MHRA PUBLIC ASSESSMENT REPORT

Orciprenaline sulphate (Alupent): planned withdrawal from the UK market following a risk-benefit analysis

November 2009

EXECUTIVE SUMMARY

(Please note that this summary is intended to be accessible to all members of the public, including health professionals)

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports, we discuss the evidence for a safety issue with a particular drug or drug class, and changes made to the product information for the drug on the basis of this evidence, which will help safeguard public health. This MHRA Public Assessment Report discusses a review of the risks and benefits of a medicine called orciprenaline sulphate.

Orciprenaline sulphate is available for oral administration as a syrup used to treat reversible airways obstruction[a], which is a symptom of asthma[b] and chronic obstructive pulmonary disease[c]. It acts on specific areas in the body called β-receptors, which relaxes the muscles used for breathing and opens the airways in the lungs. Orciprenaline sulphate was licensed in 1972 and is marketed in the UK under the brand name Alupent Syrup.

As with any medicine, the use of orciprenaline sulphate may lead to adverse reactions (side-effects) in some individuals, which are described in the product information, including the patient information leaflet (see the Electronic Medicines Compendium (product information) website). As orciprenaline is an older medicine, its place in current practice needed to be assessed. Therefore, the MHRA recently performed a risk-benefit analysis of orciprenaline sulphate, which considered the data available on its efficacy (compared to other asthma medicines) and safety. A summary of the analysis and its findings are presented in the following report.

Results and conclusions

The risks associated with orciprenaline sulphate, particularly cardiac adverse reactions such as tachycardia[d] and palpitations[e], outweigh its clinical benefits. The MHRA concluded that as there are newer medicines available for treating airways obstruction with fewer adverse reactions, orciprenaline sulphate should not continue to be licensed and marketed.

Outcome

Orciprenaline sulphate (Alupent Syrup) will be voluntarily withdrawn by the manufacturer from the market from the end of September 2010. Patients who are normally prescribed this medicine should be switched, by their doctor, to another relevant medicine as soon as convenient.

---

[a] Narrowing of the airways of the lungs
[b] Medical condition characterised by narrowing airways
[c] Disease characterised by airway obstruction
[d] Increased heart rate
[e] Irregular or forceful heartbeat

1.0 INTRODUCTION

(See glossary for explanation of terms used in this document)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest safety updates. In our Public Assessment Reports, we discuss the evidence for a safety issue with a particular drug or drug class, and changes made to the product information for the drug on the basis of this evidence, which will help safeguard public health. This MHRA Public Assessment Report discusses a review of the risks and benefits of orciprenaline sulphate.

The non-selective β-agonist[1] orciprenaline sulphate (also known as metaproterenol sulphate) was originally developed from isoprenaline. Orciprenaline sulphate is the active ingredient of Alupent syrup (10 mg/5 mL), which was registered in the UK in September 1972 and is currently indicated for the relief of reversible airways obstruction and suggested for maintenance therapy. However, the British National Formulary (BNF) considers Alupent less suitable for prescribing than selective β_2 agonists, and states that *"less selective beta$_2$ agonists such as orciprenaline should be avoided whenever possible"*. Following a report from a pharmacist expressing concern at the continued availability of Alupent, a risk-benefit analysis of orciprenaline sulphate was performed. A summary of the data and conclusions from this assessment, along with the actions taken, are presented in the following report.

2.0 SUMMARY OF DATA

2.1 Clinical pharmacology

Following oral administration of orciprenaline sulphate, a peak plasma concentration is reached between 0·75–3h (seven-fold variation among subjects) with a half-life of 2·1 hours[2]. About 60% of an oral dose is absorbed and about 45% is excreted in urine. From the literature, orciprenaline sulphate appears to have little or no β_2-selectivity[1, 3–6].

2.2. Efficacy

A resorcinol substitution in the orciprenaline structure decreases both its β_1 and β_2-related potency when compared to isoprenaline, yet provides only a marginal increase in β_2-selectivity. O'Donnell et al[7] demonstrated that orciprenaline displayed a similar potency to isoprenaline on guinea pig atria and hindlimb blood flow (1·2 and 1·0-fold respectively), but a greater potency on guinea pig trachea blood flow (11-fold). In contrast, the more selective β_2 agonist terbutaline was substantially more selective for the trachea versus atria and hindlimb, with relative potencies versus isoprenaline of 31, 0·036 and 1·7 respectively. In all studies, salbutamol was a significantly more potent bronchodilator than orciprenaline and substantially more selective for β_2 receptors[3, 4].

