Andrzej Emeryk¹, Justyna Emeryk-Maksymiuk²

¹Department of Pediatric Pulmonology and Rheumatology Medical University in Lublin, Poland

²Chair of Internal Medicine and Department of Internal Medicine in Nursing Medical University in Lublin, Poland

Short-acting inhaled β_2 -agonists: why, whom, what, how?

Abstract

We showed the present data about the efficacy and safety of inhaled short-acting β_2 -agonists (SABA), such as salbutamol and fenoterol, in the management of obstructive diseases in children and adults. Our work discusses major mechanisms of action, clinical effects, possible side effects and indications of inhaled SABA. We presented current recommendations for the position of SABA in the therapy of obstructive diseases in children and adults, particularly in asthma and chronic obstructive pulmonary disease.

Key words: short-acting β_2 -agonist, salbutamol, fenoterol, inhalation, nebulization, asthma, COPD

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Introduction

Short-acting β_2 -agonists (SABA) stimulate β_2 -adrenergic receptor (β_2 -AR). They are called β_2 -mimetics or β_2 -agonists. First selective SABA widely used in clinical practice appeared more than 50 years ago. They were introduced to the global market in the following order: terbutaline (1966 yr.), salbutamol (1968 yr.) and fenoterol (1970 yr.) [1]. Next drugs, such as levalbuterol, reproterol, rimeterol, klenbuterol and pirbuterol, were introduced afterwards [2–4]. Short-acting β_2 -agonists are selective agonists of β_2 -AR, however they differ in their degree of selectivity. Salbutamol (albuterol) is the most used SABA in the world — in US it took 9th place on the list of prescribed medicines in 2016 (70 million of prescriptions) [5]. According to World Health Organization (WHO) salbutamol ranks among the most effective and safest medicines essential to health care systems [6]. Racemic salbutamol is an equal (1:1) mixture of R-salbutamol (levalbuterol) and S-salbutamol isomers. R-isomer of salbutamol is a pharmacologically active compound which exhibits many clinical effects, including potent bronchodilation [7]. Suppression of bronchoconstriction and bronchodilation occur 5 minutes

after administration of inhaled salbutamol, but the duration of action does not exceed 4–6 hours (Figure 1) [8].

Drugs from this group provide effective protection against exercise-induced bronchoconstriction within 0.5–2.0 hours also against bronchoconstriction triggered by exposure to sensitizing allergen [9, 10]. Clinical studies show more potent bronchodilation and less side effects of R-salbutamol in comparison with racemic salbutamol [11–13]. High cost of levalbuterol justifies, however, its administration only in selected clinical conditions [13].

Salbutamol versus fenoterol

Two inhaled drugs from SABA group are available in Poland: salbutamol and fenoterol. Table 1 shows their most important properties.

Data in the table demonstrate that β_2/β_1 (selectivity index) stimulation index is 10 times greater for salbutamol than fenoterol. Having in mind similar stimulation of β_2 receptors by both drugs (0.55 salbutamol vs 0.60 fenoterol), it means that salbutamol exerts more selective β_2 -AR stimulation vs fenoterol and both cause similar bronchodilation. Studies from the 1990s

Address for correspondence: Andrzej Emeryk, Department of Pediatric Pulmonology and Rheumatology Medical University in Lublin, Lublin, Poland;

e-mail: andrzejemeryk@plusnet.pl

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Figure 1. Effect of single dose of salbutamol, formoterol, and salmeterol on FEV₁ value in asthma patients [8].
FEV₁ — forced expiratory volume in the first second

Table 1. Comparison of short-acting β_2 -agonists' (salbutamol and fenoterol vs isoproterenol) ability to stimulate β -adrenergic receptors (β_1 , β_2 , β_3) [14, 15]

	β_1 inotropic activity (atrium)	β_2 dilatory activity (bronchi)*	β_3 lipolytic activity (adipocytes)	β_2/β_1 index
Isoproterenol	1,0	1,0	1,0	1,0
Salbutamol	0,0004	0,55	0,002	1375
Fenoterol	0,005	0,6	0,02	120

*Increase in FEV₁ (forced expiratory volume in the first second) $\geq$ 15% from baseline

proved similar or better clinical efficacy and better safety of salbutamol in comparison with inhaled fenoterol in different age groups of asthma patients [16, 17]. Better safety is also a result of the fact that salbutamol shows more features of β_2 -AR partial agonist than fenoterol. It determines that asthma patients using salbutamol have lower risk of death vs patients using fenoterol [17, 18]. It should be stressed that adverse effects of fenoterol increase in hypoxemia, which occurs during severe and prolonged episode of bronchoconstriction [19].

