Review Article

Antihypertensives in dermatology Part II - Cutaneous adverse reactions to antihypertensives

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Abstract

Antihypertensive drugs are prescribed frequently and can cause cutaneous adverse reactions. The exact incidence and frequency of these reactions are unknown. Multiple antihypertensive drug consumption has contributed to a substantial increase in the number of cutaneous adverse reactions to them. Thus, there is a need for dermatologists and physicians to be aware of the wide range of available antihypertensives and the type of reactions that can be expected. This review article focuses on the various clinical presentations that have been implicated or associated with them. The diagnosis and management have been discussed in brief.

Key words: Antihypertensives, cutaneous adverse drug reactions, lichenoid drug reaction, psoriasiform eruption

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Introduction

Antihypertensives are used extensively for hypertension as well as other indications including migraine, alopecia, hemangioma, etc., Cutaneous adverse drug reactions to them are common, but the exact incidence and frequency are unknown. Turk *et al*. found these drugs to be the incriminating cause in 8.5% of hospitalized patients, preceded by antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants.[1] Upadhayai *et al*. found that 2% of such patients developed drug reactions.[2] The information obtained from the Danish National Board of Health's Committee on Adverse Drug Reactions showed that 10–60% of reactions caused by antihypertensives are dermatological.[3] There is lack of comprehensive data on the incidence and different types of cutaneous reactions occurring with common and newer antihypertensives. Relevant articles from the PubMed database were collected and analyzed. Case control studies or meta-analyses which showed significant association of drugs with any cutaneous adverse drug reaction were highlighted. Observations have been mentioned as reports.

Some classes of antihypertensives are commonly associated with certain reactions.

1. Angiotensin converting enzyme (ACE) inhibitors: The overall incidence of adverse effects is estimated at 28%, approximately half of which are cutaneous. The common cutaneous reactions are potentially life threatening angioedema, pruritus, bullous eruptions, urticaria, photosensitivity and hair loss.[4]
2. Calcium channel blockers: The most common reactions are gingival hyperplasia (21%) and flushing (10%). Other reactions described are facial or truncal telangiectasia, photosensitivity, new-onset psoriasis (as well as exacerbation), purpuric exanthems, pemphigoid, subacute cutaneous lupus erythematosus, gynecomastia, erythromelalgia and oral ulcers. The frequency of these reactions may be as high as 48%. The more serious reactions associated are toxic epidermal necrolysis with diltiazem. Stevens–Johnson syndrome, erythema multiforme and exfoliative dermatitis have been associated with all three drugs in this class.[5] Reactions occur more frequently with diltiazem than others.[6]
3. Beta blockers: The pathogenetic mechanism responsible is still obscure. It may be due to blockade of the epidermal cell and T-lymphocyte beta-receptors, rather than direct immunologic, allergic or toxic mechanisms.[7] Beta blockers have been commonly associated with lichenoid drug eruptions, eczematous and psoriasiform eruptions.[8]

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4. Diuretics: Thiazides can cause vasculitis, phototoxic/allergic reaction, erythema multiforme and eczema.[3] Furosemide can cause bullous pemphigoid as well as pseudoporphyria.

There are very few studies on the prevalence of cutaneous adverse drug reactions due to antihypertensives. An Indian study showed beta-blockers as the most common agent, followed by calcium channel blockers. The most common patterns observed were urticaria, followed by lichenoid drug eruptions.[2] In a Danish study, amiloride and hydrochlorthiazide had the highest number of cutaneous reactions.[3] The common and rare cutaneous adverse drug reactions reported with antihypertensives are tabulated [Table 1]. The individual cutaneous adverse drug reaction patterns are discussed below.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis is characterized by the rapid development of non-follicular, sterile pustules on an erythematous base. It is attributed to drugs in most cases. Systemic involvement with hepatic, renal or pulmonary insufficiency occurs in approximately 20% of the cases.[9] The eruption occurs 2 to 5 days after drug intake. Although antibiotics are the most common cause, a few cases with diltiazem[10] and terazosin hydrochloride[11] have been described. In a multinational case control study (EUROSCAR), which assessed the risk factors, diltiazem was found to be associated with a higher risk along with antibiotics.[12] T-cell involvement is suggested by positive patch test reactions to the suspected drug.[13] They may directly orchestrate a neutrophilic inflammation by releasing the neutrophil attracting chemokine CXCL8.[14] Discontinuance of the drug is the only treatment necessary, although corticosteroids may be needed in some cases.

