DRUG SAFETY CONCEPT

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Safety Considerations in Treating Concomitant Diseases in Patients with Asthma

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Summary

The treatment for asthma usually involves a combination of drugs used for bronchodilation and to treat underlying airway inflammation. When asthma is severe, the regimen used to treat asthma can become quite complicated, often using as many as 3 or 4 separate pharmacological agents. As patients with asthma get older, their medication regimen can become even more complex with the development of numerous other age-related diseases requiring their own list of medications. Diseases of the joints, diseases of the eye, cardiovascular disease, neurological disease and urological problems represent the most common conditions that patients develop, at times needing medications which might interfere with asthma management. Many of these diseases require the use of nonsteroidal anti-inflammatory agents, well known to provoke wheezing in patients with intrinsic asthma, and diseases of the eye and cardiovascular system frequently require use of β-blockers which can cause or exacerbate asthma. Managing patients with asthma who have other diseases requires constant supervision of their

medication usage and careful and cautious review of the entire list of medications at each presentation.

Asthma is a common inflammatory disease of the airways which affects individuals at all stages of life. Prevalence studies have revealed that nearly one-quarter of patients with asthma are over the age of 50 years[1] and about 3 to 4% of patients with asthma have the onset of their disease after the age of 50 years.[2] Once past the fifth or sixth decades of life, the probability is much greater that patients with asthma will have concomitant diseases requiring other medications for control. Treatments for hypertension, cardiovascular or neurological disease, glaucoma or arthritic conditions can have a profound affect on asthma control if they are known to be associated with worsening of asthma, provocation of attacks, or to interact with agents used for asthma. Younger patients with asthma, while usually not having other diseases requiring treatment, still occasionally require medications for orthopaedic injuries, migraines, tachyarrhythmias or anxiety which can affect asthma control. Table I lists several diseases or conditions which often require agents that can adversely affect the status of asthma.

1. Orthopaedic and Rheumatological Conditions

Osteoarthritis affects approximately 30% of the population between the ages of 45 and 64 years[3] and more than half of the population over the age of 65 years.[4] Inflammatory arthritis is also common, affecting 1 to 3% of all age groups.[5] These arthritides, combined with acute injuries, result in a tremendous demand for pharmacological agents that will provide relief of pain and stiffness and improve functional ability. Prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) accounted for over 70 million prescriptions in the US in 1991 or around 4% of all prescribed drugs.[6] The volume of over-the-counter aspirin (acetylsalicylic acid) and ibuprofen purchased, in addition to the dozens of cold and sinus preparations which contain aspirin, make the total amount of aspirin and NSAIDs used incalculable. Newer agents such as ketorolac, which can be used parenterally, have extended the use of NSAIDs to the emergency department and postoperative setting because of the ability of this drug to eliminate or reduce the use of narcotic analgesics in these settings.

1.1 Aspirin (Acetylsalicylic Acid) Sensitivity

NSAIDs should be used with caution in patients with asthma because between 4 to 20% of patients with asthma are sensitive to these agents.[7,8] The frequency of aspirin sensitivity is increased in older age groups and in those patients with asthma who are not atopic.[9] As many as 10% of acute asthma exacerbations are drug-induced and sensitivity to aspirin and other NSAIDs is suspected of accounting for two-thirds of such reactions.[10] Reactions to aspirin are usually of 2 types: rhinoconjunctivitis and bronchospasm, and urticaria and angioedema.