Clinical effects of SABA

Short-acting β_2 -agonists in conditions with bronchoconstriction exert many following clinical effects [1, 15]:

- bronchodilation (removal of bronchial smooth muscles constriction);
- prevention of bronchoconstriction induced by different bronchoconstrictive factors;

- reduction of capillary permeability (reduction of plasma exudate);
- suppression of sensory nerves activation;
- improvement of mucociliary clearance;
- dilatation of pulmonary vascular bed (decrease in pO₂);
- increased release of surfactant.

They can depend on the polymorphism of gene encoding β_2 -AR located on chromosome 5q31-q32 [20, 21]. Some studies showed relationship between response to SABA, course of asthma and the polymorphism of gene encoding β_2 -AR [22]. It is mainly about 2 polymorphisms: genotype Arg/Arg at codon 16 of gene encoding β_2 -AR and Gln/Gln at codon 27 of this gene. It was revealed that homozygotes for Arg/Arg at codon 16 of gene encoding β_2 -AR with chronic obstructive pulmonary disease (COPD) are predisposed to more severe clinical course of the disease [23]. Similar relationship was shown in patients with cystic fibrosis with altered response to SABA [24].

Short-acting β_2 -agonists usage can be associated with many side effects described many years ago [25]: tachycardia, skeletal muscle tremor, hypokalaemia, increased level of lactic acid in plasma (lactic acidosis), headaches, hyperglycaemia. Systemic side effects are observed rarely after inhalation administration and increased risk of cardiovascular side effects appear in patients with comorbid cardiovascular disease, especially in the elderly [26, 27]. It is worth mentioning that paradoxical bronchoconstriction after inhalation of SABA occurs in 4.4% of the general population [28].

There are additional possible side effects and adverse clinical effects when SABA are used in asthma. These effects occur in patients receiving SABA as monotherapy or/and if SABA are used very often or regularly without inhaled corticosteroids (ICS). It can lead to increased risk of the following adverse outcomes [29–35]:

- decrease in the number and sensitivity of β_2 -AR;
- diminished bronchial response to SABA or/and LABA;
- increased bronchial hyperresponsiveness;
- increased allergic reactions and eosinophilic airway inflammation;
- increased risk for asthma exacerbation (with regular or frequent use: ≥ 3 SABA canisters/year, average 1.7 puffs/day);
- increased risk of death in patients with asthma (≥ 11 SABA canisters/year);
- deterioration in spirometric parameters.

These facts which are known for many years and other new clinical evidences for efficacy and safety of SMART therapy (Single Maintenance and Reliever Therapy) changed the perception of the role and place of SABA in the management of asthma in last Global Initiative for Asthma report (GINA) 2019 [36], which will be discussed further below. Another way of limiting the SABA overuse relies on monitoring use of SABA by patients preferably with electronic inhalers [37,

38], including inhalers transmitting information to the health care system in real time [39].

Salbutamol in pressurised metered-dose inhaler in comparison to other pharmaceutical forms of SABA

Short-acting β_2 -agonists have different routes of administration (inhalation, oral and intravenous), because they are available in different pharmaceutical forms. Many forms of salbutamol are available [40]:

- inhalation aerosol (suspension) from pressurised metered-dose inhaler (pMDI) (children and adults);
- powder from dry powder inhaler (DPI), types: Diskus (children over 4 years and adults), Turbuhaler (children over 3 years and adults) and Easyhaler and (children over 4 years, adults);
- inhalation solution for nebulizers (children and adults);
- sirup (children over 2 years, adults);
- tablets (children over 2 years, adults);
- solution for injection (adults).