A number of trials on the efficacy of orciprenaline sulphate have been performed, including those described below:

In a study, 75 children with asthma, aged 2–6 years, were recruited to a 6-week parallel group single-blind study, comparing the efficacy and safety of salbutamol sugar-free syrup (0·1 mg/kg) versus orciprenaline sulphate syrup (0·6 mg/kg)[8]. There was a significant rise during the treatment period in both morning and evening peak expiratory flow rates (PEFR) in the salbutamol group over 6 weeks. However, there were no significant changes in the orciprenaline group. Adverse events occurred in both the treatment groups, but were tolerated and disappeared with continued use of the trial drug in all but two patients in the orciprenaline sulphate group. Pulse rate was significantly increased from baseline values in the orciprenaline sulphate group. The final overall clinical evaluation showed significantly ($p<0·01$) more "improved" (judged by subjective analysis) patients in the salbutamol group.

Another trial compared the acute and chronic effects of salbutamol (2 mg) versus orciprenaline sulphate (10 mg) three times per day over 28 days, in 65 children aged 6–9 years with mild–moderate asthma[9]. Children had to meet the following criteria: (1) a FEV_1 predicted value of 40–80%; (2) a peak flow reversibility of ≥15%; (3) a theophylline level of ≤2 µg/mL; and (4) no significant medical problems other than bronchial asthma. Baseline values were recorded after all bronchodilators had been withheld for 12 hours and long-acting theophylline withheld for 24 hours. Wright peak flow, symptom scores, and rescue medication use were recorded twice daily during the trial. The acute cardiopulmonary effects of the study medications were compared over 8 hours following administration of treatment on days 1 and 28 of the study. Salbutamol syrup produced a significantly greater peak magnitude of bronchodilation than orciprenaline (29% vs 20% above baseline, respectively; $p<0.05$) on treatment day 1. Importantly, salbutamol also had a significantly longer duration of action (8 hours vs 3–4 hours; $p<0.05$). This additional benefit was maintained throughout the study with a similar profile observed on day 28.

Baseline FEV_1 values on day 28 versus day 1 were similar for orciprenaline (+0·5%) but increased for salbutamol (+8·1%; $p<0·05$ vs orciprenaline). There was a trend toward higher morning and evening peak flow measurements during the 28 days of treatment in the salbutamol group. However comparable control of asthma symptoms was provided by both drugs as shown by similar asthma symptoms scores and frequencies of rescue medication use. In line with its lack of β_2-selectivity, there was a significantly greater increase in heart rate seen with orciprenaline than with salbutamol at 1–1·5 hours post-dose on treatment days 1 and 28 ($p<0·05$). No changes in diastolic blood pressure were observed, supporting the conclusion that the effect of orciprenaline on heart rate arose from its direct stimulation of cardiac β_1 receptors.

Apart from their effects on heart rate, the other side effects of both drugs were similar. These findings imply substantial therapeutic advantages of salbutamol syrup over orciprenaline syrup in currently recommended doses with respect to improvement in pulmonary function, effects on heart rate, and the frequency of dosing required to maintain optimum bronchodilation over a 24–hour period.
Hence, none of the results from these trials would support the preferential use of orciprenaline over salbutamol in terms of either efficacy or side effects.

2.3. Safety

Side-effects of β_2-agonists are greatest in severity and frequency when they are administered orally or intravenously. Unwanted β_2-related side effects include muscle tremor, increases in blood glucose and lactate, decreases in serum potassium and serum calcium, palpitations and arrhythmias[10]. Cardiac β_1-related effects include those on heart rate and heart muscle contraction, and are particularly relevant to the use of

the non selective β-agonist orciprenaline, especially as it is only available as an orally-administered syrup.

The risk-benefit assessment summarised in this report was performed as orciprenaline is an older drug and its place in practice required assessment. It also followed a pharmacist's concern about the inappropriate use of orciprenaline, following a Yellow Card[a] report of chest pain, atrial fibrillation and confirmed non-ST elevated myocardial infarction associated with its use. Adverse drug reactions (ADRs) from case reports and clinical trials were assessed and are discussed below.

