

Beta-2 agonist bronchodilators

Agonists at the beta-2 adrenoceptor on airway smooth muscle that raise intracellular cyclic AMP and open the airways, divided in practice not by how they work but by how long the effect lasts: minutes-to-hours relievers against twice-daily and once-daily maintenance agents.

Online guide: <https://www.medguideglobal.com/pharmacology/respiratory-and-allergy/beta2-agonist-bronchodilators>

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Quick revision

One Liner: Every drug in this class does the same thing to the same receptor; what separates them is duration, and duration is what decides whether an agent is a reliever or a maintenance treatment.

1. Short-acting agents work within minutes. In responders, the VENTOLIN HFA label reports a mean time to onset of 5.4 minutes, a mean time to peak effect of 56 minutes and a mean duration of about 4 hours. [1]
2. Long-acting agents split again by dosing interval: salmeterol and formoterol are given twice daily, while indacaterol and olodaterol hold bronchodilation across a 24-hour period. [4][5][7][6]
3. The single-ingredient salmeterol label carries a boxed warning headed WARNING: ASTHMA-RELATED DEATH, and states that use of the product for asthma as monotherapy without a concomitant inhaled corticosteroid is contraindicated. [4]
4. That warning is specific to monotherapy. The fluticasone furoate and vilanterol combination label has no boxed warning and states that fixed-dose combination with an inhaled corticosteroid does not show a significant increase in serious asthma-related events compared with the steroid alone. [8]
5. Tremor, nervousness, headache, tachycardia and palpitations are the class adverse effects, and they are stimulation of beta-2 receptors outside the airway rather than an idiosyncratic reaction. [2][3]
6. Hypokalaemia arises possibly through intracellular shunting of potassium, and concomitant xanthine derivatives, steroids or diuretics may potentiate it. [5][7]
7. Paradoxical bronchospasm can follow a dose and may be life threatening; the labels direct immediate discontinuation and substitution of alternative therapy. [1][4]
8. Beta blockers are the mirror image of this class: they block the pulmonary effect of a beta agonist and may themselves produce severe bronchospasm in asthma or COPD. [4][1]
9. Rising reliever consumption is a warning sign rather than a treatment: increasing use of inhaled short-acting beta-2 agonists is described in the labelling as a marker of deteriorating asthma. [4]
10. Route decides how much of the systemic burden a patient carries: tremor is reported in 20% of patients on oral salbutamol tablets and 38% after subcutaneous terbutaline, but does not reach the 3% threshold table for the inhaled aerosol. [2][3][1]

Overview

1. Beta-2 agonists are the direct pharmacological opposite of airway smooth muscle contraction. Binding the beta-2 adrenoceptor stimulates adenylyl cyclase, the enzyme catalysing conversion of adenosine triphosphate to cyclic adenosine monophosphate, and the rise in cyclic AMP relaxes bronchial smooth muscle and inhibits release of mediators of immediate hypersensitivity, especially from mast cells. Nothing in that sequence is anti-inflammatory, which is why the class treats airway narrowing without touching the disease driving it. [4]
2. Because the mechanism is shared, the useful division is temporal. A short-acting agent such as salbutamol opens the airway within minutes and is spent within hours, which suits it to acute bronchospasm and to pre-emptive use before exercise. A long-acting agent holds the receptor for a dosing interval of twelve or twenty-four hours, which suits it to maintenance but makes it useless in an attack: the long-acting labels state plainly that they are not indicated for

the relief of acute bronchospasm. [1][4][6]

3. The class carries one safety point that outranks all the others, and its wording has moved over time. After a 28-week placebo-controlled United States trial found more asthma-related deaths among patients given salmeterol added to usual therapy, regulators applied a boxed warning across long-acting agents. That warning has since been narrowed rather than withdrawn. The current single-ingredient salmeterol label keeps a boxed warning and makes asthma monotherapy a contraindication; the fixed-dose steroid combination label carries no boxed warning; and the products licensed only for chronic obstructive pulmonary disease had theirs removed, with the class statement retained in warnings and precautions. [4][8][5][6]

4. Selectivity for the beta-2 receptor is relative, not absolute. Salmeterol is described as at least fifty times more selective for beta-2 adrenoceptors than albuterol, and formoterol as having more than two-hundred-fold greater agonist activity at beta-2 than at beta-1 receptors, yet beta-2 receptors themselves make up between 10% and 50% of the adrenergic receptors in the human heart. Their precise cardiac function is not known, but their presence raises the possibility that even highly selective agents may have cardiac effects. [4][5][7][1]

Classification and drug examples

Intro: Grouped by duration of action, because that is the property that decides how an agent is used and where it becomes dangerous. Every member acts on the same receptor by the same second messenger.

