**Allergy and Immunology Review Corner:** Chapter 85 of *Middleton’s Allergy Principles and Practice, 7th Edition*, edited by N. Franklin Adkinson, et al.

**Chapter 85: Beta-Adrenergic Agonists**

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1. Compared to the closed mouth technique of using an MDI, the open-mouth technique (where the MDI is held two inches away from the mouth) has the following advantage:
   A. Consistent enhancement of efficacy in clinical trials.
   B. Increased time for the propellant to evaporate before being inhaled, resulting in a more uniform particle size.
   C. Increased turbulence of air flow, which decreases deposition in the upper airway.
   D. Additional time for the medication to settle in the lungs.
   E. Improved “hand-lung” coordination

2. An important advantage of a jet nebulizer versus an MDI with spacer and holding chambers is:
   A. Less tachycardia with the nebulizer
   B. Better clinical response
   C. Better improvement in pulmonary function
   D. Less time required by staff for administration and maintenance of therapy
   E. Longer duration of response

3. Non-bronchodilator actions of beta-2 agonists include which of the following:
   A. Increased eosinophils in sputum and BAL fluid
   B. Decreased ion and water secretion
   C. Increased microvascular permeability
   D. Enhancement of cholinergic transmission
   E. Priming of the glucocorticoid receptor

4. Adverse effects of inhaled beta-2 agonists include which of the following:
   A. Hypoglycemia
   B. Hyperkalemia
   C. Tremor
   D. Increased gastric acid secretion
   E. Shortened QTc

5. Which of the following statements about salmeterol is true?
   A. It possesses a long, hydrophilic side chain that increases its uptake into cell membranes, prolonging its duration of action.
   B. Compared with formoterol, it has a more rapid onset of action.
   C. Because of its anti-inflammatory action, it is recommended as monotherapy for long-term control of asthma
D. The SMART study concluded that there were no statistically significant increases in respiratory-related and asthma-related deaths in the total population receiving salmeterol.
E. It is resistant to degradation by catechol-O-methyltransferase (COMT) because one of the hydroxyl groups on the benzene ring has been replaced by a hydroxymethyl group.

6. Which of the following is an advantage of using a pressurized metered-dose inhaler (MDI)?
A. Little hand-lung coordination is needed
B. The MDI is effective with tidal breathing
C. There is high dose-dose reproducibility
D. There is low oropharyngeal deposition with use

7. What structural characteristic of catecholamines leads to more selectivity for the \( \beta_2 \)-receptor?
A. Modification of the 3, 4-hydroxyl groups on the benzene ring
B. Increasing the bulk of the side chain
C. Substitution of a hydroxymethyl group for a 3-hydroxyl group
D. Substitution of a formylamino group

8. Which of the following is an example of a short acting beta-agonist?
A. Formoterol
B. Salmeterol
C. Terbutaline
D. Aformoterol

9. Which of the following is true regarding the use of \( \beta_2 \) adrenergic agonists?
A. Adverse reactions including paradoxical bronchoconstriction are commonly seen in diabetic patients with multiple co-morbidities
B. Continued therapy leads to hypoglycemia to which tolerance rapidly develops
C. Chronic use leads to high levels of magnesium in the blood from \( \beta_2 \)-adrenergic stimulation
D. Administration of \( \beta_2 \)-adrenergic agonists may cause a transient fall in arterial oxygen tension (\( \text{PaO}_2 \))

10. What is the limitation in using \( \beta_2 \)-agonists by the oral route?
A. The oral route is limited by dose dependent side effects of tremor
B. Bronchodilation was only effectively demonstrated in adult patients
C. The oral formulations last for more than 24 hours because only extended release formulas are available
D. When used as a sole bronchodilator there was no improvement in pulmonary function

Answers
1. B, page 1490

Particles leaving an MDI consist largely of propellant, which must evaporate for the particles to achieve a size suitable for entering the lungs. It would be anticipated that a longer distance from actuator to oropharynx would allow more complete evaporation of
propellant as well as slowing of the particles. Some investigators have advocated use of an “open-mouth technique,” where the MDI is held 2 inches away from the open mouth. However, this technique has not been shown to enhance clinical benefit consistently compared with the “closed-mouth technique.”

2. D, page 1492
The delivery of β2-agonists in the acute care setting by nebulizers or MDIs with holding chambers is equally effective for improving pulmonary function and reducing symptoms of acute asthma in both adult and pediatric patients. Nebulizer use in the emergency department is associated with greater increases in heart rate than the use of an MDI with spacer/holding chamber, suggesting that a larger systemically absorbed dose is administered by nebulizer. In the inpatient setting, the available evidence suggests that there is no difference in the pulmonary function response between using a nebulizer and using an MDI with a spacer/holding chamber for administering short-acting β2-agonists.

