Review Article

Antihypertensives in dermatology Part I - Uses of antihypertensives in dermatology

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Abstract

Hypertension is a global health problem. Antihypertensives are the mainstay of treatment for hypertension. Some of them were accidentally found to be useful in alopecias and infantile hemangiomas and have now become standard treatment for these conditions as well. Antihypertensives are also being studied for other dermatological indications, where they have shown promising efficacy. This review focuses on the dermatological indications for antihypertensives, discussing the drugs that have been tried, as well as their efficacy, dosage, duration of therapy, and adverse effects.

Key words: Antihypertensives in dermatology, minoxidil in alopecia, propranolol in hemangiomas

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Introduction

Antihypertensives(AHTs) are extensively used in the field of medicine, they are classified into different classes based on their mechanism of action viz. calcium channel blockers, beta-blockers, ACE inhibitors, alpha1 blockers, direct vasodilators, diuretics, aldosterone antagonists, angiotensin receptor antagonists and centrally acting drugs.[1] Of the various antihypertensives available now, some are being used effectively in dermatological conditions. Minoxidil, which was used as an emergency drug for hypertension in 1971, was accidentally found to cause increased hair growth when used for a longer duration.[2] Similarly, Leaute-Labreze reported the serendipitous discovery of the dramatic response of infantile hemangiomas to propranolol, when it was used in children with infantile hemangiomas with various cardiac problems like obstructive hypertrophic cardiomyopathy, increased cardiac output etc.[3] The efficacy of these antihypertensives in hemangiomas and androgenetic alopecia has been subsequently proved without doubt in various randomized controlled trials. While they are being used 'off-label' for certain indications, many more are under study and promising results have been shown in various dermatological diseases.

Uses of Antihypertensives in Dermatology

Antihypertensives are being used extensively for the treatment of various dermatological diseases, which are tabulated in Table 1.

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Nonscarring alopecia

Nonscarring alopecias are more common than scarring alopecias and include male and female pattern hair loss (androgenetic alopecia), alopecia areata, telogen effluvium, trichotillomania, and other less common conditions.

Minoxidil

Minoxidil, originally used as an oral drug for hypertension, was discovered to cause increased hair growth as a side effect, and has since been extensively studied and used in the management of various types of alopecia.

Mechanism of action

Minoxidil is supposed to prolong the duration of the anagen phase and convert vellus hair to terminal hair. However, there is no convincing evidence for this; although, it may prevent or delay follicular miniaturization.[2]

The active form of minoxidil is minoxidil sulphate. Conversion of minoxidil into minoxidil sulfate is higher in hair follicles than in the surrounding skin. The exact biochemical mechanism is not known, but proposed mechanisms include[2,4,5]

1. ATP-sensitive potassium channel opening, decreasing calcium entry into hair follicle cells, thereby preventing

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epidermal growth factor (EGF)-induced inhibition of hair growth
2. The increased ATP causes release of adenosine, which stimulates vascular endothelial growth factor (VEGF), a promoter of hair growth
3. Activation of cytoprotective prostaglandin synthase-1, an enzyme that may stimulate hair growth
4. Increased expression of hepatocyte growth factor (HGF) m-RNA, a hair growth promoter.

The strengths available, adverse effects and contraindications for minoxidil are tabulated [Table 2].[2,6-8]

Uses

Male pattern hair loss/androgenetic alopecia and female pattern androgenetic alopecia

While 2% scalp lotion (1988) and subsequently 5% lotion (1997) and 5% foam (2006) were approved for the treatment of male pattern hair loss, 2% minoxidil solution was the only concentration initially approved by the US Food and Drug Association (FDA) and regulatory equivalents (such as the European Dermatology forum) of other countries for treating female pattern hair loss. A few studies found that once-daily 5% minoxidil foam when compared with 2% solution twice daily was efficacious and safe in female pattern hair loss.[9] Five percent minoxidil foam has been recently approved by FDA (2014) and in Canada for use in female pattern hair loss.[10] It is yet to be approved by the Drug Controller General of India (DCGI) for female pattern hair loss.