2.3.1. Case-reports of cardiac-related adverse drug reactions

Disproportionality analyses of cases of ADRs identify drug-event combinations that are being reported unusually frequently compared to the background of other reports in the same database. The Empiric Bayes Geometric Mean (EBGM) gives a statistical estimate of the relative reporting rate (where EB05 and EB95 are the lower and upper bounds of the 2-sided 90% confidence intervals around the EBGM). The size of the EBGM may give some idea about the strength of evidence from case reports for a particular reaction (ie, the larger the value, the stronger the potential association between the drug and the reaction). More than three reports of a reaction, with an EBGM≥2·5 and an EB05≥1·8, is classed as a signal[b].

The EBGM for cardiac ADRs with orciprenaline use is 6·24 compared with 1·85 for salbutamol. However, comparisons of EBGM values across drugs in a class must be interpreted with extreme caution since there are many sources of bias with reporting, and these biases will vary for different drugs. Nevertheless, the data suggest an increased risk of palpitations and tachycardia for orciprenaline with substantially raised EBGM values of 11·94 and 17·5, respectively. In contrast, values for salbutamol are much lower with EBGMs of 2·93 and 2·88 for palpitations and tachycardia, respectively.

These data are also demonstrated graphically in Figure1, with the salbutamol values shown for comparison in Figure 2.

[a] Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our Yellow Card Scheme (www.yellowcard.gov.uk)

[b] An indicator or reported information that suggests that a drug may be associated with a previously unrecognised ADR or an existing ADR that is different from current expectations

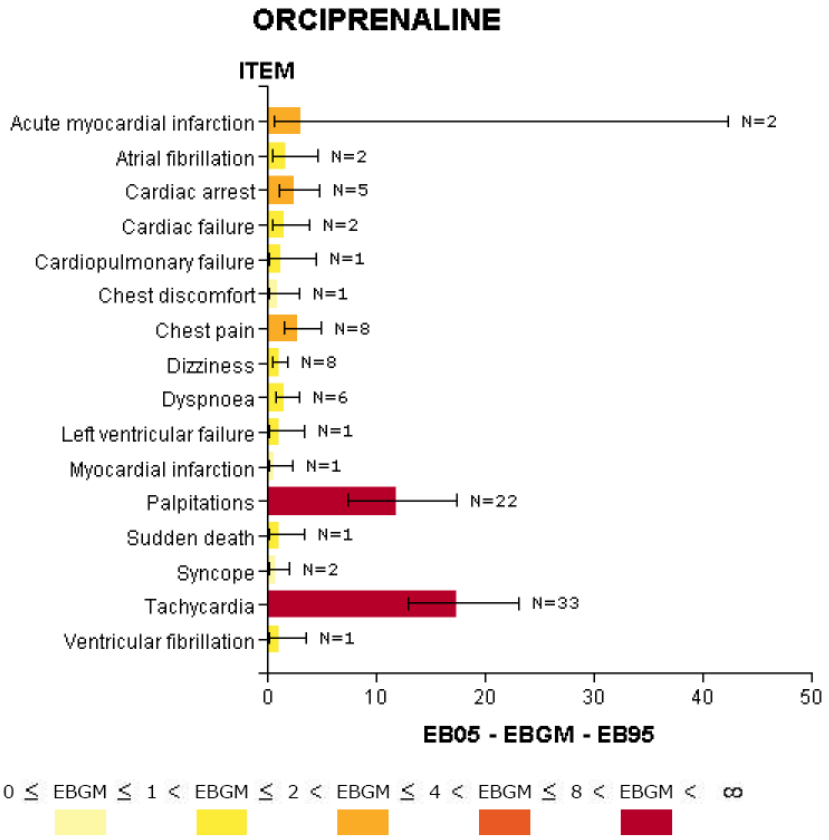

Figure 1: EBGM, EBO5 and EB96 for orciprenaline sulphate for cardiac adverse drug reactions.

