THE NORTHERN HOSPITAL

SALMETEROL

"Women Leaning on a Railing", pastel on paper, 1890, Edgar Degas

Love is like the wild rose-briar, friendship like the holly-tree, the holly is dark when the rose-briar blooms, but which will bloom most constantly?

Emily Brontë

For acute exacerbation of asthma, we turn to salbutamol for comfort. But like the rose - briar bloom, it struts and frets its hour upon the stage, and then is heard no more....for a somewhat longer lasting comfort salmeterol will be our holly bloom.

SALMETEROL

Introduction

Salmeterol belongs to a class of selective **long acting** beta$_2$-adrenoreceptor agonists, (**LABAs**)

It is administered by metered dose inhalers.

Its onset of action is about **10 - 20 minutes**, and so is **not** suitable for acute emergencies, where **salbutamol** is the agent of choice.

Its main advantage is that it has a long duration of action at around 12 hours, and so when given twice daily is an effective preventive agent.

However salmeterol is not a replacement for oral or inhaled corticosteroids. Its use is *complementary* to these agents.

Salmeterol is not designed to relieve *acute* asthmatic symptoms, for which an inhaled short acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have such rescue medication available at all times.

It can be given as monotherapy, but is usually given as a **fixed dose combination** with the long acting corticosteroid inhalant, **fluticasone propionate.**

History

Salmeterol was developed by Glaxo (now GlaxoSmithKline, GSK) in the 1980s.

It was released for clinical use under the trade name of **Serevent** in 1990.

Chemistry

Salmeterol xinafoate is a racemate, the R-enantiomer being active.

Classification

The inhalational beta-2 agonists can be classified thus;

1. Short-acting beta-2 agonists (**SABAs**)
    - Salbutamol
    - Terbutaline
2. Long-acting beta-2 agonists (**LABAs**)
    - Eformoterol

- Indacaterol
- **Salmeterol**
- Vilanterol (only available with fluticasone or umeclidinium)

Preparations

Salmeterol xinafoate as:

Mono-inhalation devices:

- Dry powder inhaler (DPI) 50 mcg/dose, (*Serevent Accuhaler*)

Fixed dose combination inhaler devices:

A wide range of fixed dose combinations with the long acting corticosteroid inhalant agent fluticasone are available.

In asthma, Fixed-dose combination inhalers are preferred to separate inhalers as they ensure use of a LABA with an inhaled corticosteroid, avoiding the risks associated with LABA monotherapy

In COPD, LABA monotherapy appears safe, however, fixed-dose combination inhalers are more convenient for patients needing a LABA and either an inhaled corticosteroid or a long-acting anticholinergic.

Available fixed dose combinations include:

- MDI, (metered dose inhaler) Salmeterol 25 mcg, fluticasone propionate 50 mcg/dose
- MDI, Salmeterol 25 mcg, fluticasone propionate 125 mcg/dose
- MDI, Salmeterol 25 mcg, fluticasone propionate 250 mcg/dose
- DPI, (dry powder inhaler) Salmeterol 50 mcg, fluticasone propionate 100 mcg/dose
- DPI, Salmeterol 50 mcg, fluticasone propionate 250 mcg/dose
- DPI, Salmeterol 50 mcg, fluticasone propionate 500 mcg/dose

Mechanism of Action

Salmeterol is a selective $beta_2$-receptor stimulant.

Its primary therapeutic effect is via its action on the bronchioles, where it causes bronchodilation.

Beta$_2$ effects are thought to be mediated via stimulation of adenyl cyclase by salbutamol, resulting in increased levels of **cyclic AMP** within cells.

Increased levels of **cyclic AMP** are thought to inhibit the entry of calcium ions into the cells, thus inhibiting smooth muscle contraction.

Pharmacodynamics

Salmeterol is a **long acting** selective beta$_2$-receptor stimulant.

Its onset of action is about **10 - 20 minutes**, and so is **not suitable for acute emergencies**, **where salbutamol** is the agent of choice.

