

References

[1] James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8). JAMA 2014;311:507–20.
[2] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC). Eur Heart J 2013;34:2159–219.
[3] Bangalore S, Gong Y, Cooper-DeHoff RM, Pepine CJ, Messerli FH. 2014 eighth joint national committee panel recommendation for blood pressure targets revisited: results from the INVEST study. J Am Coll Cardiol 2014;64:784–93.
[4] Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension 2012;59:926–33.
[5] Toh S, Reichman ME, Houstoun M, Ross SM, Ding X, Hernandez AF, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012;172:1582–9.
[6] de Graaff LC, van EM, Schipper EM, Boom H, Duschek EJ. Unnecessary surgery for acute abdomen secondary to angiotensin-converting enzyme inhibitor use. Am J Emerg Med 2012;30:1607–12.
[7] Amey G, Waidyasekara P, Kollengode R. Delayed presentation of ACE inhibitor-induced angio-oedema. BMJ Case Rep 2013:2013.
[8] Miller DG, Sweis RT, Toerne TS. Penile angioedema developing after 3 years of ACEI therapy. J Emerg Med 2012;43:273–5.

[9] Gallitelli M, Alzetta M. Icatibant: a novel approach to the treatment of angioedema related to the use of angiotensin-converting enzyme inhibitors. Am J Emerg Med 2012;30:1664–72.
[10] Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, Chan C, et al. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med 2013;44:764–72.
[11] Doane J, Stults B. Visual hallucinations related to angiotensin-converting enzyme inhibitor use: case reports and review. J Clin Hypertens (Greenwich) 2013;15:230–3.
[12] Lewis JC, Alsop JA. A 13-year review of lisinopril ingestions in children less than 6 years of age. Clin Toxicol (Phila) 2013;51:864–70.
[13] Douros A, Kauffmann W, Bronder E, Klimpel A, Garbe E, Kreutz R. Ramipril-induced liver injury: case report and review of the literature. Am J Hypertens 2013;26:1070–5.
[14] Spaggiari E, Heidet L, Grange G, Guimiot F, Dreux S, Delezoide AL, et al. Prognosis and outcome of pregnancies exposed to renin-angiotensin system blockers. Prenat Diagn 2012;32:1071–6.
[15] Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension 2012;60:444–50.
[16] Patel DK, Bilkha N, Schnee D. Angiotensin II type 1 receptor blocker-induced immune thrombocytopenia: a case report. J Med Case Rep 2013;7:183.
[17] Lee SE, Kim YJ, Lee HY, Yang HM, Park CG, Kim JJ, et al. Efficacy and tolerability of fimasartan, a new angiotensin receptor blocker, compared with losartan (50/100 mg): a 12-week, phase III, multicenter, prospective, randomized, double-blind, parallel-group, dose escalation clinical trial with an optional 12-week extension phase in adult Korean patients with mild-to-moderate hypertension. Clin Ther 2012;34:552–68.
[18] Ma CC, Shiah IS, Chang SW, Kao YC, Lee WK. Telmisartan-induced lithium intoxication in a patient with schizoaffective disorder. Psychiatry Clin Neurosci 2012;66:165–6.
[19] Nabbi R, Riess ML, Woehlck HJ. Angiotensin-receptor-blocker-induced refractory hypotension responds to methylene blue. Acta Anaesthesiol Scand 2012;56:933–4.
[20] Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–95.
[21] Murray AV, Koenig W, Garcia-Puig J, Patel S, Uddin A, Zhang J. Safety and efficacy of aliskiren/amlodipine/hydrochlorothiazide triple combination in patients with moderate to severe hypertension: a 54-week, open-label study. J Clin Hypertens (Greenwich) 2012;14:821–7.
[22] Harel Z, Gilbert C, Wald R, Bell C, Perl J, Juurlink D, et al. The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. BMJ 2012;344:e42.
[23] Kalra A, Yokogawa N, Raja H, Palaniswamy C, Desai P, Zanotti-Cavazzoni SL, et al. Hydralazine-induced pulmonary-renal syndrome: a case report. Am J Ther 2012;19:e136–8.
[24] Marina VP, Malhotra D, Kaw D. Hydralazine-induced ANCA vasculitis with pulmonary renal syndrome: a rare clinical presentation. Int Urol Nephrol 2012;44:1907–9.
[25] Liew HM, Morris-Jones R, Diaz-Cano S, Bashir S. Pseudofolliculitis barbae induced by oral minoxidil. Clin Exp Dermatol 2012;37:800–1.
[26] Takatsuki S, Rosenzweig EB, Zuckerman W, Brady D, Calderbank M, Ivy DD. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr Pulmonol 2013;48:27–34.
[27] Markert C, Hellwig R, Burhenne J, Hoffmann MM, Weiss J, Mikus G, et al. Interaction of ambrisentan with clarithromycin and its modulation by polymorphic SLCO1B1. Eur J Clin Pharmacol 2013;69:1785–93.
[28] Ben-Yehuda O, Pizzuti D, Brown A, Littman M, Gillies H, Henig N, et al. Long-term hepatic safety of ambrisentan in patients with pulmonary arterial hypertension. J Am Coll Cardiol 2012;60:80–1.
[29] Le MP, Gervais A, Le BC, Long K, Larrouy L, Papy E, et al. Serious neuropsychiatric adverse effects in a hepatitis C virus/hepatitis B virus/HIV-coinfected patient receiving bosentan and telaprevir. J Antimicrob Chemother 2013;68:1208–9.
[30] Sandoval J, Torbicki A, Souza R, Ramirez A, Kurzyna M, Jardim C, et al. Safety and efficacy of sitaxsentan 50 and 100 mg in patients with pulmonary arterial hypertension. Pulm Pharmacol Ther 2012;25:33–9.
[31] Chin M, Levy RD, Yoshida EM, Byrne MF. Sitaxsentan-induced acute severe hepatitis treated with glucocorticoid therapy. Can Respir J 2012;19:e1–2.
[32] Koman G, Alfieri A, Rachingter J, Strauss C, Scheller C. Erectile dysfunction as rare side effect in the simultaneous intrathecal application of morphine and clonidine. Pain Physician 2012;15:E523–6.
[33] Grigoriadis C, Tympa A, Liapis A, Hassiakos D, Bakas P. Alpha-methyldopa-induced autoimmune hemolytic anemia in the third trimester of pregnancy. Case Rep Obstet Gynecol 2013;2013:150278.
[34] Khan MA, Jain G, Soltys SM, Takahashi A. A case of excessive weight gain with guanfacine extended release: 9.53 kg in 4 weeks. J Child Adolesc Psychopharmacol 2012;22:256–7.
[35] Altiaylik OP, Altiparmak UE, Unlu N, Hazirolan DO, Kasim R, Duman S. Intraoperative floppy-iris syndrome: comparison of tamsulosin and drugs other than alpha antagonists. Curr Eye Res 2013;38:480–6.
[36] Wang J, Zhao Y, Jiang SB, Xia QH, Wei CX, Wang MW, et al. Assessment of tamsulosin as a potential male contraceptive in healthy volunteers. Urology 2012;80:614–7.
[37] Truitt CA, Brooks DE, Dommer P, LoVecchio F. Outcomes of unintentional beta-blocker or calcium channel blocker overdoses: a retrospective review of poison center data. J Med Toxicol 2012;8:135–9.