1. Name: Short-acting beta-2 agonists (SABA)

1. Note: Relievers. Onset in minutes, effect measured in hours, and licensed for the treatment or prevention of bronchospasm rather than for maintenance of control.

1. Name: Salbutamol

1. Albuterol

2. Ventolin

1. Route: Inhaled, oral and intravenous

1. Note: The reference reliever. Activation of airway beta-2 receptors raises cyclic AMP, activating protein kinase A, which inhibits phosphorylation of myosin and lowers intracellular ionic calcium, producing relaxation. [1]

2. Name: Terbutaline

2. Route: Inhaled, oral and subcutaneous

2. Note: Exerts a preferential effect on beta-2 adrenergic receptors. The subcutaneous injection is licensed for prevention and reversal of bronchospasm from twelve years of age, and carries a boxed warning against prolonged tocolysis. [3] [1][3]

2. Name: Twice-daily long-acting beta-2 agonists (LABA)

2. Note: Maintenance agents with a twelve-hour dosing interval. In asthma these are the agents around which the monotherapy warning was written.

1. Name: Salmeterol

1. Route: Inhaled

1. Note: In vitro at least fifty times more selective for beta-2 adrenoceptors than albuterol. Its single-ingredient label restricts asthma use to patients already taking, but inadequately controlled on, an inhaled corticosteroid. [4]

2. Name: Formoterol

Eformoterol

2. Route: Inhaled

2. Note: Shows more than two-hundred-fold greater agonist activity at beta-2 than at beta-1 receptors. The single-ingredient nebuliser solution is licensed twelve-hourly for chronic obstructive pulmonary disease and is not indicated to treat asthma. [5] [4][5]

3. Name: Once-daily long-acting beta-2 agonists

3. Note: Agents whose bronchodilation is sustained across twenty-four hours. Their single-ingredient products are licensed for chronic obstructive pulmonary disease only.

1. Name: Indacaterol
Onbrez

1. Route: Inhaled

1. Note: A partial agonist at the human beta-2 receptor with more than twenty-four-fold greater activity at beta-2 than beta-1. Onset comes within five minutes of inhalation, yet the effect is sustained over a 24-hour period. [7]

2. Name: Olodaterol

Striverdi

2. Route: Inhaled

2. Note: Binds and activates beta-2 adrenoceptors after topical administration by inhalation. Licensed for long-term once-daily maintenance of airflow obstruction, and explicitly not indicated to treat asthma. [6]

3. Name: Vilanterol

3. Route: Inhaled

3. Note: Reaches patients only inside fixed-dose combination inhalers, such as the once-daily fluticasone furoate and vilanterol product licensed for maintenance treatment of asthma and of chronic obstructive pulmonary disease. [8]
[7][6]

Mechanism of action

Summary: One receptor, one second messenger, one downstream consequence. Beta-2 adrenoceptor occupancy stimulates adenylyl cyclase, cyclic AMP rises, protein kinase A is activated, myosin phosphorylation falls and intracellular calcium drops, so the smooth muscle relaxes. The same receptor sitting on skeletal muscle, on the heart and on the cells that handle potassium produces the entire adverse-effect profile.

Target: The beta-2 adrenoceptor on bronchial smooth muscle, with off-target consequences at beta-2 receptors in skeletal muscle, the heart and elsewhere

Cidal Static: Bronchodilator, not anti-inflammatory

Kill Kinetics: Effect lasts only while the receptor is occupied, so duration is a property of the molecule rather than of the disease

1. Step: 1

1. Title: Agonist binds the beta-2 adrenoceptor in the airway

1. Detail: The drug is delivered topically to the lung and acts locally there. Inhaled formoterol is described as acting locally in the lung as a bronchodilator, and olodaterol exerts its effect by binding and activation of beta-2 adrenoceptors after administration by inhalation. [5][6]

2. Step: 2

2. Title: Adenylyl cyclase is stimulated and cyclic AMP accumulates

2. Detail: Receptor occupancy stimulates intracellular adenylyl cyclase, the enzyme that catalyses conversion of adenosine triphosphate to cyclic adenosine monophosphate. Raised cyclic AMP is the signal that everything downstream depends on. [4][7]

3. Step: 3

3. Title: Protein kinase A relaxes the smooth muscle cell

3. Detail: The rise in cyclic AMP activates protein kinase A, which inhibits phosphorylation of myosin and lowers intracellular ionic calcium. With less calcium available to the contractile apparatus, the airway smooth muscle relaxes and the calibre of the airway increases. [1]