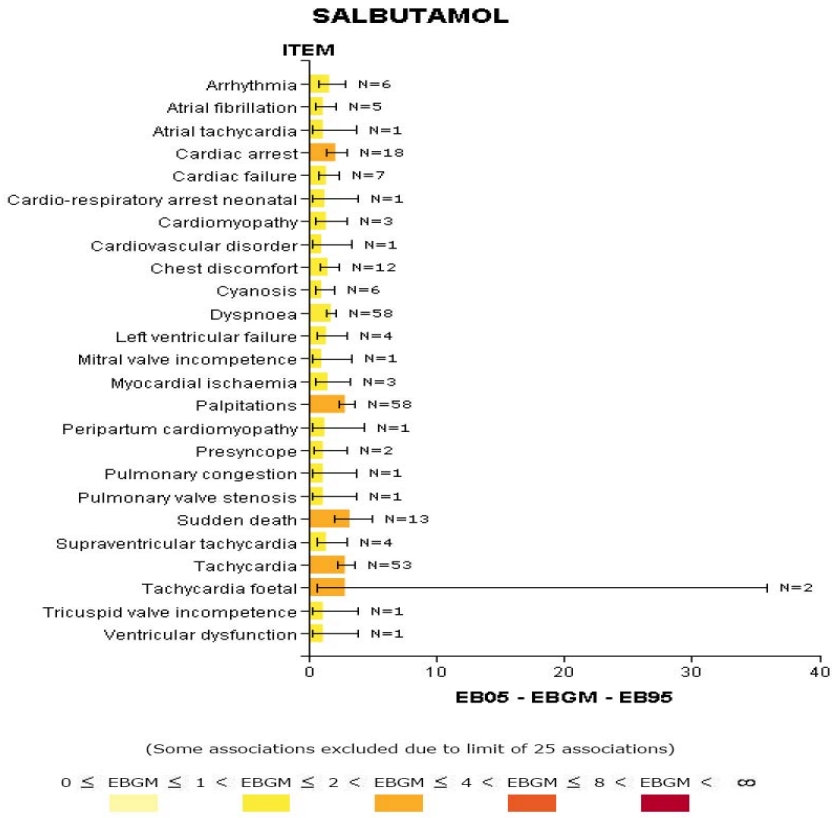

Figure 2: EBGM, EBO5 and EB96 for salbutamol for cardiac adverse drug reactions.

2.3.2. Cardiac ADRs from clinical trials

There are few clinical trials investigating the cardiac side effects of orciprenaline; those that are available date from the 1980s.

A randomised double-blind crossover study compared the β-receptor selectivity of orciprenaline, fenoterol (which is indicated for reversible airways obstruction and has relative β_2 selectivity), isoproterenol and adrenaline in 12 patients aged 21–41 years with stable asthma (mean FEV_1 predicted = 59%)[11]. Patients withheld inhaled β-agonist for at least 6 hours prior to the study. After resting supine, subjects inhaled two puffs (via a metered dose inhaler) of either adrenaline (280 µg/puff), fenoterol (200 µg/puff), isoproterenol (100 µg/puff) or orciprenaline (750 µg/puff) at the following times: 0, 15, 30, 45 and 60 minutes. Measurements of heart rate, blood pressure, total electromechanical systole, QTc interval, plasma potassium and FEV_1 were measured 5 minutes after each dose and 30 minutes after the final dose. Although high doses were used, both fenoterol and orciprenaline had significantly greater effects on heart rate, the force of heart muscle contraction, electrocardiographic readings and blood potassium levels than either isoproterenol or adrenaline ($p<0{\cdot}0042$).

However, despite the worse cardiac side-effect profiles for orciprenaline and fenoterol, there was no difference in the bronchodilator effect between orciprenaline and fenoterol versus isoproterenol.

The cumulative effects of fenoterol and orciprenaline result from the lack of metabolism of either drug within the lung, in contrast to isoproterenol and adrenaline. Despite this, the data demonstrate that fenoterol and orciprenaline increase heart rate and the force of heart muscle contractions. Importantly, substantial changes in QS2I, QTc interval, and plasma potassium occur considerably before maximum bronchodilation is achieved. These data are in line with the study by Wolfe et al[9], demonstrating a greater increase in heart rate following orciprenaline sulphate syrup versus salbutamol syrup in asthmatic children.

2.3.3. Respiratory-related ADRS

No clear safety signal for respiratory-related ADRs with orciprenaline use was detected from either case reports or from clinical trials. There were 22 case reports from Yellow Cards of respiratory ADRs up to June 2009, six of which related to dyspnoea, six to asthma, three to epistaxis and four to status asthmaticus. However, usage of salbutamol was substantially higher, yet cases of status asthmaticus were half (two versus four, respectively).