Minoxidil usually preserves if not reduces the horizontal diameter of alopecia in the crown area. Vellus hair constitutes much of the regrowth in the first 4 months, thereafter terminal hair growth becomes noticeable. It may cause temporary hair shedding during the first month that lasts for 4–6 weeks by inducing anagen from the resting phase. This shedding may be viewed as a clinical indication that the treatment is working. The response to treatment should be assessed at 6 months. If successful, the treatment needs to be continued indefinitely to maintain efficacy.[4] It is important to stress that treatment is long-term and stopping minoxidil will shed all minoxidil-dependent hair within 4–6 months.[11,12]

Minoxidil is best recommended for mild-to-moderate androgenic alopecia in males (Hamilton–Norwood Grade II–IV).[11,12] Two studies comparing minoxidil 2% solution applied twice daily and minoxidil 5% solution twice daily in male pattern hair loss showed that the outcome in the minoxidil 5% group was superior to that with minoxidil 2%.[11,13] Further studies are required to compare the efficacy of minoxidil (5%) solution and foam formulation in male pattern hair loss.

Although topical minoxidil has a good safety profile, efficacy in the overall population remains relatively low at 30–40%. A study by Goren *et al*. of a sulfotransferase enzyme (SULT1A1) activity assay demonstrated 95% sensitivity and 73% specificity in predicting response to minoxidil treatment in androgenic alopecia.[14]

Minoxidil has also been combined with zinc pyrithione,[15] tretinoin[16] and topical finasteride[2] with variable results.

Alopecia areata

Minoxidil 5% is mainly used as an adjuvant to conventional therapy in alopecia areata. The response is variable depending on the strength of minoxidil used (38% and 81% terminal hair regrowth with 1% and 5% topical minoxidil, respectively).[17] Better results were obtained in a study when it was used in combination with topicalor intralesional steroids, or anthralin.[18] Topical minoxidil is far less effective in alopecia totalis and universalis.[19] Hair loss generally recurs after treatment is stopped because minoxidil does not change perifollicular lymphoid infiltration even in improved cases of alopecia areata.[20]

Table 1: Dermatological uses of antihypertensives

Indication	Antihypertensive
Nonscarring alopecia MPHL/FPHL, alopecia areata, pre- and post-hair transplantation Chemotherapy alopecia	Minoxidil (topical)
Infantile hemagiomas	Beta blockers (oral and topical propranolol, topical timolol)
Raynaud's phenomenon	CCBs (nifedepine, amlodipine, felodipine), diltiazem Others - nitrates, ARBs (losartan), alpha blocker (prazosin)
Flushing Rosacea-related erythema and flushing	Clonidine (oral, transdermal), beta blockers, alpha blocker (phentolamine) Brimonidine tartrate gel (topical)
Keloids	Verapamil (intralesional)
Chilblains	Nifedepine
Calcinosis cutis	Diltiazem
Acne, FPHL, hirsuitism, and hidradenitis suppurativa	Spironolactone
Cyclosporine-induced hypertension	CCBs (nifedepine, isradipine)
Chronic nonhealing ulcers	Timolol (topical) Nifedepine, azelnidipine (in animal studies) (topical)
Role in wound healing prevention of skin cancers, cutaneous infiltration analgesia and topical steroid induced skin atrophy	AHTs are still being studied

MPHL: Male pattern hair loss, FPHL: Female pattern hair loss, CCBs: Calcium channel blockers, AHTs: Antihypertensives, ARBs: Angiotensin receptor blockers

Table 2: Minoxidil in alopecias

Strengths and formulations available	Recommended dose	Adverse effects	Contraindications
Solution containing propylene glycol (2%, 5%, 10%) Spray, roll-on, foam NLC gel,[6] chitosan microparticles[7] and iontophoresis[8] have been shown in vitro to enhance the drug delivery	1ml of both 2% and 5% formulation or half a cup of foam applied twice daily over the dry scalp[2] to be left in place for 4 h	Allergic and irritant contact dermatitis (<10%) Hypertrichosis of face and hands	Absolute - pregnant and Lactating women To be used with caution in patients with cardiovascular disease[2]

NLC: Nanostructured lipid carrier

Congenital hypotrichosis

Minoxidil alone and in combination with tretinoin has been found to be effective in a few cases of congenital alopecia associated with hypohidrotic ectodermal dysplasia.[21,22] There was an increase in hair density on the scalp without any side effects. In ectodermal dysplasia, there may be a decrease in the maturation of hair follicles rather than a complete absence, which might explain the improvement seen with minoxidil. Bang *et al*. reported the successful use of minoxidil in a 1-year-old child with temporal triangular alopecia with marked improvement; however there was a recurrence of hair loss after its discontinuation.[23]

Pre- and post-hair transplantation

The use of topical minoxidil in hair transplant patients with viable but suboptimally functioning follicles in the region to be transplanted can add to the density and complement surgical results by slowing down or stopping further hair loss. Results from preliminary uncontrolled clinical trials suggest that topical concentration 2% may speed up regrowth in transplanted follicles, prolong the anagen phase, slow the progression of future hair loss, and reduce post-surgical telogen shedding.[24,25] Controlled clinical trials are needed to substantiate these preliminary data.