Its duration of action is about **12 hours.**

Peak effect is seen at around **3-4 hours**.

At dosages of less than 100 microgram twice daily it has little measurable cardiovascular effect.

In vitro tests have shown salmeterol is also a potent and long lasting inhibitor of the release, from human lung fragments, of mast cell mediators, e.g. histamine, leukotrienes and prostaglandin D_2.

The mechanism for this is different from the anti-inflammatory effect of corticosteroids, which should **not** be stopped or reduced because salmeterol is being taken.

Pharmacokinetics

Absorption:

- Salmeterol is given via inhalation.

  Salmeterol acts **locally** in the lung, therefore, plasma levels are **not** predictive of its therapeutic effect.

Distribution

- Salmeterol xinafoate is extensively bound to plasma proteins, (95 - 98 %) .

Metabolism and excretion:

- Elimination of radioactivity from plasma following oral administration of radio-labelled salmeterol xinafoate is slow (mean $t_{1/2}$ is 67 hours).

- Excretion is predominantly through the GUT and, to a lesser extent, urine.
- Aliphatic hydroxylation appears to be the major route of metabolism in humans.

Indications

The LABAs are indicated for: [3]

1. Maintenance treatment of asthma in patients not controlled on inhaled or oral corticosteroid
    - It should **not** be used in patients whose asthma can be managed by occasional use of short acting inhaled beta$_2$-agonists.
2. Maintenance treatment of COPD (the reversible component thereof) in patients not controlled on inhaled or oral corticosteroids
3. Prevention of exercise-induced bronchoconstriction

Salmeterol is not designed to relieve acute asthmatic symptoms, for which an inhaled short acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have such rescue medication available at all times.

Note that salmeterol is not a replacement for oral or inhaled corticosteroids. Its use is *complementary* to these agents.

When salmeterol treatment is initiated in patients with asthma or COPD, corticosteroids should **not** be stopped or reduced.

Patients must be warned not to stop steroid therapy and not to reduce it without medical advice, even if they feel better on salmeterol. Any change in corticosteroid dosage should only be made after clinical evaluation.

In asthma patients not already receiving corticosteroids, these should be initiated when starting salmeterol.

Contra-indications/precautions

The following are predominantly cautions for beta -2 agonists in general, rather than absolute contraindications:

1. IHD/ ACS
2. Hypertension
3. Thyrotoxicosis
4. Hypokalaemic patients

5. Salbutamol is contraindicated in cases of antepartum haemorrhage because of the risk of further haemorrhage from an atonic uterus

6. Use with caution in conjunction with **other sympathomimetic agents**, synergistic effects can lead to toxicity.

7. Combined use of **glucocorticoids** and salbutamol may exacerbate metabolic effects, resulting in **elevation of blood glucose** and **lowering of serum potassium levels.**

Pregnancy

Salmeterol is a category B3 drug with respect to pregnancy.

Category B3 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is limited information available following the use of salmeterol during pregnancy.

Effects seen in animal studies were at considerably higher systemic exposures than those in clinical use, but there was no evidence of impaired fertility or teratogenic effects in animal studies. The medicine acts locally in the lungs and plasma levels are very low or undetectable following administration.

Therefore, salmeterol is considered safe to use during pregnancy. [4]

The pharmacological treatment of asthma during pregnancy should be the same as in non-pregnant women and should not be altered unless there is inadequate symptom control.

Poorly controlled asthma during pregnancy increases the risk of adverse pregnancy outcomes. Use salmeterol during pregnancy if the patient has been stable on the medicine prior to conception, or if it is considered the medicine of choice. [4]

Note that fluticasone is also considered to be safe in pregnancy. [4]

Breast feeding

Salmeterol is safe to use in breast feeding.