In rare instances, urticaria and angioedema may be related to use of aspirin or to a specific NSAID

Table I. Pharmacological agents which can adversely affect the status of asthma

Medical condition or disease	Agents with possible adverse effects
Orthopaedic and rheumatological problems	Aspirin (acetylsalicylic acid) and other NSAIDs
Ophthalmological conditions	β-Blockers Anticholinesterase agents Topical NSAIDs
Cardiovascular disease and hypertension	β-Blockers ACE inhibitors Aspirin Diuretics
Neurological problems	β-Blockers Aspirin and NSAIDs
Urological problems	Parasympathomimetic agents
Diagnostic studies	Radiographic contrast agents Allergy skin testing Bronchoprovocation
Dermatology	NSAIDs Transdermal use of β-blockers

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

and, in some cases, the pathogenesis of the urticaria and angioedema might be immunological.[11,12] In contrast, in most instances, aspirin sensitive urticaria/angioedema occurs in patients with pre-existing chronic urticaria among and in whom exposure to aspirin or other NSAIDs can cause exacerbation approximately 30% of the time. Aspirin desensitisation, as described later in this section, cannot be recommended for patients with aspirin sensitive urticaria/angioedema.[13]

Rhinoconjunctivitis and bronchospasm appear to be the result of distinct biochemical mechanisms, are not immunoglobulin (Ig) E–mediated and share cross sensitivity among aspirin and the other NSAIDs.[14] It is this latter phenomenon which is referred to as 'aspirin-induced asthma'. Typically in these patients, aspirin exposure induces acute wheezing, rhinorrhoea and facial and neck flushing. Symptoms can develop immediately or within 2 or more hours following aspirin ingestion.[15] The onset of symptoms in some cases can be explosive and severe with rapid onset of wheezing and facial angioedema, and in some cases, such reactions can be fatal.[16]

The diagnosis of aspirin-induced asthma is usually made by looking at the patient's medical history; the typical patient with aspirin-induced asthma develops symptoms of vasomotor rhinitis with subsequent nasal polyposis in the second or third decade of life, followed by the development of asthma that is chronic and often resistant to treatment, requiring frequent treatment with corticosteroids for exacerbations.[17] Skin tests to common allergens are usually negative and anti-aspirin IgE antibodies cannot be demonstrated.[18] The diagnosis can also be made using oral challenge[19] or by inhalation of aspirin-lysine conjugates and dosimetry.[20] These procedures should only be undertaken by specialists familiar with their methodology and preferably in a hospital setting or procedural unit with emergency equipment available should a severe reaction occur. Patients should also have adequate baseline lung function [a forced expiratory volume in 1 second (FEV_1) of at least 70% of their predicted normal value] to ensure adequate safety with both of these procedures.

Recently, a method has been developed using topical nasal challenge.[21] Using this method, it has been found that the threshold doses for a positive response are 1000-fold lower than for oral challenge and 20-fold lower than for bronchial challenge. Systemic adverse effects are much less likely with this method and patients with greater degrees of baseline airway obstruction can be tested.

The mechanism of the aspirin intolerance is related to the inhibition of cyclo-oxygenase, a key enzyme in biotransformation of arachidonic acid. Cross sensitisation with other NSAIDs occurs through the common inhibition of cyclo-oxygenase and the potency of these agents in inducing bronchospasm appears to be in proportion to their potency in inhibiting this enzyme.[22] Cyclo-oxygenase inhibition shifts arachidonic acid metabolism from the cyclo-oxygenase pathway (a pathway favouring production of prostaglandins, thromboxanes and prostacyclin) toward the 5-lipoxygenase pathway (toward production of the sulphidopeptide leukotrienes C_4, D_4 and E_4).[23] These potent molecules induce constriction of bronchial smooth muscle. The increased production of bronchoconstricting leukotrienes or the reduced production of bronchoprotective prostaglandins could, in theory, cause the resulting airway obstruction.[24]

Evidence for reduced prostaglandin production has not been demonstrated in patients with aspirin-sensitive asthma who were taking the amount of aspirin required to provoke symptoms. Increased urinary leukotriene E_4 excretion following aspirin challenge, however, has been shown in these patients, but the maximal decrease in FEV_1 does not correlate with peak urinary leukotriene E_4 levels, which suggests that increased leukotriene production alone does account for the magnitude of bronchial obstruction.[25,26] This finding also does not account for the failure of all patients with asthma to wheeze following aspirin ingestion. More recently, it has been demonstrated that there is an

increased basal level of urinary leukotriene E_4 in patients with aspirin-sensitive asthma,[26] and these patients also have an increased bronchial sensitivity to inhaled leukotriene E_4 when compared to patients with asthma who are not aspirin intolerant.[27] This enhanced sensitivity disappears following aspirin desensitisation.