Chemotherapy-induced alopecia

Chemotherapy-induced alopecia is a cause of distress among patients undergoing cancer treatment. Topical 2% minoxidil did show benefit in accelerating hair regrowth in patients who had already finished their chemotherapy regimens, though it did not prevent chemotherapy-induced alopecia when it was used during chemotherapy.[26,27]

Adverse reactions

Allergic and irritant contact dermatitis are seen in less than 10% of cases. Skin irritation can occur due to minoxidil (particularly with 5%) and propylene glycol but allergic reactions to either of these are rare. Contact dermatitis should be excluded by patch testing. If it is caused by propylene glycol, an alternative vehicle can be used, whereas if irritation and contact dermatitis are due to minoxidil itself, drug withdrawal is unavoidable.[2,4] Minoxidil is poorly absorbed after topical application. Only 0.3–4.5% reaches systemic circulation and the drug is eliminated within 4 days. Hence, the occurrence of cardiovascular events or headache is very rare.[28]

Facial hypertrichosis and hypertrichosis of the hands was observed in 4% of females using minoxidil in placebo-controlled clinical trials.[29]

Women who already have mild hirsutism are more likely to develop this adverse effect. A few studies have shown this effect with twice- daily applications of 5% solution in females. Hypertrichosis is entirely reversible on discontinuation of the drug.[4,29]

Central serous chorioretinopathy[30] and erosive pustular dermatosis of scalp[31] have been rarely reported with minoxidil.

Infantile Hemangiomas

Hemangiomas are benign tumors, commonly encountered in infancy and early childhood. While most of them regress spontaneously, a minority of infantile hemangiomas can be problematic or even life-threatening because of their size and/or location. Among the treatments used before the propranolol era, steroids were considered first-line by many authors.

Propranolol

In 2008, Leaute-Labreze *et al*. published a case series describing the serendipitous discovery that oral propranolol was effective in the treatment of infantile hemangiomas.[3] Within a very short period after its discovery and long before the publication of randomized controlled trials, propranolol became the preferred agent for treatment of complicated infantile hemangiomas. A meta-analysis comparing corticosteroids and propranolol for the treatment of cutaneous infantile hemangiomas demonstrated the corticosteroid studies to have a pooled response rate of 69% versus a rate of 97% with propranolol.[32]

Indications

The major indications for propranolol treatment in infantile hemangiomas are described in Table 3.[33-37]

Mechanism of action

Different mechanisms of action have been proposed for the efficacy of propranolol in infantile hemangiomas viz

1. Vasoconstriction and lowering of renin[38]
2. Inhibition of angiogenesis and proliferation by decreasing expression of VEGF and bFGF (fibroblast growth factor) genes through the downregulation of the rapidly accelerated fibrosarcoma (RAF)–mitogen activated protein kinase pathway in a dose-dependent manner[39]
3. Induction of apoptosis of hemangioma endothelial cells through activation of caspase-9 and caspase-3, up-regulation of the pro-apoptotic genes p53 and Bax and down-regulation of the antiapoptotic gene *Bcl-Xl*[40]
4. Accelerated adipogenesis of hemangioma stem cells.[41]

Dosage and monitoring

There is no uniformly accepted protocol for the administration of oral propranolol in infantile hemangiomas. Prospective randomized studies on the optimal modality and duration of therapy, and long-term outcomes after discontinuing propranolol are lacking. The choice between in-hospital and outpatient treatment should be made on a case-by-case basis. McSwiney *et al*. demonstrated the safety of giving propranolol on a day-care basis with targeted cardiac screening only if necessary.[42] Drolet *et al*. recommended inpatient care for infants less than 8 weeks of age and those with cardiovascular/respiratory comorbidity[43] In a recent study, it was concluded that routine electrocardiogram (ECG) prior to the start of propranolol therapy may not be necessary in the treatment of children with infantile hemangiomas.[44]