4. Step: 4

4. Title: Mediator release from mast cells is inhibited

4. Detail: Raised cyclic AMP also inhibits release of mediators of immediate hypersensitivity from cells, particularly mast cells. This is a useful adjunct effect, but it is not equivalent to suppressing established airway inflammation. [4]

5. Step: 5

5. Title: The same receptor is stimulated outside the lung

5. Detail: Beta-2 receptors predominate in bronchial smooth muscle, but they also make up between 10% and 50% of the adrenergic receptors in the human heart. Their precise cardiac function is not known; their presence raises the possibility that even highly selective beta-2 agonists may have cardiac effects. [1][7]

6. Step: 6

6. Title: Potassium shifts into cells and glucose rises

6. Detail: Beta-adrenergic agonist medicines may produce significant hypokalaemia, possibly through intracellular shunting of potassium, and inhalation of high doses may increase plasma glucose. The fall in serum potassium is usually transient and normally requires no supplementation. [4][7]

Major clinical uses

1. Drug: Salbutamol

1. Organism: Not applicable

1. Indication: Treatment or prevention of bronchospasm in reversible obstructive airway disease from four years of age

1. Line: first-line reliever

1. Note: The inhalation aerosol is indicated for treatment or prevention of bronchospasm in adult and paediatric patients aged four years and older with reversible obstructive airway disease. [1]

2. Drug: Salbutamol

2. Organism: Not applicable

2. Indication: Prevention of exercise-induced bronchospasm

2. Line: pre-emptive use

2. Note: A separate licensed indication from acute relief, and the one situation in which a reliever is used before symptoms rather than in response to them. [1]

3. Drug: Terbutaline

3. Organism: Not applicable

3. Indication: Prevention and reversal of bronchospasm from twelve years of age, including in bronchitis and emphysema

3. Line: alternative short-acting agent

3. Note: The injection is given subcutaneously. Its boxed warning concerns an unlicensed obstetric use rather than its respiratory one: it has not been approved and should not be used for prolonged tocolysis. [3]

4. Drug: Salmeterol

4. Organism: Not applicable

4. Indication: Asthma from four years of age together with an inhaled corticosteroid, prevention of exercise-induced bronchospasm, and maintenance of bronchospasm in chronic obstructive pulmonary disease

4. Line: add-on maintenance

4. Note: The label restricts the asthma indication sharply: it is used only as additional therapy for patients already taking but inadequately controlled on an inhaled corticosteroid, and not for those adequately controlled on a low or medium steroid dose. [4]

5. Drug: Formoterol

5. Organism: Not applicable

5. Indication: Twice-daily maintenance treatment of bronchoconstriction in chronic obstructive pulmonary disease

5. Line: maintenance

5. Note: The single-ingredient nebuliser solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease, and is not indicated to treat asthma at all. [5]

6. Drug: Indacaterol

6. Organism: Not applicable

6. Indication: Maintenance bronchodilator treatment of airflow obstruction in adults with chronic obstructive pulmonary disease

6. Line: once-daily maintenance

6. Note: The European summary of product characteristics states that it should not be used in asthma because long-term outcome data in asthma are absent, and that it must not be combined with another long-acting beta-2 agonist. [7]

7. Drug: Olodaterol

7. Organism: Not applicable

7. Indication: Long-term once-daily maintenance of airflow obstruction in chronic obstructive pulmonary disease, including chronic bronchitis and emphysema

7. Line: once-daily maintenance

7. Note: Its label directs that a short-acting beta-2 agonist is prescribed alongside it for acute symptoms, since the maintenance agent is not rescue therapy. [6]

8. Drug: Vilanterol

8. Organism: Not applicable

8. Indication: Available only within fixed-dose combination inhalers, including a once-daily corticosteroid combination for asthma and for chronic obstructive pulmonary disease

8. Line: combination only

8. Note: The fluticasone furoate and vilanterol product is not indicated for relief of acute bronchospasm, and covers asthma maintenance from five years of age. [8]