Inhalation is the most effective way of SABA therapy in airway diseases. Oral therapy can be alternative only exceptionally in small children, who do not accept inhalation or cannot inhale properly [38]. Additional parenteral therapy (salbutamol) is necessary rarely in patients with severe exacerbation of asthma, who do not respond to proper inhalation therapy [41].

Inhalation formulations of SABA most often used are listed in Table 2 [43].

According to table 2, four inhalation formulations of salbutamol are available: pMDI, pressurised metered-dose inhaler — breath actuated pMDI (pMDI-BA), DPI and inhalation solution for nebulizers; fenoterol is available only as pMDI. The expected therapeutic clinical effects and probability of side effects can depend on the choice of SABA inhalation method. Below we present the most important rules of SABA inhalation therapy:

Table 2. Inhalation formulations of SABA and SABA/ipratropium bromide combinations. Abbreviations according to [44]

Type of inhaler	pMDI	pMDI-BA	MDLI (respimat)	DPI	Nebulization
Salbutamol	+	+	–	+	+
Fenoterol	+	–	–	–	–
Salbutamol + ipratropium bromide	+*	–	+	–	+
Fenoterol + ipratropium bromide	+	–	+	–	+

pMDI — pressurised metered-dose inhaler; pMDI-BA — pressurised metered-dose inhaler — breath actuated; MDLI — metered dose liquid inhaler; DPI — dry powder inhaler

1. pMDI with properly fitted inhalation chamber is preferred method of SABA inhalation in children below 6 years, irrespective of severity of asthma attack, place of administration (home, admission ward, clinical ward, intensive care unit) [36, 45, 46].
2. Dose of salbutamol from pMDI depends mainly on the severity of asthma attack, not on patient age. According to GINA 2019 report during the first hour children below 6 years can receive up to 6 puffs, older children and adults can receive up to 12–30 puffs [36].
3. Salbutamol can be inhaled from DPI (e.g: Diskus and Easyhaler) in children above 6 years and adult with asthma, which provides similar clinical efficacy to pMDI [36].
4. Nebulization with pneumatic nebulizer — both intermittent and continuous — should be used in case of insufficient response or lack of response to SABA and life-threatening bronchoconstriction [36, 48, 49]. In adults with severe exacerbation of asthma continuous nebulized salbutamol more effectively improves lung function than intermittent nebulization [50].
5. Clinical effects of salbutamol nebulization to a considerable degree depend on the type of nebulizer: breath actuated pneumatic nebulizer provides better effect than continuous nebulization and mesh nebulizer in comparison to pneumatic nebulizer [51, 52].

Table 3. Current indications for SABA in children and adults [36, 55–64]*

Disease/state	Indications	Comment
Asthma	Attacks of dyspnoea, cough, and wheeze Disease exacerbations Prevention of exercise-induced bronchoconstriction Prevention of bronchoconstriction triggered by allergen exposure	Alternative to SMART therapy in patients < 12 years Always with ICS — evidence A
Obstructive bronchitis — so-called early childhood asthma	Exacerbation of bronchoconstriction	First-line treatment Number of doses should be adjusted to the patient's clinical condition
Stable COPD	Initial treatment — dyspnoea attack or/and respiratory difficulties As-needed SABA	— Only patients from group A — Reduction in symptoms and an increase in FEV ₁ — evidence A — Combination of SABA + SAMA is superior to SABA or SAMA alone (symptoms and FEV ₁) — evidence A
COPD — exacerbation	Acute exacerbation of disease SABA added to other medication	Increase the dose or frequency of SABA or combine SABA and SAMA in the initial treatment of acute exacerbation — evidence C
Bronchiolitis	Selected cases with confirmed positive clinical response to treatment	In most cases there are no indications to routine therapy
Cystic fibrosis	Pulmonary exacerbation with features of bronchoconstriction and confirmed positive clinical response or in patients with positive BDR test, before inhalation of hypertonic saline	Rather commonly used, however recommendations are not explicit
Transient tachypnoea of the newborns		Very poor evidences for the efficacy
Chronic lung disease in premature babies	Prevention and treatment	Poor evidences for the efficacy
Familial dysautonomia	SABA + SAMA	1 study confirming SABA efficacy
Other diseases with reversible bronchoconstriction	Acute chest syndrome in sickle cell disease	Further studies are needed
Bronchodilator reversibility (BDR) test	Spirometric features of bronchoconstriction (FEV ₁ /%FVC < 80 % predicted value, FEV ₁ /VC < 80% predicted value, PEF < 80% predicted value)	2–4 puffs of salbutamol pMDI + inhalation chamber as the standard of BDR test

