Immunologic adverse reactions of β-blockers and the skin (Review)

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Abstract. β-Blockers are a widely utilised class of medication. They have been in use for a variety of systemic disorders including hypertension, heart failure and intention tremors. Their use in dermatology has garnered growing interest with the discovery of their therapeutic effects in the treatment of haemangiomas, their potential positive effects in wound healing, Kaposi sarcoma, melanoma and pyogenic granuloma, and, more recently, pemphigus. Since β-blockers are deployed in a variety of disorders, which have cutaneous co-morbidities such as psoriasis, their pertinence to dermatologists cannot be overstated. Likewise, β-blockers, like any other drug category, carry risks of side effects, some of which are dermatologic. These include triggering and exacerbation of psoriasis, psoriatic and rheumatoid arthritis, anaphylaxis, contact dermatitis, occupational contact dermatitis, Raynaud's disease, alopecia, lichen planus-like drug eruption, hyperhydrosis and vitiligo. While recent articles have focussed on the positive uses of β-blockers, it may also be wise to call our attention to the potential dermatologic adverse effects that may follow β-blocker use, as well as possible therapeutic approaches to these. This short review will focus on those dermatoses resulting from β-blocker use, which have an immunologic basis.

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Contents

1. Introduction

β-Blockers remain one of the most widely used class of therapeutic agents in both cardiac and non-cardiac ailments. Cardiologic diseases for which β-blockers are presently used include ischemic heart disease, hypertension, arrhythmia and heart failure. Important non-cardiologic applications include glaucoma, migraines, situational anxiety, benign essential tremors and cardiac symptoms of thyrotoxicosis. Not all β-blockers are equal as they comprise a heterogeneous class of drugs with differing selectivity for β-adrenoreceptors and extra qualities such as lipophilicity, inverse agonist, intrinsic sympathomimetic and membrane stabilising activities, as well as α-receptor blocking properties. The third generation β-blocker, nebivolol, has additional nitric oxide mediated vasodilating and antioxidant activity (1). Recent data suggest that their metabolic and immunomodulatory effects may extend the scope of their use (2).

β-Blockers, have garnered interest amongst dermatologists. This growth of interest is based on the discovery of their demonstrated and potential effects in disorders such as vascular malformations (hemangiomas), tumours (Kaposi sarcoma, melanoma), wound healing, pyogenic granulomas and erythemato-telangiectatic rosacea (3).

β-Blockers are important for dermatology as well, due to their potential adverse reactions. They share the ability

to produce potentially severe adverse effects, especially in predisposed areas or areas of *locus minoris resistentiae* in the skin. Consequent upon review, potential alternatives have been proposed (4-10).

We believe this will be a useful complementary article to those works that have highlighted their usefulness (11). A variety of dermatoses may be caused or aggravated by β-blockers. These include psoriasis, lichen planus-like drug eruptions (LDE), contact dermatitis, anaphylaxis, Raynaud's disease, acrocyanosis, alopecia and hyperhydrosis.

2. Cutaneous side - effects of β-blockers

Keratinocytes possess adrenergic receptors, which have been reported as being exclusively of the β2-subtype (12). β2-adrenergic receptors are densest at the basal cells and decrease in number towards the stratum corneum, while intracellular calcium concentrations are lowest at the basal cells, increasing towards the stratum corneum thus correlating with keratinocyte differentiation (13).

Psoriasis. Drugs may influence the course of psoriasis in certain ways, including: i) Precipitation of psoriasis *de novo* in predisposed individuals and in those with a family history; ii) exarcerbation of pre-existing psoriasis lesions; iii) production of psoriatic lesions in clinically normal skin of patients with psoriasis; and iv) development of treatment-resistant psoriasis (11-13).

'Psoriasiform drug disorder' refers to a group of diseases, which mimick psoriasis at some point in their course; these psoriasiform reactions are elicited by inflammatory events leading to dysregulation of cytokines, growth factors and keratinocyte differentiation (14). True drug-induced psoriasis tends to occur in a *de novo* fashion in patients without a family or prior history and may mimick pustular psoriasis, but without nail or joint involvement (15). Delayed-type hypersensitivity reaction, impaired lymphocyte transformation or alterations in cyclic adenosine monophosphate (cAMP) have been proposed (13-16). cAMP is an intracellular messenger, which brings about the stimulation of proteins for cellular differentiation and inhibition of proliferation (17). Biopsy specimens from β-blocker-induced (metoprolol and atenolol) eruptions are characterised by excessive degranulation of neutrophils in the dermis. Nonselective β-blockers (propranolol, nadolol and sotalol) were associated with excessive release of macrophage proteolytic enzymes (18). Metoprolol, nebivolol and bisoprolol are highly selective β1-receptor blockers. Nebivolol brought about diminished proinflammatory gene expression in endothelial and vascular smooth muscle cells (19).