Pharmacokinetics

1. Drug: Salbutamol (inhaled aerosol)

1. Route: Oral inhalation

1. Absorption: Delivered topically to the airway

1. Half Life: Mean duration of a 15% rise in FEV1 approximately 4 hours

1. Dose Adjust: Onset in responders averaged 5.4 minutes with peak effect at 56 minutes [1]

2. Drug: Salbutamol (oral tablets)

2. Route: Oral

2. Absorption: Gastrointestinal, delivering the drug systemically before it reaches the airway

2. Dose Adjust: Tremor and nervousness were each reported in 20% of patients on this route [2]

3. Drug: Terbutaline (injection)

3. Route: Subcutaneous

3. Absorption: Complete, bypassing the airway entirely

3. Dose Adjust: Tremor 38%, nervousness 30.7% and palpitations 22.9% at the studied dose [3]

4. Drug: Salmeterol

4. Route: Oral inhalation

4. Absorption: Topical to the lung

4. Metabolism: Cytochrome P450 3A4

4. Half Life: Twelve-hourly dosing interval

4. Dose Adjust: Concomitant strong CYP3A4 inhibitors are not recommended [4]

5. Drug: Formoterol

5. Route: Oral inhalation

5. Absorption: Acts locally in the lung as a bronchodilator

5. Half Life: Twelve-hourly dosing interval

5. Dose Adjust: Median time to onset of bronchodilation with the nebuliser solution was 11.7 minutes [5]

6. Drug: Indacaterol

6. Route: Oral inhalation

6. Absorption: Acts locally in the lung after inhalation

6. Metabolism: CYP3A4 and P-glycoprotein are the key contributors to clearance

6. Half Life: Bronchodilation sustained across 24 hours

6. Dose Adjust: Inhibiting CYP3A4 and P-glycoprotein raises systemic exposure by up to two-fold [7]

7. Drug: Olodaterol

7. Route: Oral inhalation

7. Absorption: Topical administration by inhalation

7. Half Life: Once-daily dosing interval

7. Dose Adjust: Not for relief of acute episodes of bronchospasm [6]

1. No dose regimens appear on this page. Device choice, strength, frequency and the decision to add or withdraw a long-acting agent belong to the treating clinician working from a current prescribing reference.

2. The pharmacokinetic fact that matters most in this class is not clearance but duration, because duration is what makes one agent a reliever and another a maintenance treatment. [1][6]

3. Speed of onset and length of action are separable properties. Indacaterol reaches a measurable effect within five minutes of inhalation yet holds bronchodilation for a full day, so a rapid onset does not make an agent suitable as rescue therapy. [7]

Adverse effects

1. Effect: Tremor and nervousness

1. Detail: Skeletal muscle beta-2 stimulation produces a fine tremor that patients notice most in the hands. Both were listed at 20% for oral salbutamol tablets, and tremor at 38% with nervousness at 30.7% after subcutaneous terbutaline. [2][3]

2. Effect: Tachycardia and palpitations

2. Detail: Reported in 5% of patients on oral salbutamol tablets, and palpitations in 22.9% of those given terbutaline by injection. Beta-2 receptors present in the human heart provide the mechanism. [2][3][7]

3. Effect: Headache

3. Detail: Listed at 7% among patients receiving oral salbutamol tablets, and among the most frequent reactions at 3.7% in the indacaterol chronic obstructive pulmonary disease programme. [2][7]

4. Effect: Local and upper airway effects of the inhaled route

4. Detail: For the inhaled aerosol the commonest reactions are throat irritation at 10% against 7% on placebo, viral respiratory infections at 7%, and cough and upper respiratory inflammation each at 5%. [1]

5. Effect: Muscle cramps

5. Detail: Reported in 3% of patients on oral salbutamol tablets, and muscle spasms in 3.5% of patients in the indacaterol programme. [2][7]

1. Effect: Asthma-related death with long-acting monotherapy

1. Detail: The single-ingredient salmeterol label states that long-acting beta-2 agonists as monotherapy, without an inhaled corticosteroid, increase the risk of asthma-related death. A 28-week placebo-controlled United States trial recorded 13 deaths among 13,176 subjects on salmeterol against 3 among 13,179 on placebo, with background steroid not required. A United Kingdom surveillance trial showed a numerically greater rate of asthma-related death on salmeterol than on albuterol, though not statistically significant.

1. Action: Given the similar basic mechanisms of action of beta-2 agonists, the label treats the finding as a class effect, and makes asthma monotherapy a contraindication. [4]

2. Effect: Paradoxical bronchospasm

2. Detail: As with other inhaled medicines, these drugs can produce paradoxical bronchospasm, which may be life threatening. It is the same clinical picture the drug was given to relieve, appearing immediately after a dose.

2. Action: The labels direct that it is treated at once with an inhaled short-acting bronchodilator, that the offending agent is discontinued immediately, and that alternative therapy is instituted. [4][1][7]

3. Effect: Hypokalaemia

3. Detail: Beta-adrenergic agonist medicines may produce significant hypokalaemia, possibly through intracellular shunting, with the potential to produce adverse cardiovascular effects. In severe chronic obstructive pulmonary disease hypoxia and concomitant treatment may potentiate it, increasing susceptibility to cardiac arrhythmias.