2.3.4. Other ADRS

A significant ADR associated with the use of β_2-agonists is tremor. The EBGM for tremor associated with orciprenaline is 24·349 (EB05=19·461; EB95=29·301; n=65). For comparison the EBGM for salbutamol is 8.935 (EB05=8.025; EB95=9.922; n=257). Thus the lack of β_2-selectivity of orciprenaline is not reflected in a lower EBGM for a β_2-related side effect. Conversely, the higher incidence of tremor likely results from the greater systemic exposure due to oral administration of orciprenaline.

2.3.5. Other ADRs from clinical trials

Wolfe et al[9] reported no differences between the frequency of side-effects of salbutamol and orciprenaline syrups in a 1-month study of 65 children aged 6–9 years. The most commonly reported side-effects involved the central nervous system, eg, headache, dizziness and hyperactivity/restlessness; and gastrointestinal tract, eg, nausea and vomiting, decreased appetite and stomach ache. One patient in each group reported tremor.

3.0. CONCLUSIONS

Orciprenaline sulphate has been licensed for the relief of reversible airways obstruction since 1972, and is suggested for maintenance therapy. However it has a substantially worse risk-benefit ratio than other more selective β_2-agonists such as salbutamol. In terms of benefit, all of the trials in which salbutamol and orciprenaline were directly compared reported significantly better efficacy for salbutamol. In addition, Wolfe et al[9] highlighted the significantly shorter duration of action of orciprenaline compared with salbutamol.

In terms of risk, due to its lack of β_2-selectivity, orciprenaline produces similar increases in heart rate and contractile force as isoprenaline which may explain the substantially raised EBGMs for the cardiac ADRs tachycardia and palpitations with orciprenaline use. Clinical trial data supports the conclusions of the case report assessments, and demonstrates clear effects of orciprenaline on heart rate and force of heart muscle contractions, even when administered via inhalation. Even β_2-related side effects of orciprenaline are substantial with Yellow Card data, revealing a significantly raised EBGM for tremor.

Taking all data into consideration and given the fact that more selective β_2-agonists are currently available, the risk-benefit assessment concluded that there was no justification for the continued licensing of orciprenaline. Following this advice, orciprenaline sulphate (Alupent Syrup) will be voluntarily withdrawn by the manufacturer from the market from the end of September 2010. Patients who are prescribed this medicine should be switched, by their doctor, to another relevant medicine as soon as convenient.

4.0 REFERENCES

1. Daly MJ et al. Comparison of the bronchodilator and cardiovascular actions of salbutamol, isoprenaline and orciprenaline in guinea-pigs and dogs. *Br J Pharmacol* 1971; **43**: 624–638.
2. Hatch K et al. Relative bioavailability of metaproterenol in humans utilizing a single dose, stable isotope approach. *J Pharm Sci* 1986; **75**: 886–890.
3. Farmer JB et al. A comparison of the β-adrenoceptor stimulant properties of isoprenaline, with those of orciprenaline, salbutamol, soterenol and trimetoquinol on isolated atria and trachae of the guinea pig. *J Pharm Pharmacol* 1970; **22**: 61–63.
4. Brittain RT. A comparison of the pharmacology of salbutamol with that of isoprenaline, oricprenaline and trimetoquinol. *Postgrad Med* 1971; **47**(Suppl): 11–16.
5. Brittain RT et al. Sympathomimetic bronchodilator drugs. *Pharmacol Thera Bull* 1976; **2**: 423.
6. Shanks RC et al. Stimulation of adrenergic β-receptors by orciprenaline. *BMJ* 1967; **1**: 610–612.
7. O'Donnell SR et al. Potency and selectivity in vitro of compounds related to isoprenaline and orciprenaline on β-adrenoceptors in the guinea-pig. *Br J Pharmacol* 1974; **52**: 407–417.
8. Loftus G et al. A Multicentre comparison of salbutamol syrup with orciprenaline syrup in children aged 2-6 years with chronic reversible airways obstruction. J Allergy Clin Immunol 79, 151:Abstr.108 1987
9. Wolfe JD et al. Comparison of albuterol and metaproterenol syrup in the treatment of childhood asthma. *Pediatrics* 1991; **88**:312–319.
10. Sears MR, Latvall J. Past, present and future-[beta]2-adrenoceptor agonists in asthma management. *Respir Med* 2005 February; **99**(2): 152–170.
11. Burgess CD et al. Lack of evidence for beta-2 receptor selectivity: a study of metaproterenol, fenoterol, isoproterenol and epinephrine in patients with asthma. *Am Rev Respir Dis* 1991; **143**: 444–446.