Angioedema

ACE inhibitors are the leading cause of drug-induced angioedema, with an incidence of 0.1–0.2%. This is non-immunological and occurs in predisposed individuals. It is caused by accumulation of vasoactive mediators like bradykinin due to reduced activity of angiotensin-converting enzyme.[3] It is never accompanied by urticaria, can start years after beginning the treatment, and can recur irregularly while under treatment.[15] It has varying clinical presentations including isolated involvement of lip or penis,[16] one side of the tongue,[17] or small bowel involvement.[18] Common agents which have been implicated are enalapril,[3] lisinopril[2,3] and alacepril.[19] They may also cause increased frequency, intensity and duration of bouts of idiopathic angioedema during long-term use.[20] Icatibant, a bradykinin receptor antagonist has been shown to accelerate the resolution of ACE inhibitor induced angioedema.[21] Renin inhibitor aliskerin and angiotensin receptor blockers (losartan, valsartan, candesartan) have lower risk of causing angioedema. It is less severe and occurs earlier compared to ACE inhibitors.[22,23] There is less than a 10% chance for these groups of drugs to cause angioedema compared to patients who had angioedema due to ACE inhibitors.[23] Angioedema has also been described in children, most commonly to the dihydropyridine group of calcium channel blockers (amlodipine and nicardipine).[24]

Table 1: Common and rare cutaneous adverse drug reactions reported with antihypertensives

Common	Rare
• Angioedema	• Acute generalized exanthematous pustulosis
• Bullous eruptions	• Eczematous reaction
• Pemphigus	• Drug induced lichenoid eruption
• Bullous pemphigoid	• Oral and mucocutaneous ulcers
• Pseudoporphyria	• Drug reaction with eosinophilia and systemic symptoms
• Lichenoid eruptions	• Erythema multiforme
• Photodistributed hyperpigmentation and telangiectasia	• Erythema annulare centrifugum
	• Exanthematous eruption
• Photosensitivity	• Erythroderma
• Psoriasiform eruption	• Fixed drug eruption
• Pseudolymphoma	• Pityriasis rosea
• ANCA positive vasculitis	• Toxic epidermal necrolysis
• Dry mouth	• Alopecia
• Gingival hyperplasia	• Onycholysis

This list is prepared by the authors based on the current literature and available evidence. ANCA: Anti-neutrophil cytoplasmic antibody

Annular Erythema

Hydrochlorthiazide and spironolactone have caused erythema annulare centrifugum like eruptions.[25,26]

Bullous Eruptions

Pseudoporphyria

Pseudoporphyria is a porphyria like blistering on exposed areas in the absence of abnormal porphyrin metabolism. It may be caused by high dose furosemide,[27] torsemide,[28] bumetanide,[29] flutamide,[30] chlorthalidone[31] and dyazide (combination of triamterene and hydrochlorthiazide).[32]

Pemphigus group (pemphigus foliaceus and pemphigus vulgaris)

Drug-related pemphigus can be of two types, (i) induced pemphigus, in which exogenous factors play a major role and (ii) triggered pemphigus, in which endogenous factors play a major role. Induced pemphigus is usually caused by thiol group of drugs such as captopril. It has a long incubation period of up to one year and mostly resembles pemphigus foliaceus or pemphigus vegetans. Triggered pemphigus mimics pemphigus vulgaris, has a shorter incubation period (128 days average) and is usually caused by non-thiol drugs.[33] The various non-thiol antihypertensives which trigger this are mentioned in Table 2[34-38]. Thiol drugs provoke acantholysis *in vitro* possibly by increasing the activity of plasminogen activators.[39] An active amide group in the molecule of non-thiol drugs may be responsible for inducing pemphigus.[40]

The diagnosis of drug-induced pemphigus is challenging. It resembles idiopathic pemphigus in clinical findings, histopathology and immunofluorescence, thus making it difficult to differentiate the two.[34] Approximately 70–90% of patients have a positive direct immunofluorescence.[41] More than half of the cases caused by thiol drugs remit following drug withdrawal, whereas only 15% of those caused by non-thiol drugs do so.[33] The treatment starts with the immediate withdrawal of the suspected drug (s). Medium to high dose of systemic steroids (about 2/3 of the dose normally used in idiopathic pemphigus) is usually recommended until all symptoms of active disease disappear. In most cases, remission can be achieved within weeks, and steroid doses may be gradually tapered down to zero after a few months.[42]

Drug-induced bullous pemphigoid

Drugs may induce anti basement membrane zone antibody production by acting as haptens that bind to proteins in the lamina lucida and change their antigenic properties. They may stimulate an autoimmune response by structurally modifying molecules

Table 2: Common cutaneous adverse reactions and the antihypertensives that have been implicated