3. Action: The decrease in serum potassium is usually transient and does not normally require supplementation, but the combination of a beta-2 agonist with a xanthine, a steroid or a diuretic deserves attention. [4][7][5]

4. Effect: Fatalities associated with excessive use

4. Detail: The salbutamol aerosol label records that fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

4. Action: Heavy reliever use is therefore read as a sign that the underlying disease is out of control; reassessment rests with the treating clinician. [1]

5. Effect: Cardiovascular and electrocardiographic effects

5. Detail: These agents can produce a clinically significant cardiovascular effect measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. Beta agonists have been reported to produce electrocardiogram changes such as flattening of the T wave, prolongation of the QTc interval and ST segment depression.

5. Action: Caution applies in known or suspected QT prolongation and where other QT-affecting medicines are in use. [6][7]

6. Effect: Immediate hypersensitivity reactions

6. Detail: Reported after inhaled indacaterol, with signs including difficulty breathing or swallowing, swelling of tongue, lips and face, urticaria and skin rash.

6. Action: The summary of product characteristics directs immediate discontinuation and institution of alternative therapy. [7]

1. Drug: Terbutaline injection

1. Effect: A boxed warning against prolonged tocolysis beyond 48 to 72 hours and against maintenance tocolysis at home, after reports of maternal death, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. [3]

2. Drug: Salmeterol

2. Effect: Available data from controlled trials suggest that long-acting monotherapy increases the risk of asthma-related hospitalisation in paediatric and adolescent patients, so a fixed-dose steroid combination is ordinarily preferred in that age group to secure adherence to both components. [4]

3. Drug: Indacaterol

3. Effect: Hyperglycaemia; clinically notable blood glucose changes were 1% to 2% more frequent than on placebo, and closer glucose monitoring is advised in diabetic patients when treatment begins. [7]

4. Drug: Olodaterol

4. Effect: Nasopharyngitis in 11.3%, upper respiratory tract infection in 8.2%, cough in 4.2% and dizziness in 2.3% were among the reactions occurring in at least 2% of patients and more often than on placebo. [6]

5. Drug: Formoterol nebuliser solution

5. Effect: Diarrhoea and nausea each at 4.9%, dry mouth at 3.3%, and dizziness and insomnia each at 2.4% in the twelve-week comparison against placebo. [5]

Contraindications, precautions and interactions

1. Use of the single-ingredient salmeterol product for the treatment of asthma as monotherapy, without a concomitant inhaled corticosteroid, is contraindicated. [4]

2. Hypersensitivity to the active substance or to any excipient contraindicates the product, and the salbutamol aerosol is likewise contraindicated where there is a history of hypersensitivity to albuterol or any of its components. [7][1]

1. None of the long-acting agents is indicated for the relief of acute bronchospasm, and the once-daily agents direct that a short-acting inhaled beta-2 agonist be available for acute symptoms. [4][6]

2. Beta-2 agonists should be used with caution in coronary artery disease, recent myocardial infarction, cardiac

arrhythmias and hypertension, and also in convulsive disorders, thyrotoxicosis and in patients unusually responsive to this class. [7]

3. Bronchodilators alone may not be adequate to control asthma in many patients, and the salbutamol label advises early consideration of adding anti-inflammatory agents such as corticosteroids. [1]

4. United Kingdom regulatory advice is that a long-acting agent is always prescribed with a concomitant inhaled corticosteroid and only when the steroid alone is not sufficient, is not started in rapidly deteriorating asthma, and is reviewed regularly and stopped if there is no benefit. [9]

5. The same advice states that a long-acting agent should not be prescribed for relief of exercise-induced asthma symptoms in the absence of regular inhaled corticosteroid treatment. [9]

6. Diabetic patients starting a long-acting agent warrant closer plasma glucose monitoring, since inhalation of high doses of beta-2 agonists may raise plasma glucose. [7][6]

1. With: Beta-adrenergic blocking drugs

1. Effect: The mirror-image interaction. Beta blockers not only block the pulmonary effect of a beta agonist but may also produce severe bronchospasm in patients with asthma or chronic obstructive pulmonary disease, so such patients should not normally be treated with them; where there is no acceptable alternative, cardioselective agents may be considered with caution. [4][1][7]

2. With: Xanthine derivatives, corticosteroids and non-potassium-sparing diuretics

2. Effect: Concomitant treatment with any of these may potentiate the hypokalaemic effect of an adrenergic agonist, and the electrocardiographic changes or hypokalaemia produced by loop or thiazide diuretics can be acutely worsened by a beta agonist. [5][2][7]

3. With: Monoamine oxidase inhibitors and tricyclic antidepressants

3. Effect: Extreme caution is directed during treatment with these agents, or within two weeks of stopping them, because the action of a beta agonist on the vascular system may be potentiated. [1][6]