The most commonly used dosage of propranolol is 2 mg/kg/d, although some evidence suggests that infants may respond well at 1–1.5 mg/kg/d, or require as much as 3 mg/kg/d.[34,43,45] The usual initial dose is 0.5 mg/kg, gradually increased to a maximum of 3 mg/kg/day. Gunturi *et al*.[35] conducted a systematic review on propranolol use for infantile hemangiomas and recommended that propranolol solution (prepared by dissolving 10 mg tablet in 5 ml water) should be given thrice daily, with inpatient monitoring for adverse effects (listed below under adverse reactions) for 6 hours after the first dose. Propranolol, in solution form is FDA approved and commercially available as Hemangeol (4.28 mg/ml) for use in children with infantile hemangiomas in USA and the European Union. Parents need to be educated about the warning signs of hypoglycemia

Table 3: Indications for propranolol in infantile hemangiomas

Cutaneous hemangiomas[33]
Vision compromise, airway obstruction, nasal obstruction, auditory canal obstruction, feeding difficulty
Bleeding and/or ulceration
Risk of permanent disfigurement (nasal tip/columella, lips involving the vermillion border), large hemangioma (rapidly growing), compression of neck structures and spinal cord
Some centres also use it for a segmental or facial location of IH
Hepatic, subglottic, orbital, mediastinal, retroperitoneal and IH with PHACES syndrome[34,35]
Kassabach-Merritt phenomenon associated with kaposiform hemangioendothelioma, tufted angioma - propranolol in combination with vincristine or steroids[36,37]

PHACES: Posterior fossa defects, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal clefting or supraumbilical raphe, IH: Infantile hemangiomas

and the importance of maintaining a regular feeding schedule. The mean duration of propranolol therapy in a meta-analysis of 41 studies of more than 1200 infants was 6.4 months.[46] However, the optimal length of treatment is yet to be determined prospectively. There are reports of rebound growth of infantile hemangiomas after stopping propranolol,[47] and it seems prudent to continue therapy until beyond the proliferative phase (9–12 months of age) to reduce this. Bertrand *et al*. suggested that treatment with propranolol should be continued until stabilization has been maintained for 6 months or more, with the duration of therapy depending on the age at which propranolol was initiated.[34] Topical propranolol 1% ointment has been found to be safe and can be tried in patients in whom oral doses cannot be given.[48]

Adverse reactions

In a randomized controlled trial, bradycardia and hypotension were observed to be the most common adverse effects.[48] Others which have been reported include hypoglycemia, hypotonia, wheezing, stridor, sleep disturbances, agitation, nightmares, daytime drowsiness, digestive symptoms like decreased or increased appetite, gastroesophageal reflux, irritability, poor weight gain and acrocyanosis.,[3,34] There has been a report of allergic contact dermatitis to topical propranolol in a 5-month-old baby.[49] Langley and Pope suggested that caution be exercised in the use of propranolol in children for infantile hemangiomas, considering the evidence from adult volunteer studies regarding its effects on the central nervous system.[50] However, no evidence of psychomotor developmental delay was found in infants with infantile hemangiomas treated with propranolol.[51]

Response to therapy

Better results are obtained if patients are treated during the the early proliferative phase. Late treatment may yield partial improvement.[33] Twenty-four hours after the initiation of propranolol, a change in the color of the lesion from intense red to purple with palpable softening can be observed. Ultrasound examination may show an objective regression in thickness associated with an increase in the resistive index of vascularization of the hemangioma.[3,48] Symptoms such as dyspnea or hemodynamic abnormalities usually resolve within 48 hours.[45] In the case of orbital infantile hemangiomas with palpebral occlusion, spontaneous ocular opening may be observed within 7 days. Ulcers heal completely within 2 months.[45] Lesions become nearly flat after 6 months of treatment, with persistence of residual skin telangiectasias in some cases.[3]

Risks for relapse

There is rapid recoloration of the infantile hemangiomas on cessation of propranolol therapy, which may be explained by the release of pharmacological vasoconstriction. This observation is common and does not require readministration of propranolol.[34,48]

In a study by Ahogo *et al*., 25% of the infants treated with oral propranolol for infantile hemangiomas relapsed. However in half of them the relapse was minor and did not necessitate further therapeutic intervention.[52] They found that the risk of a major relapse (with a true regrowth phase) was 12% in infants treated early (before 5 months of age) with oral propranolol for 6 months. Children at risk of relapse were those with segmental infantile hemangiomas, a deep component to their lesions, and those with infantile hemangiomas involving the head and neck region. Interestingly, they found that the dosage of oral propranolol did not influence the risk of relapse.