Type of cutaneous adverse drug reaction	Antihypertensives implicated
Pemphigus[34-36,38]	Thiol drugs - captopril Non-thiol - enalapril, ramipril, fosinopril, lisinopril, cilazapril and quinapril Others Propranolol Angiotensin receptor blockers - candesartan, telmisartan[37] Indapamide
Bullous pemphigoid[47,48]	Diuretics (furosemide, bumetanide, spironolactone) calcium channel blockers (amlodipine, nifedipine) ACE inhibitors (captopril, enalapril, lisinopril) Beta blockers (nadolol, practolol) Angiotensin receptor blockers (losartan, valsartan) Clonidine Methyldopa
Cutaneous small vessel vasculitis[58-66]	Hydralazine Diuretics (furosemide, hydrochlorthiazide, metolozone) Beta blockers (propranalol, carvedilol, sotalol, atenolol, acebutalol) ACE inhibitors (captopril, enalapril, ramipril) Calcium channel blockers (amlodipine, nifedepine, diltiazem) Angiotensin receptor blockers (losartan)
Lichenoid eruption[119-124]	ACEi (captopril, enalapril, alacepril) Beta blockers (atenolol, propranolol, labetalol, pindolol, levobunolol, metoprolol, sotalol, acebutalol, timolol eye drops, oxprenolol, nebivalol) Diuretics (hydrochlorthiazide, furosemide, spironolactone diazoxide) ARBs CCBs (nifedepine, amlodipine), nicorandil, terazosin, and methyl dopa
Subacute cutaneous lupus erythematosus[132,134]	Calcium channel blockers (diltiazem, verapamil, nifedipine, nitrendipine), ACE inhibitors (cilazapril, captopril, enalapril) Thiazide diuretics (hydrochlorothiazide, triamterene) Beta blockers (oxprenolol, acebutalol)
Pseudolymphoma[165,167-175]	ACE inhibitors (captopril, enalapril, benazepril, lisiniopril) Calcium channel blockers (amlodipine, diltiazem, verapamil) Beta blockers (atenolol, labetalol) Angiotensin receptor blockers (losartan, valsartan) diuretics (hydrochlorthiazide) Clonidine

and uncovering hidden epitopes. In drug induced bullous pemphigoid, patients tend to be younger. The clinical presentation is heterogenous and variable. Nikolsky sign may be positive in some cases. Tissue bound and circulating anti basement membrane zone IgG antibodies may be absent. Additional antibodies such as intercellular or anti-epidermal cytoplasmic antibodies may be detected. Histopathologically, there may be perivascular infiltration of lymphocytes with a few eosinophils and neutrophils, intraepidermal vesicles with foci of necrotic keratinocytes and thrombi in dermal vessels.[43,44] Marked eosinophilia may be found in serum as well as tissue. Apart from the classical presentation, milder forms are devoid of erythematous bases. Unusual presentations in the form of scarring plaques, nodules with bullae, or excoriations located on scalp and extremities (papular and nodular pemphigoid) have been described.[45] It can mimic other entities such as bullous erythema multiforme[46] and pemphigus (overlapping variants). Some cases are short-lived whereas others become chronic, in the form of drug-triggered bullous pemhigoid.[43]

Various antihypertensives can induce bullous pemphigoid [Table 2].[47,48] Drugs such as furosemide and enalapril are most likely to have an association with bullous pemphigoid, proven by rechallenge.[44] Bastuji-Garin *et al.* reported a strong association with neuroleptics and diuretics (mainly aldosterone antagonists).[48] ACE inhibitors, anticoagulants and diuretics were found to be commonly used by patients suffering from bullous pemphigoid.[49] In a recent case-control study that included 86 patients, loop diuretics were found to be used more frequently. This association was independent of age, cerebrovascular disease, dementia, hypertension or ischemic heart disease.[50] Mucous membrane pemphigoid has been observed with atenolol,[51] isolated ocular cicatricial pemphigoid with ophthalmic anti-glaucoma preparations,[52] and anogenital cicatricial pemphigoid with clonidine.[53] Lichen planus pemphigoides has been reported with captopril and ramipril. Its course tends to be much more indolent but it responds well to treatment.[54] Linear IgA bullous dermatosis has been induced by captopril.[55]

The possibility of a drug etiology must be considered in all patients suffering from bullous pemphigoid as most patients respond rapidly to treatment and do not experience relapses after the withdrawal of the suspect medication.[43]

Cutaneous Vasculitis

Approximately 20% cases of cutaneous small vessel vasculitis are an adverse reaction to drugs and most represent hypersensitivity vasculitis.[56] Therapeutic agents from virtually every pharmacologic class have been implicated. The offending drugs can be generally categorized into: Anti-neutrophil cytoplasmic antibody (ANCA) associated and ANCA negative group. Development of systemic vasculitis may take a few months to years following exposure. The ANCA negative group usually presents with cutaneous involvement within a few days to weeks after drug exposure.[57] An average lag period of 28.9 days was found in an Indian study.[2] Hydralazine has been incriminated in ANCA positive vasculitis, lupus erythematosus like syndrome and digital gangrene.[58] Table 2 depicts the various antihypertensives that cause cutaneous small vessel vasculitis.[58-66]