4. With: Other long-acting beta-2 agonists

4. Effect: Stacking two long-acting agents is prohibited: indacaterol should not be used together with another long-acting beta-2 agonist or with a product containing one, and concomitant sympathomimetics may potentiate adverse reactions. [7]

5. With: Strong CYP3A4 inhibitors

5. Effect: Concomitant use with salmeterol is not recommended, and for indacaterol inhibition of CYP3A4 and P-glycoprotein raises systemic exposure by up to two-fold. [4][7]

6. With: Digoxin

6. Effect: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol. [1]

Comparison tables

1. Title: Duration decides the job

1. Caption: The mechanism is identical across the class, so onset and duration are what separate a reliever from a maintenance agent. Choice of agent and device belongs to the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: group

2. Label: Group

3. Key: interval

3. Label: Dosing interval

4. Key: role

4. Label: Licensed role

1. Drug: Salbutamol
1. Group: Short-acting
1. Interval: As required
1. Role: Treatment or prevention of bronchospasm, and prevention of exercise-induced bronchospasm [1]
2. Drug: Terbutaline
2. Group: Short-acting
2. Interval: As required
2. Role: Prevention and reversal of bronchospasm from twelve years of age [3]
3. Drug: Salmeterol
3. Group: Long-acting
3. Interval: Twice daily
3. Role: Asthma only alongside an inhaled corticosteroid; also COPD maintenance [4]
4. Drug: Formoterol
4. Group: Long-acting
4. Interval: Twice daily
4. Role: COPD maintenance as a single-ingredient nebuliser solution [5]
5. Drug: Indacaterol
5. Group: Once-daily long-acting
5. Interval: Once daily
5. Role: COPD maintenance in adults; not for asthma [7]
6. Drug: Olodaterol
6. Group: Once-daily long-acting
6. Interval: Once daily
6. Role: COPD maintenance; not indicated to treat asthma [6]
7. Drug: Vilanterol
7. Group: Once-daily long-acting
7. Interval: Once daily
7. Role: Only within fixed-dose combination inhalers [8]
2. Title: What the route does to the adverse effects
2. Caption: The same drug, delivered three ways. Inhalation puts the agonist where it is needed and keeps the systemic share small; the oral and subcutaneous routes do not.
1. Key: route
1. Label: Route
1. Is Row Header: true
2. Key: product
2. Label: Product studied
3. Key: tremor
3. Label: Tremor reported
4. Key: comment
4. Label: Comment
1. Route: Oral inhalation
1. Product: Salbutamol inhalation aerosol
1. Tremor: Below the 3% reporting threshold for the adverse reaction table
1. Comment: The reactions that do appear are local: throat irritation, cough and upper respiratory inflammation [1]
2. Route: Oral tablets
2. Product: Salbutamol sulfate tablets
2. Tremor: 20%

2. Comment: Nervousness also 20%, headache 7%, tachycardia and palpitations each 5% [2]
3. Route: Subcutaneous injection
3. Product: Terbutaline sulfate injection
3. Tremor: 38%
3. Comment: Nervousness 30.7% and palpitations 22.9%; the whole dose reaches the circulation [3]

High-yield exam pearls

1. Pearl: The boxed warning on the single-ingredient salmeterol product is specifically about monotherapy: long-acting agents without an inhaled corticosteroid increase the risk of asthma-related death, and that use is contraindicated.
 1. Why: Candidates who remember only the phrase asthma-related death often mis-state the warning as applying to every long-acting agent in every setting, which the current label does not say. [4]
2. Pearl: The steroid combination labelling states that fixed-dose combination with an inhaled corticosteroid does not show a significant increase in serious asthma-related events compared with the steroid alone, and carries no boxed warning.
 2. Why: It is the reason a long-acting agent is safe to use in asthma inside a combination inhaler and unsafe on its own, which is the whole clinical point of the class. [8]
3. Pearl: A rapid onset does not make a long-acting agent a rescue treatment: indacaterol produces a measurable effect within five minutes yet is licensed only for maintenance.
 3. Why: Onset and duration are independent properties, and the examiner is testing whether the candidate confuses them. [7]
4. Pearl: Hypokalaemia from this class is a shift, not a loss, and it is potentiated by xanthine derivatives, corticosteroids and non-potassium-sparing diuretics.
 4. Why: It links a mechanism to a real prescribing scenario, since a patient with severe airways disease is often on several of those agents at once. [5][7]
5. Pearl: Beta-2 receptors make up between 10% and 50% of the adrenergic receptors in the human heart, and their precise function there is not known.
 5. Why: It explains why selectivity for beta-2 does not abolish cardiac effects, and the labels are candid that the significance is uncertain. [1][7]
6. Pearl: Increasing use of an inhaled short-acting agent is a marker of deteriorating asthma requiring immediate reassessment of the treatment regimen.
 6. Why: The signal is a reason to reassess the patient, not a reason to keep using the reliever, and that distinction is what is being examined. [4]