A longer duration of therapy may reduce the chances of relapse. A retrospective cohort study of 30 patients with complicated infantile hemangiomas found that the group treated with propranolol for ≤8 months had a 90% relapse rate, whereas ≥12 months of treatment resulted in a 5% relapse rate.[53]

Combination therapies

Propranolol may be combined with prednisolone in selected cases to achieve a rapid response, following which the steroid can be tapered and stopped. In patients with an incomplete response to propranolol, medical therapy may still limit the extent of surgery necessary and thereby aid in an easy and cosmetically acceptable excision.[35]

Other beta blockers and antihypertensives

Other beta blockers including timolol, acetabutolol, nadolol and atenolol have been successfully used in the treatment of infantile hemangiomas. Prospective clinical trials are required to better define the role of each beta blocker according to patient characteristics and lesion type.

In a randomized controlled trial, topical timolol maleate (0.5%) gel or solution applied 2–3 times daily in infants below 6 months of age was found to be efficacious and safe for the treatment of small superficial lesions that were not on mucosal surfaces and were not ulcerated.[54] It has also been used safely in ulcerated hemangiomas and small deep facial hemangiomas in individual reports.[55] In a systematic review and meta-analysis of topical beta blockers for infantile hemangiomas, Ovadia *et al*. found that the response rates for topical propranolol and topical timolol were not significantly different. They concluded that topically administered beta blockers are effective treatment for superficial infantile hemangiomas that pose fewer adverse effects and should be considered for primary treatment.[56]

Propranolol was found to have a greater benefit than captopril in a randomized controlled trial.[57] More basic and clinical studies are needed to investigate the potential effectiveness of other cardiovascular drugs such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in the management of infantile hemangiomas.

Raynaud's Phenomenon

Antihypertensives which act as direct vasodilators (nitrates, calcium channel blockers) and those which inhibit vasoconstriction (angiotensin receptor blockers, alpha adrenergic

receptor blockers) have been tried in the medical management of Raynaud's phenomenon. Dihydropyridine calcium channel blockers are by far the most commonly studied and prescribed class of agents for Raynaud's phenomenon. Calcium channel blockers promote relaxation of vascular smooth muscle cells via inhibition of voltage-gated channels, leading to peripheral vasodilation. A meta-analysis of calcium channel blockers in patients with primary Raynaud's disease revealed significant reductions in frequency and severity of Raynaud attacks.[58] In another meta-analysis of Raynaud's phenomenon secondary to systemic sclerosis, calcium channel blockers reduced attack frequency by 8.3 attacks over 2 weeks and severity by 35%.[59] However, in a head-to-head comparison of 40 mg nifedipine with intravenous iloprost in patients with secondary Raynaud's phenomenon, there was no effect after 1 year of treatment with nifedipine, implying that the beneficial effects due to calcium channel blockers may be lost with long-term treatment.[60]

In clinical practice, calcium channel blockers are the first choice in primary Raynaud's disease and have been suggested for secondary Raynaud's phenomenon as well. Treatment should start with low dosages with titration according to response. In patients with CREST syndrome, calcium channel blockers can reduce sphincter tone in the lower esophagus and hence should be used with caution.[61] The different calcium channel blockers that have been tried include nifedipine (20–120 mg once daily), felodipine (2.5–20 mg once daily), amlodipine (2.5–20 mg once daily), nicardipine and isradipine. Common side effects encountered with calcium channel blockers are hypotension with reflex tachycardia, headache, flushing, dizziness and peripheral edema.[62]

Among the non-dihydropiridine calcium channel blockers, verapamil was found to be ineffective in the management of Raynaud's phenomenon.[63] Diltiazem in a dose of 120 mg/d was found to be useful in both primary and secondary Raynaud's phenomenon, with a more pronounced effect in primary Raynaud's phenomenon.[64] It can also be effective in the long-term treatment of patients with occupation associated Raynaud's syndrome.[65] Diltiazem was found to be ineffective in secondary Raynaud's phenomenon in another study.[66]

Nitrates have been used in both primary and secondary Raynaud's phenomenon in various formulations: topical with transdermal patches, cream or gel, as well as in oral preparations. They have been found to decrease the frequency and severity of attacks in primary and secondary Raynaud's phenomenon, and they may also improve digital ulcers.[67] The efficacy and duration of possible beneficial effects of nitrates are still not clear in patients with secondary Raynaud's phenomenon. Their usage is highly limited by their frequent side effects, mainly headache (80%) and hypotension, irrespective of the route of administration.[61]