Two new categories of drugs have been helpful in further elucidating the importance of altered leukotriene metabolism in aspirin sensitive patients. Leukotriene receptor antagonists have been shown to partially inhibit bronchoconstriction following administration of either oral or inhaled aspirin.[28,29] The use of the 5-lipoxygenase enzyme inhibitor zileuton, prior to oral challenge with aspirin, by contrast, resulted in near total inhibition of the respiratory, naso-ocular, gastrointestinal and dermal manifestations of aspirin challenge, suggesting that the 5-lipoxygenase products play a central role in this sensitivity.[30]

Bronchial biopsies obtained after aspirin-lysine airway challenge show evidence of mast cell and eosinophil degranulation.[31] Whether these cells are the source of leukotriene production and their mechanism of activation in aspirin sensitivity remain unknown.

1.2 Alternatives to Aspirin and Nonsteroidal Anti-Inflammatory Drugs

As a general rule, aspirin and other NSAIDs should be avoided in aspirin sensitive asthmatic patients when treatment with an analgesic is required. Often, pain relief can be obtained using paracetamol (acetaminophen), sodium salicylate or choline salicylate. Alternatively, dextropropoxyphene or codeine, either alone or in combination with paracetamol, can be used. These drugs are usually well tolerated when taken in their usual doses. Care should be taken in emergency treatment or trauma centres that patients with asthma are questioned carefully about aspirin sensitivity prior to using injectable or topical NSAIDs such as ketorolac or ketoprofen, which have been known to provoke severe episodes of wheezing.[32]

1.3 Desensitisation

Aspirin desensitisation is rarely indicated for orthopaedic conditions, but it may be attempted in selected patients with inflammatory arthritis in whom NSAID therapy might dramatically alter their quality of life or reduce their degree of glucocorticoid use. Under close observation and monitoring, patients with aspirin sensitivity can achieve desensitisation by ingestion of graded doses of aspirin. The desensitisation procedure should only be undertaken by individuals highly experienced with the procedure and in a special care unit setting with emergency resuscitation equipment readily available. Desensitisation, if successful, extends to other NSAIDs[33] and once achieved, dosages of aspirin of 325 to 650mg daily are required for maintenance of desensitisation.[34] If daily aspirin is discontinued, sensitivity reappears within 2 to 7 days. For the moment, aspirin desensitisation is the only recommended treatment for patients with aspirin-sensitive asthma in whom the use of aspirin or other NSAIDs is essential because of the severity of their rheumatological disease. Whether or not newer agents such as 5-lipoxygenase inhibitors will have a degree of efficacy high enough to allow aspirin sensitive patients to ingest NSAIDs with impunity is doubtful. Another study involving a new 5-lipoxygenase inhibitor showed prevention of symptoms following aspirin challenge, but one patient still sustained a significant drop in pulmonary function.[35] To date, patients tested in these challenges have had baseline FEV_1 greater than 67% of predicted normal value. It is interesting to speculate as to whether the 5-lipoxygenase inhibitors will allow aspirin desensitisation to be accomplished with a greater degree of safety, particularly in those patients with low levels of lung function, but at the moment the role of anti-leukotriene drugs in aspirin desensitisation has not been studied and is unproven.

2. Ophthalmological Conditions

The management of ophthalmological conditions carries a special risk for patients with asthma

because both physicians and patients may be unaware that topical medications used for topical treatment of the eye are often absorbed in concentrations which can produce a systemic response to the treatment drug. In addition, many patients do not consider topical eye drops as their regular medications and may not list them on medical questionnaires, and thus, the physician may be unaware that such medications are being used.