3. E, page 1493 and Table 85.2
LABAs, when added to suboptimal concentrations of ICS, resulted in enhanced translocation of the glucocorticoid receptor into the nucleus of cells. The mechanism appears to be through priming of the glucocorticoid receptor by mitogen-activated protein kinases (MAPKs) generated as a result of prolonged stimulation of the β2-adrenergic receptor.

4. C, page 1494
The principal side effect of adrenergic therapy is tremor, which is caused by direct stimulation of β2-adrenergic receptors in skeletal muscles (Box 85.3). Tremor is inseparable from the bronchodilator action but does decrease significantly over 2 weeks of continuous therapy; it is not clear whether tolerance reflects desensitization of the β2-receptors of skeletal muscle or adaptation within the central nervous system (CNS). Other side effects include hyperglycemia, hypokalemia, and prolonged QTc.

5. E, page 1486
The basic structure of the catecholamines can be modified by two strategies (Fig. 85.1). The first strategy is modification of the 3,4-hydroxyl groups on the benzene ring, which are required for the action of the enzyme catechol O-methyltransferase (COMT). This can be accomplished by substituting a hydroxymethyl group for the 3-hydroxyl, as in the case of albuterol (salbutamol), pirbuterol, and salmeterol. See also page 1497. The SMARTdata represented a serious safety concern for the use of LABAs but the significant benefit provided to a large number of patients, particularly in conjunction with ICS therapy, warranted continued use of LABA as adjunctive therapy for patients who have asthma that is not well controlled with ICS alone.

6. C, page 1491, Table 85.2
Advantages of pressurized metered-dose inhalers (MDI) include high dose-dose reproducibility. MDIs require hand-lung coordination and have a high oropharyngeal deposition. With optimal MDI technique, a maximum of 12–14% of the dose released by an MDI can be deposited in the lungs.
7. B, page 1486
Increasing the bulk of the side chain results in more selectivity for the β₂-receptor. For albuterol, terbutaline, and pirbuterol, a tertiary butyl group replaces the isopropyl group of isoproterenol and metaproterenol; in the case of fenoterol, the substituted 4-hydroxybenzyl moiety is larger.

8. C, page 1486
Terbutaline is a non-catecholamine short acting β₂-agonist. Bronchodilation occurs rapidly after inhalation and effects persist for 4–6 hours.

9. D, page 1495
When a patient is initially placed on β₂-adrenergic stimulants, hyperglycemia occurs from glycogenolysis, but the response declines rapidly with chronic stimulation and β₂-Adrenergic stimulation increases urinary excretion of magnesium, partly explaining the decreased serum levels of magnesium. Administration of β₂-adrenergic agonists may cause a transient fall in arterial oxygen tension (PaO₂) of >5 mmHg in up to 50% of patients with asthma and the frequency with which this fall in PaO₂ is observed suggests the need for precautionary administration of oxygen-enriched air before beginning intensive therapy with β₂-adrenergic agonists in acutely ill patients.

10. A, page 1490
Administration of a β₂-adrenergic agonist by the oral route is limited by dose-dependent side effects of tremor, tachycardia, and palpitations. Tremor is often the dose-limiting effect however the intensity of this symptom usually declines over 2 weeks with continued administration.

**Allergy and Immunology Review Corner:** Chapter 86 of Middleton’s *Allergy Principles and Practice*, 7th Edition, edited by N. Franklin Adkinson, et al.

**Chapter 86: Theophylline and Phosphodiesterase Inhibitors**

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1. Therapeutic concentrations of Theophylline inhibit phosphodiesterase (PDE) activity in human lung extracts by what percentage?
   A. 5-10%
   B. 20-30%
   C. 50-60%
   D. 90-95%

2. Nausea and vomiting as side effects of Theophylline are likely due to inhibition of which of the following?
   A. PDE3
   B. PDE4
C. Adenosine Receptor
D. PI3K

3. Which of the following is likely increased by Theophylline?
   A. Phosphodiesterase activity
   B. NFkB nuclear translocation
   C. Phosphoinositide-3-kinase activity
   D. Interleukin-10 secretion

4. Which of the following mechanisms of Theophylline’s ability to increase apoptosis are correct?
   A. Inhibition of adenosine for both neutrophils and T-cells
   B. Inhibition of phosphodiesterase for both neutrophils and T-cells
   C. Inhibition of adenosine for neutrophils and phosphodiesterase for T-cells
   D. Inhibition of adenosine for T-cells and phosphodiesterase for neutrophils