Losartan (50 mg/d) significantly decreased the frequency of Raynaud's phenomenon attacks compared to nifedipine after treatment for 15 weeks. Again, beneficial effects were more pronounced in patients with primary Raynaud's phenomenon.[68] Prazosin inhibits the alpha-1 postsynaptic adrenoreceptor with consequent peripheral vasodilation. It was found to be more effective than placebo in a meta-analysis which included patients with secondary Raynaud's phenomenon due to systemic sclerosis. However, several side effects such as nausea, dizziness, headache, palpitations and hypotension limited the use of this drug.[69]

In a systematic review of the effectiveness of various interventions for secondary Raynaud's phenomenon, Huisstede *et al*. found clear evidence in favor of calcium channel blockers and iloprost (oral and intravenous). For all other interventions, only limited, conflicting, or no evidence was found; hence their place in the therapy of Raynaud's phenomenon is limited to patients who fail to respond adequately to or are unable to tolerate calcium channel blockers.[70]

Flushing

Flushing has been associated with medications, rosacea, menopause, carcinoid syndrome, pheochromocytoma, polycythemia, and mastocytosis, although it can occur without a known cause. There are no known specific treatments available, though beta blockers have suppressed flushing in some patients, particularly when associated with anxiety.[71]

Both oral clonidine 0.05 mg twice daily and transdermal clonidine (0.1 mg weekly) have been found to be effective in treating postmenopausal flushing[72] and flushing in males post-orchidectomy.[73] In carcinoid-induced flushing, clonidine was found to suppress it when given with cimetidine in a case.[74] Alpha adrenoceptor blockers such as phentolamine and phenoxybenzamine have been helpful in improving flushing, diarrhoea, and wheezing in some cases of carcinoid syndrome.[75]

Flushing and erythema related to rosacea

Clonidine may provide modest improvements in flushing in some cases.[76] Rilmenidine, a central hypotensive drug acting specifically on imidazoline receptors and producing no sedation, when given in a dose of 1 mg/d was found to decrease the number of flushing episodes in rosacea.[77] Non-cardioselective beta blockers such as propranolol 40 mg/d may be useful in some cases[71] whereas nadolol is ineffective.[78] Topical brimonidine tartrate gel 0.5%, a selective alpha-2 adrenergic agonist used for ocular hypertension, has been shown to decrease the erythema of rosacea when applied once daily.[79]

Keloids

It has been shown that calcium channel blockerss inhibit the synthesis/secretion of extracellular matrix molecules including collagen, glycosaminoglycans and fibronectin, and increase collagenase.[80] Verapamil could also prohibit proliferative scars by inhibiting TGF-beta1 expression in fibroblasts, as well as by inducing apoptosis.[81]

Similar to other therapeutic options, verapamil injections may be given alone or in combination with surgical excision or other therapies. Depending on the size of the keloid, 0.5–2 ml verapamil is injected per application at a concentration of 2.5 mg/ml. Lawrence noted a cure rate of 55% when they treated earlobe keloids with surgery followed by intralesional verapamil after a week and pressure earrings applied for a minimum of 6 months after excision.[82]

Two randomized studies have been conducted in the past to compare the effects of intralesional verapamil with triamcinolone in hypertrophic scars and keloids.[83,84] They found that improvements in vascularity, pliability, height and width of the scars were similar with both agents but triamcinolone had a faster effect. Verapamil offers an advantage over triamcinolone with its extremely low cost and fewer adverse effects.

Chilblains (Perniosis)

The efficacy of nifedipine in the treatment of perniosis has been demonstrated in several studies. At a dose of 20–60 mg daily, nifedipine significantly reduces the time to clearance of existing lesions and prevents the development of new chilblains. It also reduces pain, soreness, and irritation in the lesions.[85] Patra *et al*. compared low-dose nifedepine (10 mg thrice daily) with diltiazem (60 mg thrice daily) in the treatment of chilblains and found low-dose nifedepine to be effective.[86]

Calcinosis Cutis

As calcinosis cutis is a rare syndrome, there is a lack of controlled trials on various therapeutic options. Reiter *et al*.[87] in their review suggested that, independent of the clinical diagnosis, small calcified deposits or larger localized lesions can be successfully treated by surgical intervention, whereas disseminated calcinosis often requires systemic treatment. There are reports of successful treatment of calcinosis cutis with diltiazem in adult onset and juvenile dermatomyosistis (dose of 2–4 mg/kg/d).[88,89] While there was partial improvement in a case of calcinosis cutis with Sjogren's syndrome in one study,[90] another study did not find significant improvement with diltiazem when used in a case of systemic sclerosis. The authors attributed this to the usage of a lower dose of diltiazem.[91]