NSAIDs have been useful when used topically for relief of chronic eye irritation and discomfort and for analgesia in the postoperative setting. What is not generally recognised is the excellent absorption of these agents via the conjunctival mucosa and that they can be absorbed in amounts sufficient to trigger symptoms in aspirin sensitive patients. Two agents which have been reported to cause reactions in this fashion are diclofenac and ketorolac.[36,37]

2.1 β-Blockers

Glaucoma occurs in 1 to 3% of the population over the age of 60 years and is an important cause of blindness worldwide.[38] Since the late 1970s β-blockers have been the drugs of choice for the treatment of ocular hypertension and associated glaucoma.[39] Although applied topically to the eye, these drugs are also well absorbed and may enter the systemic circulation and reach concentrations high enough to cause systemic adverse effects, including bronchoconstriction.[40]

The use of β-blocking medications can induce bronchospasm and reduced lung function in patients with established asthma,[41] in patients with no prior history of asthma,[42] and in patients with chronic obstructive lung disease.[43] These adverse effects can even commence after that patient has been taking the medication for several months or years, occasionally resulting in severe reactions and death.[44] In some cases, administration of β-blocking medications has induced exacerbations of asthma which persisted for long periods of time after withdrawal of the drug.[45] A single dose of a β-blocker can induce severe wheezing in at least 50% of patients with asthma.[46] β-Receptor blockade may also increase the severity of systemic anaphylactic/anaphylactoid reactions provoked by insect stings,[47] contrast media,[48] food and drug allergy[49,50] and immunotherapy injections.[49] In addition, if anaphylaxis or severe bronchospasm occurs, it may be more difficult to treat because of the diminished response to epinephrine (adrenaline) or other β-agonists in the presence of the β-blocker.[51]

The mechanism of β-blocker–induced bronchospasm is complex. β-Receptors can be divided into subtypes, with cardiac tissue containing mainly β_1-receptors, and the lung mainly β_2-receptors.[52] This division is not exclusive, however, with the heart also containing a population of β_2-receptors and the lung, β_1-receptors.[53,54] The ratio of β_1- to β_2-receptors in the lung is approximately 1 : 3 with an inhomogeneous distribution such that the airway epithelium and airway and vascular smooth muscle contain almost exclusively the β_2 type.[55] Drugs which are more β_1 selective, such as atenolol, and which are also known to invoke wheezing in some patients, probably do so by their weak β_2 binding properties. At higher doses, once saturation of available β_1-receptors takes place, increased binding of available β_2-receptors occurs by competitive ligand binding.[54]

In addition to their presence on airway smooth muscle cells, β-receptors are present on mast cells, epithelial cells, vascular endothelium and smooth muscle, submucosal glands, inflammatory cells and cholinergic nerves in the airways.[56] Endogenous catecholamines not only have direct effects on bronchial smooth muscle to maintain bronchodilator tone, but they also exert modulatory effects on the release of inflammatory mediators from mast cells and leucocytes. Intact β-receptors, thus, serve several important protective functions in asthma and their pharmacological blockade removes these protective effects which results in profound wheezing.

The population of β-receptors is quite dynamic and varies with age, hormonal balance and dietary salt intake.[57] β-Agonists down-regulate the β-receptor population[58] and β-blockers produce up-

regulation.[59] Lacking direct sympathetic enervation in the lung, airway β-receptors and bronchodilator tone are probably regulated by endogenous catecholamines.[60] In patients with asthma, however, β-receptors are dysfunctional, with the cellular defect in β-adrenoceptor function located at the post-receptor events of stimulus-response coupling.[61] This dysfunction extends to other cells as well, e.g. peripheral blood lymphocytes and inflammatory cells.[62] The reduced number and function of the β-receptors is probably acquired during the airway inflammation and may vary with the severity of the asthma.[63]