Blood eosinophilia is found in almost 80% patients with drug-induced systemic vasculitis. However, it is less than 25% in patients who have only cutaneous involvement. The presence of tissue eosinophilia on histology is suggestive of a drug induced vasculitis.[67] Apart from withdrawal of the suspected drug, oral steroids may be needed in cases with systemic involvement. We need to be aware of possible cross reactions (among diuretics, calcium channel blockers) while substituting a drug.

Drug Reaction with Eosinophilia and Systemic Symptoms

This is a potentially life threatening adverse drug reaction with an estimated mortality of 10%, most commonly from fulminant hepatitis

with hepatic necrosis. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, hematological and multiorgan abnormalities. It has a late onset and long duration compared to other drug reactions, with a latent period of 2–6 weeks.[68] There may be associated vesicles, bullae, atypical targetoid plaques and purpura. Sterile follicular and non-follicular pustules may be evident.[69] The rash may progress to involve nearly the entire surface of the skin, producing an exfoliative dermatitis or erythroderma. This can be associated with mucosal involvement such as cheilitis, erosions, erythematous pharynx and enlarged tonsils.[70]

Even though anticonvulsants, sulphonamides and allopurinol are common causes, ACE inhibitors (captopril, enalapril, ramipril[71]), beta-blockers (atenolol, celiprolol) and spironolactone[72] are reported to induce drug reaction with eosinophilia and systemic symptoms. Prolonged systemic corticosteroid therapy may be required. A gradual taper of this therapy over 3–6 months after clinical and laboratory stabilization is recommended to avoid relapse.[73] Incomplete recurrences with structurally unrelated culprit drugs are a frequent phenomenon in such patients.[74]

Erythema Multiforme

Less than 10% of cases of erythema multiforme are drug induced.[75] Although NSAIDs, sulphonamides and antibiotics are common culprits, isolated reports have been described with furosemide, indapamide, carvedilol, metoprolol, fenoterol, nifedepine, amlodipine, diltiazem, cardiazem, topical dorzolamide and candesartan axetil.[76-85] It may be associated with a flu-like prodrome. Blisters and mucosal involvement is more prominent than herpes simplex virus associated erythema multiforme. The course is self limiting with no recurrences after stopping the drug. A mortality rate of 5–15% has been reported in severe cases.[75]

Exanthematous Eruptions

Exanthematous eruptions with various morphological and localization patterns are the most frequently encountered cutaneous adverse drug reactions. They can occur after almost any drug, usually within 2-3 weeks of drug administration. They may be accompanied by fever, pruritus and eosinophilia.[86] The course of these benign exanthems lasts for a few days to some weeks. If the drug is continued, an exfoliative dermatitis may develop. Occasionally, the eruption subsides despite continuation of the medication.[86] Immunological effector mechanisms include drug-specific CD4+ T cells, various chemokines and cytokines.[87] Exanthematous drug eruption has been reported with diltiazem and valsartan.[88,89] Telmisartan has caused symmetrical drug related intertriginous and flexural exanthem.[90]

Eczematous Eruptions

Eczematous drug reactions may be localized or generalized. The term ‘endogenous contact eczema’ refers to the occurrence of an eczematous contact drug reaction following primary sensitization by oral therapy. These may develop following therapy with methyldopa and clonidine.[91] Among ACE inhibitors, captopril has been shown to cause an eczematous reaction, confirmed in many cases with patch testing, without any cross-reactivity with enalapril , lisinopril or benazepril.[92] The latency period can vary from a few months to several years. A lag period of 4–30 months was observed in a study.[93]

Eyelid dermatitis was seen with the use of beta-blocker eyedrops (timolol, befunolol, carteolol, propranolol, practalol) with cross-sensitivity among these. The proposed hypothesis of cross-sensitivity is primary metabolism of the drug to a common aldehyde.[94] Stasis dermatitis has been described with amlodipine.[95] Topical diltiazem used for anal fissures is known to cause contact dermatitis.[96] In a study of 23 cases of localized and generalized eczematous drug reactions caused by antihypertensives, the class of drugs implicated were ACE inhibitors, angiotensin receptor blockers and hydrochlorthiazide in combination with ACE inhibitors or angiotensin receptor blockers.[93] Extensive allergic contact dermatitis has been seen in factory workers coming in contact with alprenolol.[97] Localized contact allergy with transdermal clonidine has also been described.[98]