Rheumatoid arthritis. Autoimmune disorders may be associated with β2-adrenoreceptor dysfunction and examples include: rheumatoid arthritis or systemic lupus erythematosus (20). Modification of β2-adrenoreceptor structure could augment sensitivity levels of T-lymphocytes to β2-stimulation. This could be a basis for the genetic predisposition to rheumatoid arthritis (21). One study involving murine cells demonstrated a bimodal activity of the sympathetic nervous system. There was proinflammatory activity during the asymptomatic phase and inhibitory activity during the chronic symptomatic phase of arthritis. This supported the idea that β2-adrenergic receptor stimulus is time-dependent and may play a role in the treatment of bone destruction in rheumatoid arthritis (22,23).

Thus, β2-adrenoreceptor activity is implicated in the generation, progression and treatment of rheumatoid arthritis, and this complex relationship has been mimicked by a variety of other autoimmune diseases, such as psoriasis or psoriatic arthropathy (24). A metoprolol-associated onset of psoriatic arthropathy has been described in a case report (25).

Anaphylaxis. Not surprisingly, as with any other drug, hypersensitivity reactions have occurred to β-blockers. Epinephrine-resistant anaphylaxis was reported in a patient taking propranolol 40 mg b.d. and intubation was necessary for successful recovery (26). The mechanism of action may in part be due to mast cell priming, which was noted with metoprolol and this augmenting effect was increased when metoprolol was combined with angiotensin coverting enzyme inhibitor (ACE) (27).

Perioccular and occular reactions. Periorbital dermatitis and punctate keratitis, as well as conjunctival and eyelid symptoms were reported in patients on treatment with topical β-blockers over a 3-month survey period of opthalmologists in The Netherlands (28). Periorbital dermatitis was the most commonly encountered phenomenon and the most commonly encountered culprit was timolol.

One study compared *in vitro* cytotoxicity, using the MTT assay, of 8 β-blockers (propranolol, alprenolol, atenolol, labetalol, metoprolol, pindolol, timolol and bisoprolol) on cell lines of the human corneal epithelium and retinal pigment epithelium. Primary and immortalised corneal and retinal cell lines were compared for susceptibility to the cytotoxic action of the drugs. β-Blocker cytotoxicity was also evaluated on human cutaneous keratinocytes and fibroblasts in order to assess susceptibility differences as a function of tissue of origin. Results demonstrated large variations in cytotoxicity (~60-fold) for these closely related drugs from the same cell line (29).

Vitiligo. Patients on systemic β-blocker therapy could suffer an exacerbation of their vitiligo. Accelerated deterioration of vitiligo lesions was observed in patients treated with β-blockers (30). Doppler flowmetry and iontophoresis showed increased blood flow in lesions of vitiligo as compared with normal skin, with a more marked increase in segmental vitiligo patients. Segmental vitiligo patients also had an increased density of α- and β-adrenoceptors (31). This dysfunction of the sympathetic nervous system in the skin of vitiligo patients may provide a basis for the effect of β-blockers in the pathogenesis of vitiligo and caution should be exercised when vitiligo is part of one of the multiple autoimmune syndrome (vitiligo, lupus and thyroiditis) (32).

Alopecia. Alopecia has been described following topical timolol use in a patient with glaucoma (33). This manifested as tellogen effluvium, which remitted following drug discontinuation and pretreatment hair volume was restored in 14 months. The patient also developed periorbital contact dermatitis after the onset of alopecia. No mechanism was proposed for this

Table I. Other adverse cutaneous drug reactions of β-blockers.