Common exam traps

1. Trap: Saying that long-acting beta-2 agonists are simply contraindicated in asthma.
 1. Correction: It is monotherapy that is contraindicated. The salmeterol label restricts asthma use to patients already taking but inadequately controlled on an inhaled corticosteroid, and asthma from four years of age is a licensed indication on that basis. [4]
2. Trap: Assuming every long-acting product still carries the boxed warning applied after the salmeterol trial.
 2. Correction: The labelling has narrowed. The single-ingredient salmeterol product retains it, the formoterol nebuliser solution records that its boxed warning was removed in 2019, and the olodaterol and steroid combination products carry none while keeping the class statement in warnings and precautions. [4][5][6][8]
3. Trap: Treating a beta blocker as merely a relative caution in obstructive airways disease.
 3. Correction: Non-selective blockade does more than blunt the agonist: it may itself produce severe bronchospasm, and patients with asthma or chronic obstructive pulmonary disease should not normally be treated with beta blockers at all. [4]
4. Trap: Reading paradoxical bronchospasm as a sign the patient needs a larger dose of the same inhaler.

4. Correction: The labels direct the opposite: treat it immediately with an inhaled short-acting bronchodilator, discontinue the offending agent at once, and institute alternative therapy. [4]
5. Trap: Calling salbutamol an anti-inflammatory because it relieves wheeze.
5. Correction: It relaxes smooth muscle and inhibits mediator release from mast cells, but bronchodilators alone may not adequately control asthma, and the label advises early consideration of adding corticosteroids. [1][4]
6. Trap: Assuming the terbutaline boxed warning concerns its use in asthma.
6. Correction: It concerns obstetric use: the drug has not been approved and should not be used for prolonged tocolysis beyond 48 to 72 hours, nor for maintenance tocolysis in the outpatient or home setting. [3]

Self-test questions

1. Question: According to the current single-ingredient salmeterol label, what is the status of using a long-acting beta-2 agonist for asthma without a concomitant inhaled corticosteroid?
 1. Contraindicated
 2. Permitted at the lowest effective dose
 3. Permitted only in adults over 65
 4. Permitted for up to twelve weeks

1. Explanation: The boxed warning states that use of the product for the treatment of asthma as monotherapy without a concomitant inhaled corticosteroid is contraindicated, and that it should be used only as additional therapy in patients inadequately controlled on a steroid. [4]
2. Question: A patient using an inhaled short-acting beta-2 agonist reports needing it far more often than previously. What does the labelling say this represents?
 1. A marker of deteriorating asthma requiring reassessment of the regimen
 2. Expected tolerance at the beta-2 receptor
 3. Evidence that the device is being used incorrectly
 4. A normal seasonal fluctuation requiring no action

2. Explanation: Increasing use of inhaled short-acting beta-2 agonists is described as a marker of deteriorating asthma, calling for immediate reevaluation with special consideration of additional inhaled or systemic corticosteroid. [4]
3. Question: Which mechanism do the labels give for hypokalaemia caused by beta-2 agonists?
 1. Intracellular shunting of potassium
 2. Increased renal potassium excretion through aldosterone
 3. Reduced gastrointestinal potassium absorption
 4. Chelation of potassium in plasma

3. Explanation: The labels state that beta-adrenergic agonist medicines may produce significant hypokalaemia in some patients, possibly through intracellular shunting, and that the fall in serum potassium is usually transient. [4][7]
4. Question: Immediately after taking an inhaled beta-2 agonist a patient becomes acutely more wheezy and breathless. What does the label direct?
 1. Treat at once with an inhaled short-acting bronchodilator, discontinue the agent and institute alternative therapy
 2. Repeat the same inhaler at double the number of actuations
 3. Continue the agent and add an oral antihistamine
 4. Withhold all bronchodilators and observe

4. Explanation: This is paradoxical bronchospasm, which may be life threatening. The label directs immediate treatment with an inhaled short-acting bronchodilator, immediate discontinuation of the causative product, and institution of alternative therapy. [4]
5. Question: Why is a non-selective beta blocker a particular problem in a patient with asthma taking salbutamol?
 1. It blocks the pulmonary effect of the agonist and may itself produce severe bronchospasm
 2. It accelerates hepatic clearance of the agonist
 3. It prevents absorption of the agonist from the airway

4. It converts the agonist into an inactive metabolite

5. Explanation: The labels state that beta blockers not only block the pulmonary effect of beta agonists but may also produce severe bronchospasm in patients with asthma or chronic obstructive pulmonary disease. [1][4]