Eczematoid Photosensitive Reactions

Most systemic drug photosensitivity is due to phototoxic mechanisms. Different patterns of phototoxic reactions occur in the skin, including an immediate prickling/burning sensation, urticaria, sunburn-like reaction, late onset erythema, dermatitis, skin fragility and telangiectasias.[99] Drucker and Rosen, suggested ten drugs to be considered potent photosensitisers, of which hydrochlorthiazide was the only antihypertensive.[100] Other drugs include diuretics (triamterene, furosemide), ACE inhibitors (ramipril, enalapril, quinapril), calcium channel blockers (nifedepine), beta-blockers (tilisolol), angiotensin receptor blockers (valsartan), centrally acting agents (clonidine, methyldopa), valsartan and methyl-dopa have been described to cause photosensitivity in the past, but these are mostly individual case reports. Amlodipine and nifedepine can cause photodistributed facial telangiectasia.[99,100] In a study of 62 cases of thiazide induced photosensitivity, eczematous presentation was found to be the most common.[101] In most cases, phototesting revealed an abnormal response to UVA rays alone, or to both UVA and UVB. For systemic drug phototoxicity, the key investigation is phototesting with a monochromator and drug rechallenge phototesting. Photopatch testing is needed in suspected cases of photo-allergy. Drug-induced photosensitivity is usually managed by stopping the suspected drug. Other measures are sometimes necessary, including phototherapy using wavelengths that do not elicit the response.[99]

Erythroderma

Exfoliative dermatitis is one of the most dangerous cutaneous adverse drug reactions. Captopril,[102] lisinopril,[103] diltiazem,[104] amlodipine, timolol eye drops[105] and glyceryl trinitrate[106] have caused erythroderma. Interstitial granulomatous drug reaction secondary to enalapril presenting as erythroderma has been reported.[107] The latency period is highly variable, ranging from a few days to several months.

Erythromelalgia

This reaction has been related to nifedipine, diltiazem, verapamil and nicardipine. It is characterized by intermittent, usually symmetrical burning pain, warmth and dermal erythema of the extremities. The symptoms are ameliorated by cooling the extremities.[5] The time lapse between the first dose of the drug and its occurrence varied from eight weeks to a year. The time from discontinuation of the drug to resolution ranged from one to fourteen days.[108]

Fixed Drug Eruptions

A fixed drug eruption characteristically recurs at the same site every time the drug is administered. The number of sites affected may increase with each exposure. Although this is rare following antihypertensives, diltiazem, enalapril and amlodipine have been

implicated.[109] Isolated reports of fixed drug eruption secondary to propranolol,[110] atenolol,[111] bisoprolol, nifedepine,[112] hydralazine[113] and indapamide[114] have been described. The latency period was 2 months to 19.6 months in an Indian study.[2]

Hyperpigmentation

Diltiazem has been implicated as the cause of photodistributed hyperpigmentation in several reports. The interval from initiation of diltiazem to the onset varies from a few months to years. Histologically, the changes are consistent with a lichenoid dermatitis that show basal vacuolar alteration and prominent pigment incontinence.[100,108,115] Kubo *et al*. propose that diltiazem associated photodistributed hyperpigmentation must be a specific type of drug-induced photosensitive lichenoid eruption, probably in the UVB range.[116] Photoprotection, hydroquinone and tacrolimus cream have been tried. Pigmentation of skin predominantly over sun-exposed areas and pigmentation of oral mucosa have been described after one year of amlodipine intake.[117]

Lichenoid Drug Eruptions

Lichenoid drug eruptions tend to be extensive and may develop weeks or months after initiation of therapy [Figure 1]. Lesions may be more psoriasiform than those seen in classic lichen planus. Oral involvement is rare. There may be atypical features such as marked scaling, eczematization, hypertrophic lesions and a tendency to more intense residual hyperpigmentation.[118] The antihypertensives which may cause lichenoid drug eruption are enumerated in Table 2.[119-124] Cross-reactivity among beta-blockers has not been demonstrated.[121] Valsartan caused linear lichenoid eruption[125], whereas lichenoid nail dystrophy was reported to angiotensin receptor blockers in another case.[126] Bullous lesions were seen with labetalol, and penile involvement with propranolol.[121] Photolichenoid eruption has been reported with hydrochlorthiazide, enalapril[119] and inhaled tiotropium bromide.[127] Isolated oral eruptions have been seen with calcium channel blockers, ACE inhibitors and beta-blockers.[128] Oral ulcerative lichen planus was observed with methyldopa.[129] The intra-oral sites of predilection include the posterior buccal mucosa, tongue, floor of mouth, palate and alveolar ridges. There appears to be a preference for unilateral distribution. They are nearly identical to oral lichen planus clinically, histologically and immunologically.[130] McCartan and McCreary have provided a structured system for reporting oral lichenoid drug eruption cases.[131]