β-Blocker	Adverse cutaneous drug reactions
Atenolol	Vasculitis Drug-induced lupus erythematosus Pseudolymphomatous reactions
Acebutolol	Lichenoid reactions Drug-induced lupus erythematosus Pincer nail deformity
Labetalol	Peyronie's disease Lichenoid reactions Drug-induced lupus erythematosus
Metoprolol	Pincer nail deformity Peyronie's disease
Propranolol	Erythema multiforme Alopecia Peyronie's disease Lichenoid reactions
Pindolol	Lichenoid reactions Drug-induced lupus erythematosus
Oxprenolol	Oculocutaneous syndrome Lichenoid reactions Drug-induced lupus erythematosus
Sotalol	Vasculitis

observation by the authors. Hair growth cycles have, however, been found to be modulated by adrenergic stimulation (34). Nonetheless, the simultaneous onset of contact dermatitis and alopecia, both autoimmune disorders suggests an autoimmune mechanism. Alopecia has long been recognized as an adverse effect of β-blockers and the suggested mechanism was described by Fraunfelder *et al* as 'probably a direct toxic effect on the hair follicle'. They also discussed an impressive number of cases and reversibility after stopping the treatment (35-41).

Lichen planus-like drug eruption. Lichenoid drug eruptions may be associated with various β-adrenergic blocking agents (42,43). Histopathologic analysis has shown increased necrotic keratinocytes grouped in clusters, with increase in plasma cells and eosinophils being more associated with lichen planus-like drug eruption as opposed to lichen planus or other lichenoid disorders (44-47).

The first case in the literature describing lichenoid type cutaneous hyperpigmentation as a form of phototoxicity induced by nebivolol was reported in a 46-year-old female patient. In this case, alternative diagnoses, such as idiopathic lichen planus, systemic connective tissue disease, cutaneous forms of lupus erythematosus, lichenoid contact reaction, and hepatobiliary disease, could be excluded due to the history of the patient, clinical picture, biopsy findings, and time course of the skin lesions. Ultimately, it was concluded that nebivolol may cause lichenoid cutaneous hyperpigmentation. Therefore, in patients using nebivolol, this side effect should be kept in mind (48).

Hyperhydrosis. Hyperhydrosis has been reported in association with β-adrenoreceptor blockade. Axillary area appears to be the most affected (49). It is not clear whether there is an underlying immune mechanism. Mechanisms based on receptor changes or mediator imbalances (as both cholinergic and adrenergic pathways seem to be involved in sweating) are more likely than autoimmune mechanisms (50). The fact that 'diabetics who become hypoglycemic actually sweat more on propranolol as compared with those who are not on propranolol', may also be relevant in building a working hypothesis (51).

Contact dermatitis. Occupational contact dermatitis was noted in a 48-year old male worker in a pharmaceucitical factory. This affected the patient's hands and the agent was determined to be proproanolol after patch testing (52). The patient improved after he was moved to a different department. Allergic contact dermatitis to β-adrenergic agents in eye drops has been reported. It is unusual, but timolol was considered by far the greatest culprit (53). The treatment for contact dermatitis to β-adrenergic agents is topical steroids, which are also known for their own cutaneous adverse reactions (54-57).

β-Blockers have been successfully used in dermatoses such as hemangiomas, kaposiform haemangioendothelioma, pyogenic granulomas, erythemato-telangiectatic rosacea, angiolymphoid hyperplasia with eosinophillia. There have been promising results in adrenergic urticaria, aquagenic pruritus, wound healing, pemphigus vulgaris, other autoimmune blistering diseases and potentially in melanoma (58,59).

Other immunological and some non-immunological adverse cutaneous drug reactions of β-blockers are included in Table I: for atenolol-vasculitis (V), drug-induced lupus erythematosus (DILE), pseudolymphomatous reactions (PR); for acebutolol-lichenoid reactions (LR), DILE, pincer nail diformity (PND); for labetalol-Peyronie's disease (PD), LR, DILE; for metoprolol-PND, PD; for propranolol-erythema multiforme, alopecia, PD, LR; for pindolol-LR, DILE; for oxprenolol-oculocutaneous syndrome, LR, DILE; for sotalol-V (60-63).

3. Conclusion

This summary review has delved into the immunologic side-effects of β-blockers. These should be borne in mind by dermatologists, cardiologists, opthalmologists, neurologists, pediatricians, internists, family physicians and other specialists that prescribe this category of drugs.

With regard to medical ethics, it may be useful, prior to the prescription and administration of β-blockers to inform our patients of the possible adverse reactions and making them sign an informed consent form (64,65). In the future, in order to obviate such potential risks perhaps plant extracts with limited potential for adverse reactions and benign alternative treatments could be investigated and utilised (66,67), especially as knowledge removes discomfort (68,69).

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ALT, VC, MM contributed to the conception, design, and drafting the study. AME and LCN contributed to the interpretation of the data, and revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript and contributed equally in all the stages of the study. They reached an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests

The authors declare that they have no competing interests.

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