β_2-Receptors which inhibit the release of acetylcholine have recently been demonstrated on the cholinergic nerves of human bronchi.[64] In the airways, release of acetylcholine is under the local control of inhibitory muscarinic receptors on postganglionic parasympathetic nerves.[65] By binding to these β-receptors, circulating catecholamines, particularly epinephrine, could inhibit cholinergic nerves in human airways. β-Receptor blockade would thus allow increased acetylcholine release provoking bronchoconstriction. This would not occur in normal individuals because of autoreceptors of the muscarinic M_2 type which would shut off further acetylcholine release; in patients with asthma, however, the muscarinic autoreceptor appears to be defective and thus the shut off does not occur.[66] The inability to inhibit acetylcholine release, in combination with the enhanced response to acetylcholine seen in asthma, could produce the often profound bronchoconstrictor response to β-blocking agents in patients with asthma.[67]

The source of the muscarinic M_2 receptor defect has been the subject of numerous recent studies. Airway allergen challenge in guinea pigs results in a decrease in M_2 receptor function thought to be caused by inflammatory mediators.[68] Because the airway inflammation subsequent to allergen challenge is mainly eosinophils, these experiments were repeated with an antibody to interleukin (IL)-5, the cytokine associated with airway eosinophil infiltration and activation. The anti–IL-5 antibody inhibited eosinophil influx to the lungs of challenged animals and M_2 receptor function was protected.[69] It is quite likely that eosinophil granule proteins secreted during the bronchial inflammation mediate the reduced M_2 receptor function. Challenged animals pretreated with antibodies to the major basic protein of eosinophils develop intense airway eosinophilia, but M_2 receptor function is similarly protected.[70]

2.2 Anticholinesterase Agents

Anticholinesterase agents are also commonly used in the treatment of glaucoma. Ecothiopate, a potent, long-acting topical agent, has significant systemic absorption and has been reported to cause bronchospasm.[71] Anticholinesterase agents inhibit acetylcholinesterase activity causing acetylcholine to accumulate at cholinergic receptor sites. The result is the equivalent of excessive stimulation of cholinergic receptors which produces bronchospasm. These agents also should be used with caution in patients with asthma.

3. Cardiovascular Disease

According to the Framingham study, it is estimated that as many as one-quarter of the adult population may have hypertension to a degree that requires medical therapy.[72] Similarly, atherosclerotic cardiovascular disease affects more than one-third of the population over 65 years of age and remains the leading cause of death in both genders.[73] Several categories of drugs have proven to be quite useful in the management of hypertension, atherosclerotic cardiovascular disease and arrhythmia, and have successfully reduced morbidity and mortality associated with these diseases. The 5 categories of drugs most frequently used include aspirin or other platelet-inhibiting agents, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists and diuretics. At least 4 of these drug types have the potential to adversely affect asthma control or management.

3.1 Aspirin

Aspirin, in the group of patients with asthma who are aspirin sensitive, can induce severe wheezing by the mechanisms outlined in section 1.1, and should be avoided in these patients. If the antiplatelet effect is needed for prevention of acute vascular events, and alternative treatments are not possible, then aspirin desensitisation can be considered (section 1.3). As desensitisation in this group would pose a high risk if a severe reaction should occur, it is not generally recommended in these patients. If, however, the antiplatelet effect of aspirin is absolutely needed, the procedure should only be performed by personnel with a high degree of experience in the procedure and in an intensive care unit with close respiratory and cardiovascular monitoring and emergency resuscitation equipment readily available.

3.2 β-Blockers and Calcium Antagonists

Nonselective β-blockers should generally be avoided in all patients with asthma and alternative treatments should be sought. Selective β_1-blocking agents such as atenolol and metoprolol can be used cautiously in lower doses, and are generally tolerated,[74,75] but should be stopped if wheezing occurs. In contrast, calcium antagonists appear to be well tolerated alternatives and do not adversely affect the status of asthma.[76]

3.3 Angiotensin Converting Enzyme Inhibitors

ACE inhibitors have been extremely useful in cardiovascular disease management and have successfully reduced mortality associated with these diseases.[77,78] While not a cause of asthma nor presenting an increased risk to patients with asthma,[79] these agents can produce 2 idiosyncratic reactions that can confuse the diagnosis or management of asthma, or mimic allergic reactions.