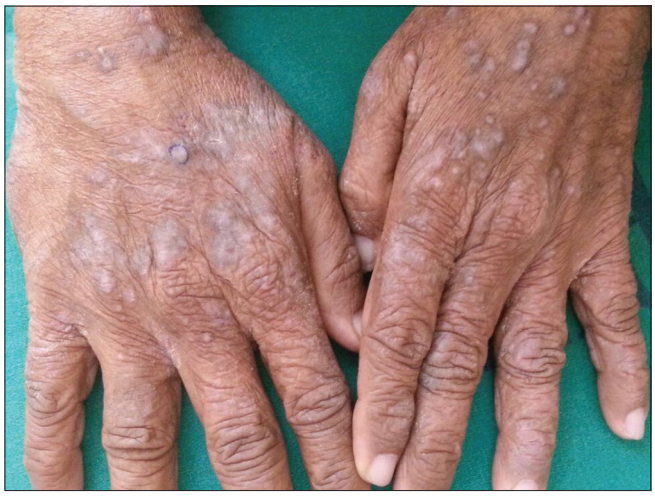

Figure 1: Lichenoid papules and plaques over the dorsal aspect of both hands

The lag period is variable and the latency period ranges from one month to two years (19.6 months average). Resolution of the skin and mucosal eruptions may be slow and variable, with a resolution time of 1–4 months.[2] Withdrawal of the drug and symptomatic treatment is often sufficient. Severe cases may require corticosteroid therapy as in idiopathic lichen planus.

Lupus Erythematosus

Drug-induced lupus erythematosus is defined as a lupus erythematosus like syndrome temporally related to continuous drug exposure, which resolves after discontinuation of the offending drug. Similar to idiopathic lupus erythematosus, this can be divided into systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus.[132] It is believed that Fas-dependent apoptosis of epidermal basal keratinocytes plays an important role. A reduction of immunohistochemical expression of Bcl-2, an antiapoptotic protein, has been demonstrated in lesional skin along the epidermal basal layer among such patients.[133] In general, old patients are affected and there is no sex predilection as seen in idiopathic SLE. The time between drug exposure to onset of symptoms varies from a month to more than a decade.[134]

Skin involvement is less frequent in drug-induced SLE, although its exact incidence remains controversial. Certain non-specific cutaneous manifestations such as purpura, erythema nodosum and photosensitivity are frequently present in drug-induced SLE than its idiopathic counterpart. Features such as malar rash, discoid lesions, mucosal ulcers, alopecia and Raynaud's phenomenon are usually absent in drug-induced SLE. Other non-specific features such as urticaria, urticarial vasculitis and signs of necrotising vasculitis may be considered characteristic of drug-induced lupus erythematosus.[132,134,135] Fever, arthralgia, myalgia, pleurisy and pericarditis are present, whereas renal and central nervous system involvement is rare. Anti-nuclear antibody and anti-histone antibodies are positive, whereas Anti-ds DNA is usually negative and complement levels are normal. Deposition of immunoreactants in uninvolved skin is rare. A negative ANA test should not automatically preclude a diagnosis of drug-induced lupus erythematosus, particularly if the patient has other autoantibodies associated with SLE or drug-induced lupus erythematosus.[132,134] Hydralazine induced lupus erythematosus with Sweet's syndrome has been reported.[136]

Of the antihypertensives implicated in drug-induced SLE [Table 2][134,135], hydralazine and methyldopa have a definite association while others have a probable or possible association.[137] A matched, nested, case-control study conducted in the United Kingdom to investigate drugs causing lupus erythematosus found a causal relationship only for carbamazepine, minocycline and possibly hydralazine.[138] Resolution or marked improvement of the symptoms generally occurs within 2–5 weeks of drug withdrawal, although some patients may require NSAIDS or low dose systemic steroids. Immunosuppressive drugs may be needed in severe cases with renal or neurological involvement. Patients who develop ANA positivity during treatment need not have the drug stopped. They do not require treatment unless they have clinical features of lupus erythematosus.[139] Drug-induced subacute lupus erythematosus [Table 2][132,134] is similar to its idiopathic counterpart, both clinically and serologically.[134,140] In most cases, there is spontaneous resolution within weeks of drug withdrawal. The Anti Ro/SS-A antibodies may remain positive even after resolution of disease activity.[140]