*One shouldn't be afraid of administration of SABA (salbutamol) in the elderly (> 90 years) [65] FEV₁ — forced expiratory volume in the first second; ICS — inhaled corticosteroids; COPD — chronic obstructive pulmonary disease; SABA — short-acting β_2 -agonists; SAMA — short-acting muscarinic antagonists; SMART — Single Maintenance and Reliever Therapy

Table 4. Initial emergency (as-needed) pharmacotherapy of asthma according to GINA 2019 report [36]

Age group	Preferred management	Alternative management	Comments
Patients ≥ 12 years	Low dose ICS-formoterol — Step 1–5 treatment	SABA pMDI, pMDI-BA SABA pMDI + IC SABA DPI— Step 1–5 treatment	ICS: budesonide or beclometasone
Patients 6–11 years	SABA DPI SABA pMDI + IC SABA DPI — Step 1–5 treatment	Low dose ICS-formoterol — Step 3–5 treatment*	*Children receiving ICS-formoterol combination as maintenance
Patients 5 years and younger	SABA “as-needed” pMDI + IC — Step 1–4 treatment	SABA “as-needed” by nebulizer — Step 1–4 treatment	Proper use of the equipment and estimation of appropriate dose of the drug are required

DPI — dry powder inhaler; ICS — inhaled corticosteroids; IC — inhalation chamber; pMDI — pressurised metered-dose inhaler; SABA — short-acting β_2 -agonists

- Parenteral, oral, or nebulized SABA are associated with increased risk of side effects (tachycardia, muscle tremor, headaches, hypokalaemia). In this respect inhalation from pMDI is the safest method [53, 54].
- Short-acting β_2 -agonist (alternatively in combination with ipratropium bromide) in pMDI + IC or in nebulization is the first-line initial treatment of acute exacerbation of COPD [55]. Dose of SABA from pMDI: 1–2 puffs every hour for the first 2–3 hours of treatment, then 1–2 puffs every 2–4 hours depending on the response to the treatment [56].
- Patients with COPD should receive air-driven nebulization of SABA, but not high-flow oxygen-driven nebulization to avoid hypercapnia in patients with chronic respiratory failure [57].

Indications to SABA

Short-acting β_2 -agonists have been very important drugs for many years used in the management of various bronchoconstrictive diseases in children and adults. Indications for their administration were collected in Table 3.

Current place of SABA in the management of asthma is defined by GINA 2019 report, which considerably changes former recommendations (tab. 4) [35]. Experts in this report do not recommend SABA monotherapy in all age groups (look tab. 3) because of patient's safety. Each SABA (regardless of its inhalation formulation) should be used simultaneously with ICS — from one or separate inhalers (or sometimes with oral/parenteral corticosteroid).

GINA 2019 report based on high-quality clinical studies recommends the following as-needed (emergency) step 1–5 treatment in patient ≥ 12 years: low dose ICS in combination with formoterol [36]. As-needed SABA from pMDI or

DPI remains alternative option (worse regarding the efficacy and safety). In children 6–11 years preferred emergency management is administration of SABA from pMDI + inhalation chamber in combination with ICS (any medication) or oral corticosteroid [36]. Administration of SABA from pMDI + inhalation chamber: 4–10 puffs for every 20 minutes for the first hour of symptoms. Budesonide in combination with formoterol in SMART therapy model is alternative option for some children [36]. In group of children up to 5 years the only option of emergency treatment is SABA „as-needed” — from pMDI + inhalation chamber (preferred management) or in nebulization (alternative management) in all asthma steps [36].

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