6. Question: Which finding best illustrates that the inhaled route lowers the systemic burden of a beta-2 agonist?

1. Tremor is reported in 20% of patients on oral salbutamol tablets but does not reach the 3% adverse reaction table for the inhalation aerosol

2. The inhaled product has a longer duration of action than the oral product

3. The inhaled product is contraindicated in cardiac disease while the oral product is not

4. The oral product acts locally in the lung

6. Explanation: The oral tablet label lists tremor and nervousness at 20% each, whereas the inhalation aerosol table of reactions occurring in at least 3% of patients contains throat irritation, viral respiratory infections, upper respiratory inflammation, cough and musculoskeletal pain. [2][1]

7. Question: Which statement about the once-daily agents indacaterol and olodaterol is correct?

1. Their single-ingredient products are licensed for chronic obstructive pulmonary disease and are not indicated for asthma

2. They are licensed as rescue therapy for acute bronchospasm

3. They are licensed for asthma as monotherapy in adults

4. They act at beta-1 rather than beta-2 receptors

7. Explanation: The olodaterol label states it is not indicated to treat asthma, and the indacaterol summary of product characteristics states the product is only indicated for chronic obstructive pulmonary disease and should not be used in asthma because long-term outcome data are absent. [6][7]

8. Question: Which combination is specifically flagged as potentiating the hypokalaemic effect of a beta-2 agonist?

1. Xanthine derivatives, steroids or non-potassium-sparing diuretics

2. Proton pump inhibitors and antacids

3. Potassium-sparing diuretics and angiotensin receptor blockers

4. Oral anticoagulants and statins

8. Explanation: Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate any hypokalaemic effect of adrenergic agonists, and the European text names methylxanthine derivatives, steroids and non-potassium-sparing diuretics. [5][7]

Frequently asked questions

1. Question: What actually separates a SABA from a LABA?

1. Answer: Only duration. Both bind the same receptor and use the same second messenger. The short-acting aerosol reaches onset in about five minutes and lasts roughly four hours, so it suits an acute episode; the long-acting agents cover twelve or twenty-four hours and are given on a schedule regardless of symptoms, which is why the long-acting labels state they are not indicated for relief of acute bronchospasm. [1][4][6]

2. Question: Does a long-acting beta-2 agonist still carry a boxed warning about asthma-related death?

2. Answer: It depends on the product, and the answer has changed over time. The current single-ingredient salmeterol label carries a boxed warning headed WARNING: ASTHMA-RELATED DEATH and makes asthma monotherapy contraindicated. The formoterol nebuliser solution records that its boxed warning was removed in 2019, and neither the olodaterol product nor the fluticasone furoate and vilanterol combination carries one, though each retains the class statement in warnings and precautions. [4][5][6][8]

3. Question: Why does a beta-2 agonist cause tremor and a fast pulse if it is selective for the airway?

3. Answer: Selectivity is a ratio, not an exclusion. Salmeterol is at least fifty times more selective for beta-2 than albuterol and formoterol more than two hundred times more active at beta-2 than beta-1, yet beta-2 receptors also sit on skeletal muscle and make up 10% to 50% of the adrenergic receptors in the human heart. Excessive beta-adrenergic stimulation has been associated with tachycardia, arrhythmias, nervousness, headache, tremor and

palpitation. [4][5][7]

4. Question: Why does the route of administration matter so much in this class?

4. Answer: Inhalation delivers the agonist to the target tissue and leaves a comparatively small systemic share, so the reactions that dominate the inhaled aerosol table are local ones such as throat irritation and cough. Give the same pharmacology by mouth or by injection and the systemic effects come to the front: tremor in 20% of patients on oral salbutamol tablets, and 38% after subcutaneous terbutaline. [1][2][3]

5. Question: What does a rising need for a reliever inhaler indicate?

5. Answer: It is a clinical signal about the disease rather than a dosing question. The labelling treats increasing use of an inhaled short-acting beta-2 agonist as a marker of deteriorating asthma, and needing more doses than usual as a marker of destabilisation that calls for reevaluation of the patient and the treatment regimen. What follows from that signal is a decision for the treating clinician. [4][1]

6. Question: How should the interaction with beta blockers be understood?

6. Answer: As the same receptor pharmacology run in reverse. A beta blocker occupies the receptor the agonist needs, so it blocks the pulmonary effect, and in an obstructed airway it may provoke severe bronchospasm in its own right. Patients with asthma or chronic obstructive pulmonary disease should not normally receive beta blockers; where there is no acceptable alternative, cardioselective agents may be considered with caution. [4]

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