Inhaled bronchodilators are considered safe to use during breastfeeding due to the low oral bioavailability and maternal serum levels after use. [4]

Note that fluticasone is also considered to be safe in breast feeding. [4]

Adverse Effects

The important adverse effects of the beta - agonists as a group include:

1. Tachycardia:

    - All $beta_2$ agonists can also stimulate $beta_1$-receptors to some degree; however, the effects of $beta_1$-receptor stimulation, such as tachycardia and positive inotropic and chronotropic effects on the heart, are more likely to occur with **larger doses.**

2. Cardiac tachyarrhythmias/ palpitations:

    - The most common dose-limiting adverse effects of the $beta_2$ agonists are tachycardia which can also lead to extrasystoles and paroxysmal tachyarrhythmias, such as **rapid atrial fibrillation** or paroxysmal **supraventricular tachycardia**.

      Tachyarrhythmias may be induced by direct sympathomimetic action on myocardial $beta_1$ receptors or secondarily by hypokalaemia, or due to a combination of both.

3. Hypotension, ($beta_2$ effect)

4. General sympathomimetic effects:

    - Flushing, (superficial vasodilation)
    - Tremor
    - Headache
    - Anxiety/ restlessness
    - Nausea

5. Metabolic effects:

    - Hyperglycaemia:

        - ♥ Note that although salbutamol causes a **rise** in **insulin** levels, it also causes a direct **rise** in **glucose** levels (via $beta_2$ stimulated **glycogenolysis**) - the overall result is a **rise in glucose levels**.

          The release of insulin is thought to be due to direct $beta_2$-receptor stimulation and not due to the rises in plasma glucose levels.

- Hypokalaemia:

  - ♥ **Intravenous** salbutamol can cause significant falls in plasma potassium levels.

    This is due to the intracellular shift of potassium associated with increased glucose and insulin levels. Hypokalaemia may also be due to a direct stimulation of Na/K-ATPase in muscle via β_2-receptors, independent of the rise in insulin.

    Nebulized salbutamol can also result in hypokalemia, though to a lesser degree than is seen with IV administration.

- Lactic acidosis:

  - ♥ This can be seen when higher doses are used, particularly with **intravenou**s infusions. It is the most serious adverse effect of **IV salbutamol.**

  - ♥ Significant rises in lactate levels can be seen. Serum lactate rises in response to β_2-agonists as a result of β_2 stimulated anaerobic glycolysis in muscle.

- A rise in non-esterified fatty acids

6. Paradoxical worsening oxygenation:

   - **Reduction** of partial pressure of oxygen has been observed in a *small* number of patients following administration of beta$_2$ bronchodilators, including salbutamol.

     This is possibly due to larger doses inducing pulmonary vasodilation to unventilated regions of lung, (i.e. V/Q mismatching).

Dosing

Salmeterol is not designed to relieve acute asthmatic symptoms, for which an inhaled short acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have such rescue medication available at all times.

Usual dosing is: [2]

Asthma:

For monotherapy:

Adult, child >6 years:

- DPI 1 inhalation (50 micrograms) twice daily (up to 2 inhalations (100 micrograms) twice daily in more severe airways obstruction in adults.

For fixed-dose combination with fluticasone propionate:

Adult:

- MDI 2 inhalations twice daily (of 25 micrograms salmeterol with 50, 125 or 250 micrograms fluticasone propionate).

- DPI 1 inhalation twice daily (of 50 micrograms salmeterol with 100, 250 or 500 micrograms fluticasone propionate).

Child >6 years:

- MDI 2 inhalations twice daily (of 25 micrograms salmeterol with 50 micrograms fluticasone propionate).

Child >6 years:

- DPI 1 inhalation twice daily (of 50 micrograms salmeterol with 100 micrograms fluticasone propionate).

COPD:

For monotherapy:

- DPI, 50 micrograms twice daily.

For fixed-dose combination with fluticasone propionate:

- MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 125 or 250 micrograms fluticasone propionate).

- DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 250 or 500 micrograms fluticasone propionate).

References

1. eTG - July 2017.

2. Salmeterol in Australian Medicines Handbook Website, Accessed November 2017. .

3. Salmeterol in MIMs Website, 1 October 2013.

4. RWH Pregnancy & Breastfeeding Guidelines, 18 May 2016.

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