Pityriasis Rosea-Like Eruptions

An Italian series reported cases of pityriasis rosea linked to ACE inhibitors, alone or in combination with hydrochlorothiazide. They had also reported a case of pityriasis rosea with hydrochlorothiazide plus losartan.[141]

Palmoplantar Keratoderma

Losartan has been shown to cause palmoplantar hyperkeratosis, which resolved after withdrawal of the drug.[142]

Purpura

Hydralazine[143] can cause pigmented purpuric dermatosis. A case of amlodipine induced Schamberg's purpura occurred eight years after starting treatment, and resolved within three months of stopping the drug.[2] Chlorthiazide and hydrochlorthiazide have been shown to cause thrombocytopenia and purpura.[144] Frictional purpuric eruption may occur with angiotensin receptor blockers.[145]

Psoriasiform Eruptions

The antihypertensives that are strongly related to psoriasis are beta blockers and ACE inhibitors. Other drugs also have been reported to induce or aggravate psoriasis, but the evidence is less strong. In general, most drugs tend to exacerbate psoriasis rather than induce it[146] Drug-induced psoriasiform eruption tends to occur *de novo* in patients with no prior personal or family history of psoriasis.[147] The eruptions appear 1–18 months after initiation of the drugs.[148] However, a lag period of two years has been observed.[2] Psoriasiform eruptions clear after several weeks of drug withdrawal,[148] but drug aggravated psoriasis may not clear completely. Drug-induced psoriasiform eruption is not true psoriasis. The lesions are less red, less thick and less scaly [Figure 2]. The knees and elbows tend to be spared. Histopathologically, they lack neutrophils or Munro's microabscesses. Both cardioselective and non-cardioselective beta blockers can aggravate psoriasis or induce a psoriasiform rash.[149] Topical application of timolol in the treatment of open angle glaucoma has been reported to induce psoriasis and transform psoriasis vulgaris into psoriatic erythroderma, by systemic absorption via the conjunctiva.[150]

Blockade of beta 2 receptors leads to a decrease of cAMP, causing a decrease in intracellular calcium, excessive release of enzymes by lymphocytes, neutrophils and macrophages. This consequently increases cellular proliferation and lack of differentiation.[151] ACE inhibitors have been implicated in case-control and case-crossover studies.[146,151] They act by altering the kinin-kallikrein arachidonic acid system, which may lead to increased concentrations of inflammatory metabolites, thus inducing psoriasis. Other drugs with a weak association include angiotensin receptor blockers,[152] calcium channel blockers,[153] clonidine[154] and urapidil (α1 adrenergic blocker).[155]

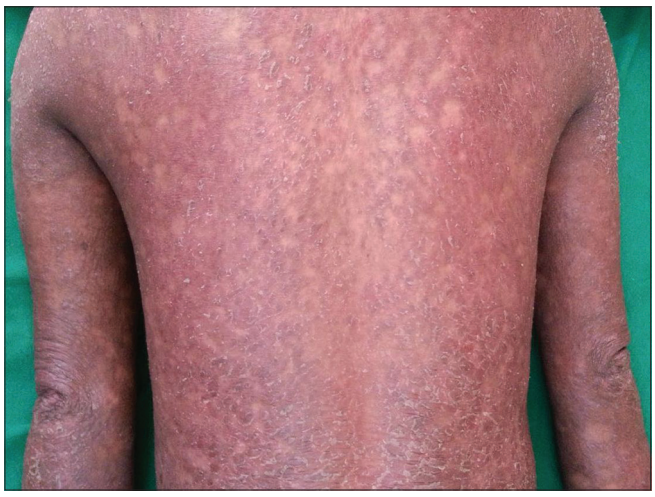

Figure 2: Psoriasiform drug eruption with diffuse erythema and scaling over the back and upper limbs

A prospective cohort study on the risk of psoriasis taking individual antihypertensives found that only beta blockers were associated with an increased risk after regular use for six or more years.[156] On the other hand, in a population based case-control study, no increased or altered risk of psoriasis was found with beta blockers or other antihypertensives.[157] Propranolol,[158] atenolol,[159] pindolol,[3] ramipril[160] and candesartan[161] have been shown to induce generalized pustular psoriasis. Captopril, enalapril and perindopril have caused palmoplantar psoriasis and palmoplantar pustulosis.[162] Oxprenolol has been shown to exacerbate psoriatic arthropathy.[163] Diltiazem has also precipitated psoriatic erythroderma.[164]

Pseudolymphomatous Drug Eruptions

Cutaneous pseudolymphomas can be either of T-cell or B-cell origin on histology. Characteristically, anticonvulsant induced pseudolymphoma hypersensitivity syndromes develop soon after the drug has been started, usually within two to eight weeks.[165] However, cases have developed as late as seven years.[166] There are numerous reports of antihypertensive induced pseudolymphomatous drug eruptions in the literature [Table 2].[167-175] They resolve in 1–32 weeks of discontinuing the medication.[175] It is postulated that the drug may promote an aberrant immune response to an antigen, which may be the drug itself, or some other stimulus. Failure of lesions to resolve months after drug discontinuation should raise suspicion of a malignant process. Appropriate investigations must be done, as true lymphomas may occasionally develop.