Acne and Hirsuitism

Spironolactone is an aldosterone antagonist and functions as both an androgen receptor blocker and inhibitor of 5-α reductase in acne. There are no currently FDA/EMEA(European Medicines Evaluation Agency)-approved dermatologic indications for spironolactone, and its off-label uses are, among others, female acne, female pattern hair loss, hidradenitis suppurativa and hirsutism [Table 4][92] It should not be used in pregnant and lactating women and it is not used in men due to the risk of feminization. The average dose used by dermatologists is 50–100 mg daily.[93] Although it has been used successfully in the management of acne, studies on its efficacy are limited by small sample sizes and poor trial design.[94] A Cochrane review concluded that there is some evidence to show that spironolactone is an effective treatment to decrease the degree of hirsutism.[94]

Antiandrogens have been suggested as a possible management strategy in female patients with hidradenitis suppurativa (HS), but there is limited literature on this. Lee and Fischer used spironolactone effectively in 20 cases and advocate it as a low-cost, first-line treatment forHS[95] Spironolactone should not be used with potassium-sparing diuretics, cyclosporine or tacrolimus, due to the risk of hyperkalemia.

Table 4: Potential clinical indications for oral spironolactone

Females with clinical signs of hyperandrogenism (e.g., hirsutism, increased seborrhoea, androgenic alopecia)
Females with late-onset acne or persistent acne, with or without signs of hyperandrogenism
Females not responding to conventional therapy who do not wish to take oral isotretinoin or cannot take isotretinoin
Females with acne flares that mirror the menstrual cycle
Females who may not be able to take oral contraceptives but require an antiandrogen as part of their acne regimen
Females on oral contraceptives who manifest signs of moderate to severe acne

Cyclosporine-induced Hypertension

As cyclosporine is being used extensively by dermatologists for various indications, we shall encounter these problems more frequently, hence this has been included here.

Several mechanisms for cyclosporine-induced hypertension have been proposed i.e. activation of the sympathetic nervous system, endothelin-mediated systemic vasoconstriction, impaired vasodilatation secondary to reduction in prostaglandin and nitric oxide, altered cytosolic calcium translocation, and activation of the renin-angiotensin system (RAS).[96] In a multicentre randomized study, the occurrence of hypertension appeared to be unrelated to the cyclosporine dose,[97] whereas in a systematic review, the effect was found to be dose-related.[98] Cyclosporine-induced hypertension is usually mild and reversible upon dose reduction or discontinuation. Development of hypertension itself is not a contraindication for continuation of cyclosporine as long as it can be controlled with antihypertensives. Calcium channel blockers, particularly of the dihydropyridine group, are preferred because of their effect on smooth muscle vasodilation. Several calcium antagonists, particularly verapamil, nicardipine, and to a lesser extent diltiazem, interfere with cyclosporin metabolism and lead to drug accumulation. Nifedepine, isradipine, and felodipine do not alter the blood levels of cyclosporine, are potent vasodilators, and can be used effectively.[99,100] It has to be kept in mind that nifedepine can act synergistically with cyclosporine and cause gum hypertrophy.[99]

Beta-blockers have also been used in cyclosporine-induced hypertension either alone or in combination with dihydropyridine calcium channel blockers in transplant recipients.[99] Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics should be used with caution because of their ability to act synergistically with cyclosporine to cause hyperkalemia.[100]

Chronic Nonhealing Ulcers

Beta-2 adrenoreceptors are the dominant receptors present on the surface of keratinocytes. Beta-2 agonists prevent activation of extracellular signal-related kinases (ERKs) which assist wound healing, thereby reducing keratinocyte migration.[101] Beta-2 antagonists transform keratinocytes into a promigratory phenotype but do not directly affect keratinocyte proliferation.[102] They have been shown to increase wound angiogenesis in rats and delay wound contraction. In a randomized controlled trial of 79 people with burns, systemic propranolol (1–1.98 mg/kg) attenuated the hypermetabolic response to burn injury, resulting in shorter healing time, better healing, shorter hospital stays, and smaller wound surface area that required skin graft.[103] Braun *et al*. reported complete epithelialization of chronic recalcitrant wounds after weekly instillation of 1 drop timolol solution per 2 cm of wound edge, followed by silicone foam dressings for 8 weeks.[104] Similar results have been observed by Tang *et al*.[105]