5. Theophylline’s effect on histone deactylase activity may increase the efficacy of which of the following treatments?
   A. Beta agonists
   B. Corticosteroids
   C. Leukotriene receptor antagonists
   D. Immunotherapy

6. Theophylline serum concentrations may be increased by which of the following?
   A. Concomitant phenobarbital use
   B. Consumption of barbecued meat
   C. Concomitant use of allopurinol
   D. Tobacco smoking

7. Regarding the side effect profile of theophylline, which of the following is correct?
   A. Side effects tend to occur when plasma levels exceed 15 mg/L.
   B. Side effects may occur at therapeutic theophylline concentrations
   C. Convulsions and arrhythmias are the most common side effects of theophylline
   D. Given its side effects profile, theophylline should routinely be used in patients visiting the ER for acute asthma.

8. Which of the following is true regarding oral administration of theophylline?
   A. Plain theophylline tablets provide steady plasma concentrations over 24 hours
   B. Aminophylline formulations are more effective than theophylline
   C. Intramuscular theophylline is preferred over oral theophylline
   D. Slow-release theophylline given at night may be effective for nocturnal asthma

9. Synergy between theophylline and β-agonists is not seen clinically because:
   A. β-agonists do not increase levels of cAMP in cells.
   B. β-agonists open maxi-K channels in cells independently of cAMP.
C. Theophylline antagonizes the effects of β-agonists.
D. β-agonists downregulate PDE-enzymes.

10. Roflumilast is a selective inhibitor of which of the following PDE isozymes?
A. PDE-4
B. PDE-5
C. PDE-6
D. PDE-7

Answers
1. A, page 1506
Theophylline is a weak and non-selective inhibitor of PDEs. Therapeutic concentrations of Theophylline inhibit PDE activity in human lung extracts by only 5-10%.

2. A, page 1506
PDE3 inhibition leads to nausea, vomiting, and headache while PDE4 inhibition leads to palpitations and cardiac arrhythmias. Adenosine antagonism may account for CNS stimulation, cardiac arrhythmias, gastric hypersecretion, gastroesophageal reflux, and diuresis. Inhibition of phosphoinositid-3-kinases (PI3K) may inhibit chemotaxis of neutrophils and monocytes.

3. D, page 1506
Theophylline inhibits phosphodiesterase activity, NFκB nuclear translocation, and phosphoinositide-3-kinase activity. It increases IL-10 secretion, apoptosis of inflammatory cells, and histone deacetylase activity.

4. C, page 1507
Theophylline reduces the anti-apoptotic protein Bcl-2 via adenosine receptor antagonism in neutrophils causing increased apoptosis. It also increases apoptosis of T lymphocytes which is mediated by phosphodiesterase inhibition.

5. B, page 1507
Theophylline is an activator of histone deacetylases and enhances the anti-inflammatory effect of corticosteroids, as well as reversing steroid resistance in cells from COPD patients.

6. C, page 1510
Use of medications that induce enzymes (e.g. rifampicin, phenobarbital, ethanol), smoking, consumption of barbecued meat, and consumption of a high protein, low-carbohydrate diet will increase the clearance of theophylline, decreasing serum concentrations and potentially increasing the amount required to reach therapeutic levels. Clearance is also increased in childhood. Enzyme inhibitors (e.g. cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton) will decrease the clearance of theophylline and result in higher serum levels.

7. B, page 1512
Theophylline side effects tend to occur when serum concentrations exceed 20 mg/L. However, they may occur at lower concentrations. The most common side effects of theophylline are nausea, headaches, abdominal discomfort, and restlessness. Given its side effects profile theophylline use in the ER should be reserved to patients who fail to show an adequate response to nebulized β2 agonists.

8. D, page 1511
A single dose of slow-release theophylline given at night may be effective for nocturnal asthma. Plain theophylline tablets or elixir give wide fluctuations in plasma concentrations and should not be used. Aminophylline and theophylline oral preparations are equally effective. IM theophylline is very painful and should never be administered.

9. B, page 1511. The lack of synergy between theophylline and β-agonists may be due in part to direct activation of maxi-K channels on smooth muscles leading to relaxation independent of cAMP levels despite the fact that β-agonists do increase levels of cAMP in cells. Theophylline effects are, however, additive to those of β-agonists. Repeated β-agonist use upregulates PDE-enzymes and may contribute to tolerance.

10. A, page 1512
Roflumilast is a selective inhibitor of PDE-4 and may improve lung functions in patients with mild to moderate asthma.