Toxic Epidermal Necrolysis

Although antihypertensive associated toxic epidermal necrolysis is extremely rare, isolated reports secondary to sodium nitroprusside,[176] amlodipine,[177] captopril,[178] carvedilol,[179] oral minoxidil,[180] indapamide,[181] alfuzosin[182] and hydralazine[183] have been described. Timolol, dalfuzomide, and latanoprost eye drops[184] may also induce this condition. A multinational case-control study conducted in Europe found that beta blockers, ACE inhibitors, calcium channel blockers, thiazide diuretics and furosemide were not associated with a detectable risk of Stevens Johnson syndrome or toxic epidermal necrolysis.[185] A similar result was found for thiazides[186] and ACE inhibitors.[187]

Hair and Nail Changes

Propranolol,[188] metoprolol[189] and certain ophthalmic beta blockers[190] can cause alopecia. Diazoxide and minoxidil can cause hypertrichosis.[191] Drug-induced changes in hair colour, usually occurs 3–12 months after the onset of treatment,[192] and has been described with verapamil.[193] Onycholysis may occur with captopril, thiazides, proctalol and indapamide.[194]

Oral Changes

Dry mouth has been reported in approximately 20% of hypertensives treated with beta-adrenergic blockers. They may decrease the total

protein content of saliva. The administration of ACE inhibitors may cause dry mouth due to reduction of the salivary flow rate. Diuretics may cause dry mouth by dehydration and salivary gland hypofunction. Alpha 1 adrenergic agents may result in altered saliva composition and secretion rates. Dry mouth is reversible on drug discontinuation.

ACE inhibitors are associated with taste disturbances. Impaired or salty taste is a frequent complaint with captopril. These tend to be self limiting and reversible within two to three months even if the drug is continued.[195] Malic acid 1% spray improved antihypertensive induced xerostomia and stimulated the production of saliva.[196] Buccal ulceration and aphthous-like ulcers have been reported with beta blockers, ACE inhibitors (captopril, enalapril), angiotensin receptor blockers (losartan), nicorandil and methyldopa.[195,197,198] Nicorandil can cause oral, anal and mucocutaneous ulcerations. It may rarely cause leg ulceration without mucosal involvement.[199] Within the calcium channel blockers family, nifedipine, diltiazem, verapamil and amlodipine can cause gingival hyperplasia. Tissue enlargement typically occurs within one to three months of therapy, usually beginning in the interdental papillae. Its pathogenesis is traced back to the increased production of collagen by gingival fibroblasts, which may account for the lack of rapid resolution after drug discontinuation.[200]

Diagnosis of Cutaneous Adverse Drug Reactions to Antihypertensive Drugs

Numerous methods for causality assessment in adverse drug reactions have been published. They fall into three broad categories – expert judgement, algorithms and probabilistic methods. Due to problems of reproducibility and validity, no single method is universally accepted.[201] At present there are no specific tests that can predict the capacity of drugs to induce allergic reactions, or of the susceptibility of individuals to experience an allergic reaction. Skin testing, especially patch test, was found to be a useful screening method if the reaction was exanthema. It was also useful if antimicrobial, cardiovascular or antiepileptic drugs were suspected.[202] Oral rechallenge needs to be considered when patch tests are negative, but cannot be performed in case of severe drug reactions. As the latency of the reaction is prolonged and variable with many antihypertensives, the utility of an oral rechallenge in such situations is doubtful. In-vitro cytokine release tests like interferon gamma release test and the cell scan apparatus to detect activation of lymphocytes may have a role in diagnosing cutaneous drug eruptions in the future.[203]

Conclusion

Cutaneous adverse drug reactions to antihypertensives are common. The time of onset and presentation is highly variable. Hypertensive patients are receiving multiple drug therapy nowadays, more than what used to be the norm a decade ago. The ever increasing list of newer antihypertensives has contributed to a substantial increase in the number of adverse reactions, especially cutaneous. Hence, dermatologists need to be aware of the various antihypertensives and the cutaneous adverse drug reactions that can occur due to them. Large scale population based prospective studies might give us further insights into the frequency, as well as the clinical presentations that can be expected. Further studies are necessary on tests for causality assessment of such reactions.

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Conflicts of interest

There are no conflicts of interest.

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