Research has found that verapamil reverses calcium-induced inhibition of chemotaxis and adhesion of cultured keratinocytes.[106] Bhaskar *et al*. found nifedepine and amlodipine to increase tensile strength of wounds in albino rats and overcome steroid-induced depression of wound healing.[107] Acceleration of wound healing was seen in rats with use of biopolymeric nifedepine powder.[108] Azelnidipine was found to enhance wound healing in diabetic rats by increasing nitric oxide production.[109]

Role in Skin Cancers

Nonmelanoma-skin cancers

The RAS(Renin-angiotensin system) is a major regulator of vascular homeostasis. Egami *et al*. showed that the host angiotensin II type 1 (AT1) receptor plays an important role in angiogenesis and growth of tumor cells engrafted in mice.[110]

The use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers was found to be associated with an approximately two-fold reduced risk of keratinocyte cancers in renal transplant recipients when compared with nonusers in a study. It was suggested that the use of these drugs, should be considered when possible in renal transplant patients with multiple risk factors.[111]

Xiong *et al*. sought to determine the risk factors for invasive squamous cell carcinomas on the face or ears in a high-risk population and found that the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers could protect against new invasive squamous cell carcinomas.[112]

Melanoma

De Giorgi *et al*. observed that beta blocker use is associated with a reduced risk of melanoma recurrence and death,[113] while Koomen *et al*. concluded that the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers does not protect against the development of cutaneous melanoma.[114]

Angiotensin II can stimulate the expression of MMP-2, MMP-13, and VEGF (MMP-Matrix-metalloproteinase, VEGF-Vascular endothelial growth factor_) in B16F10 mouse melanoma cells.[115] Otake *et al*.[116] evaluated the involvement of angiotensin II- dependent pathways in melanoma growth through the pharmacological blockage of AT1 receptors by the antihypertensive drug losartan. They showed that blockage of AT1 receptor signaling may be a promising antitumor strategy, interfering with angiogenesis by decreasing the expression of angiogenic factor receptors. In contrast, Schmidt *et al*.[117] in a case control study using population-based databases found that long-term angiotensin receptor blocker use and long-term diuretic use may be associated with the risk of developing melanoma and squamous cell carcinomas, respectively. Further studies are needed to evaluate the roles of these drugs in skin cancers.

Cutaneous Infiltration Analgesia

Recently, a solid microstructured transdermal system (sMTS) wherein lidocaine is coated onto microneedles for rapid, prolonged, and safe local analgesia has been developed. Lidocaine rapidly dissolves off the microneedles and into skin such that in 1 min, lidocaine tissue levels needed to cause analgesia are achieved.[118]

Addition of clonidine or related analogs like guanafacine and apraclonidine to the these polymeric microneedles along with lidocaine or prilocaine decreased the systemic absorption rate of the anesthetics from the site of application without impacting their performance or the rapid onset of anesthesia. It also maintained the lidocaine skin concentration above the estimated therapeutic level (100 ng/mg) for 1 h without causing any skin irritation or color change.[119] Co-administration of clonidine with oxybuprocaine, bupivacaine, or dextrorphan was found to increase the potency and duration of infiltrative cutaneous analgesia in rats after a noxious pinprick.[120] Similarly, propranolol when used alone in rats showed more potent and prolonged cutaneous analgesia compared to lidocaine. Propranolol also might prove useful as an adjuvant to lidocaine in producing cutaneous analgesia.[121]

Topical Steroid-induced Skin Atrophy

Maubec *et al*. in a recent study found that topical spironolactone gel, when used along with topical corticosteroid, could limit glucocorticoid-induced epidermal atrophy by blocking mineralocorticoid receptors in cultured human skin explants,[122] a concept that needs to be studied further. Nguyen *et al*. also observed that delayed wound re-epithelialization caused by potent steroid application in mouse skin or cultured human skin explants was rescued by local mineralocorticoid receptor antagonist application.[123]

Conclusion

Antihypertensives are becoming an important part of the dermatologic drug armamentarium. Topical minoxidil and oral propranolol have become the drugs of choice for androgenic alopecia and infantile hemangiomas respectively. Antihypertensives have been used effectively in Raynaud's phenomenon, chilblains, calcinosis cutis, and keloid management either alone or in combination with other therapies. They have also been shown to be effective in chronic nonhealing ulcers and for cutaneous infiltration analgesia; their role in skin cancers remains controversial.

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Conflicts of interest

There are no conflicts of interest.

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