A harsh cough occurs in approximately 5 to 10% of patients taking ACE inhibitors which is poorly responsive to bronchodilators and inhaled corticosteroids.[80] The cause of the cough is unknown, but may relate to the ability of ACE inhibitors to inhibit the breakdown of bradykinin and other related peptides leading to their accumulation in the lung.[81] Coughing subsides with discontinuing the medication. The cough can become severe and intractable in some cases and can confuse the diagnosis of asthma, and the ability to assess the efficacy of asthma treatment. Present data suggest that patients with asthma do not need to avoid ACE inhibitors, but should be monitored carefully for the development of cough which in most cases subsides within days to weeks following cessation of the drug.[82]

Angioedema, a much rarer adverse effect of ACE inhibitors, can cause upper airway obstruction and respiratory distress, and is occasionally confused with status asthmaticus. It does not appear to be dose related and reactions can occur with all drugs within this class.[83] Episodes of localised angioedema, usually involve the mouth, tongue, pharynx and larynx,[84] but can also involve the bowel with pain and obstructive symptoms.[85] 60% of episodes occur within the first week of treatment[84] but episodes can occur after taking the medication for several years.[86] Angioedema may be accompanied by urticaria in 5 to 10% of cases,[87] and for unknown reasons this ACE inhibitor–induced angioedema may be more common in Black patients.[88] Reactions may be severe and life-threatening, and many patients experience multiple attacks before the diagnosis is made. Patients with a past history of episodes of angioedema of other causes should not receive ACE inhibitors.[89] The mechanism of this reaction is unknown and affected patients should discontinue the drug.

3.4 Diuretics

Diuretics are also quite well tolerated when used for cardiovascular diseases in patients with asthma but may adversely affect asthma during acute exacerbations by increasing the viscosity of secretions.[90]

4. Neurological Problems

Several neurological conditions such as cerebrovascular disease, essential tremor, migraine and tension-vascular headaches often require treatment with either NSAIDs or β-blocking agents. Antiplatelet therapy with aspirin has become an important tool in the management of cerebrovascular disease for stroke prevention. As for cardiovascular disease, if aspirin therapy is indicated in an asthmatic patient with aspirin sensitivity, desensitisation can be considered (section 1.3).

It is estimated that up to 15% of the population periodically experience severe headaches including migraines.[91] Both NSAIDs and β-blockers are frequently used in the treatment of migraine. These patients are generally younger and with several alternate choices of therapy available, migraine would be a rare indication for desensitisation in a patient with aspirin-sensitive asthma.

β-Blockers, which have been shown to be beneficial as prophylaxis for migraine[92] and as treatment for essential tremor,[93] should generally be avoided in all patients who have asthma. The more selective β_1-blockers are not thought to be as effective for migraine prophylaxis as the nonselective β-blockers such as propranolol and timolol, and thus would not serve as useful substitutes.[94]

Other recent uses for β-blockers include treatment of anxiety or 'stage fright' before important engagements, or prior to surgical procedures.[95] β-Blockers might also be useful to control adverse effects of withdrawal of addictive substances.[96] In these settings the patient may not be aware that their asthma would be a contraindication to β-blockers and they may not readily mention to the prescribing physician that they have asthma.

5. Urological Conditions

Cholinergic agonists such as bethanechol stimulate smooth muscle contraction through parasympathomimetic mechanisms.[97] Bethanechol is relatively more selective to the urinary tract and gastrointestinal tract when given orally or subcutaneously, but has produced severe bronchospasm in patients with asthma.[98]

6. Diagnostic Studies

Diagnostic studies in patients with asthma can pose a small but significant risk. Asthmatic patients often require allergen skin tests as part of their evaluation, and bronchoprovocation tests, usually with methacholine are used to assist in the diagnosis of asthma. X-ray studies are also often needed in the course of evaluation of patients for the diagnosis of other diseases and contrast agents can present problems for patients with asthma.