5.0 GLOSSARY

β-receptors
A type of cell **receptor** in a part of the body's nervous system called the sympathetic system. Their stimulation causes relaxation and widening of the airways

Acute
Marked by a rapid onset, intense severity and brief duration

Adrenaline
A chemical produced by a part of the body called the adrenal gland, which increases heart rate and breathing

Asthma
A condition characterised by narrowed airways, in which patients experience symptoms of cough, wheezing and difficulty breathing

Atria
The two upper chambers of the heart

Bronchodilator
A drug that widens airways

Cardiac
Related to the heart

Chronic
Marked by a long duration, and by frequent recurrence over a long time

Clinical trial
A research study which tests the effectiveness and safety of medicines in humans

Confidence intervals (CI)
A statistical range of values, with a certain probability that the true value is contained within this range. It is also a statistical method of assessing the true difference in risk between two groups. A 90% CI means that the true value (or difference in values) has a 90% chance of being in this range.

Diastolic blood pressure
Blood pressure measured during diastole (ie, when the lower chambers of the heart are filling with blood)

Disproportionality analysis
Statistical methods used to analyse and understand the association between drugs and adverse events

Dyspnoea
Difficulty in breathing

Efficacy
The effectiveness of a medicine measured under investigational circumstances

Epistaxis
Bleeding from the nose

Fibrillation
Irregular contractions of the heart chambers

Forced expiratory flow between 25%–75% of exhalation ($FEF_{25–75\%}$)
The average flow (or speed) of air coming out in the middle of an exhaled breath (measured as part of test of lung function)

Forced expiratory volume in one second (FEV_1)
The volume of air exhaled in 1 second (measured as part of test of lung function)

Forced vital capacity (FVC)
A patient is asked to take the deepest breath they can, then to exhale it as hard as possible, for as long as possible (measured as part of test of lung function)

Half-life
The time required for the concentration or amount of drug in the body to be reduced by half

Isoprenaline
A drug that excites **β-receptors** in the body (also known as **isoproterenol**), increasing heart rate and relaxing the airways

Isoproterenol
See **isoprenaline**

Maintenance therapy
Added treatment given to a patient for a disease or condition to help the original treatment succeed

Myocardial infarction
Death of a segment of heart muscle after its blood supply is interrupted due to a blood clot in an artery (also known as a heart attack)

Non-selective β-agonist
A drug that acts at all **β-receptor types** on nerve cells, rather than selectively acting at either the β_1, β_2, or β_3 receptors

Palpitations
Awareness of the heartbeat

Parallel group single-blind study/trial
A **clinical trial** in which each participant receives one of several pre-defined treatment options, without knowing exactly what treatment it is

Peak expiratory flow rates (PEFR)
The maximum rate at which a person can forcibly exhale a breath (measured as part of test of lung function)

Peak flow reversibility
PEFR is decreased in some individuals; if PEFR increases after treatment with **bronchodilators** or steroids, it is classed as 'reversible'. Reversible peak flow is a characteristic of airway diseases such as **asthma**

Peak plasma concentration
The highest level of a drug that can be found in the blood, usually following multiple doses

Potency
The power of a medicine to produce desired effects

Pulmonary
Related to the lungs

QTc interval
Part of the electrical signal produced by the heart, which can be seen on an electrocardiogram (a machine used to show the electrical activity of the heart)

Randomised crossover study
A **clinical trial** in which a one of two or more treatments is randomly assigned to each participant and the outcome measured; then, after a suitable interval, the other treatment is given to the participants and the outcome measured again

Receptor
A structure on the surface of a cell to which specific substances can bind, causing a change within the cell and resulting in an effect on the body

Rescue medication
A type of medication used by patients with asthma to relieve its symptoms

Resorcinol
A drug that causes the skin to peel (used to treat skin conditions such as acne)

Salbutamol
A drug that stimulates β_2 receptors and is used to relieve symptoms of **asthma** and other reversible obstructive airway diseases

Spirometric indices
Measures of lung function

Status asthmaticus
A severe attack of **asthma** that often follows a period of poorly controlled asthma

Supine
Lying on the back with the face upwards

Systole
The period during heart contraction

Tachycardia
An abnormal increase in heart rate

Theophylline
A drug that relaxes and widens the airways

Trachea
The main part of the airway from the voicebox in the throat to the airways descending into the lungs

Vital signs
Measurements of body temperature, blood pressure, heart rate and breathing rate