Iodinated radiographic contrast agents are a common cause of anaphylactoid reactions, which may occur at a frequency of 3 to 4 per 1000 patients exposed.[99] As many as half of these reactions are associated with severe wheezing. The relative risk of bronchospasm was 16 times greater in patients with a history of asthma.[99] The risk of reaction is also greater in those taking β-blockers and who have cardiovascular disease. There are, as yet, no position statements from national allergy or radiology societies suggesting that monoiodinated agents be used in patients with asthma who have no history of prior anaphylactoid reactions. In patients who have previously sustained anaphylactoid reactions to contrast agents, the risk of sustaining a similar reaction with future exposure can be reduced by using monoiodinated, low-osmolality agents,[100] or administering the contrast agent after pretreating the patient with methylprednisolone, diphenhydramine and ephedrine at 13, 7 and 1 hours prior to the procedure.[101]

Allergy skin prick testing is generally quite well tolerated. In a large study of more than 10 000 patients, the frequency of sustaining a systemic reaction was less than 0.02%.[102] In a nationwide survey in the US of the years 1985 to 1989, no fatalities were observed associated with allergy skin testing.[103] Systemic reactions are more likely to occur when testing with an agent to which the patient has sustained a prior systemic reaction. Allergens that have been implicated in systemic reactions to skin testing are penicillins, insect venom,

foods (particularly peanut) and latex. Skin testing should be performed by personnel familiar with the procedure, and if prior systemic reactions have occurred to a substance, consideration should be given to either beginning with a 10- to 100-fold dilution of the allergen, or avoiding skin testing altogether and performing a serum latex-specific IgE determination (RAST).

Bronchoprovocation testing with methacholine is also quite useful in the diagnosis of asthma. This testing is generally performed in a graded fashion with inhalation of increasing amounts of methacholine while measuring the response on airflow. Although a few patients with very high degrees of bronchial hyper-responsiveness can experience severe wheezing during methacholine testing, in general such bronchoprovocation is quite well tolerated when performed by experienced personnel and induced bronchospasm is easily reversed with bronchodilators.[104]

7. Dermatological Conditions

Very few dermatological conditions require therapy which might adversely affect asthma, but systemic NSAIDs have been useful to treat milder cases of cutaneous lupus erythematosus. If the patient has coexisting aspirin-sensitive asthma this therapy would pose an obvious risk of inducing bronchospasm. In addition, the skin is an excellent delivery site for numerous categories of drugs including β-blockers. Recently developed transdermal mepindolol and propranolol patches deliver these drugs systemically in a uniform fashion and might prove useful adjuncts to the management of cardiovascular disease.[105] Because the intent of these agents is to provide adequate delivery for systemic effects, they carry the same risks to patients with asthma as oral or injected β-blockers.

8. Conclusion

Medication requirements for patients with asthma can become quite complicated when asthma is present with other diseases. The physician managing patients with asthma must be constantly aware of the full list of medications that the patient is taking in order to avoid the use of medications which are well known to cause or exacerbate asthma. This vigilance can be accomplished without too much difficulty by reviewing the entire list of medications that a patient is taking at each clinic or hospital visit. Patients should be instructed to bring all of their medications with them on each appointment and to call the physician who is managing their asthma whenever they are prescribed a new medication by another physician who is managing a concomitant condition. This precaution will avoid unnecessary medication-induced asthma flares in these patients. In addition, software programmes are used by some pharmacies that automatically trigger an inquiry to the prescribing physician if a patient is simultaneously prescribed topical glucocorticoids, theophylline or bronchodilators concomitantly with agents such as β-blockers. Severe medication-induced asthma attacks are thus preventable in most instances.

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