

BETA2-ADRENERGIC BRONCHODILATOR DRUGS USED TO TREAT ASTHMA IN ORADEA CITY

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Abstract

Asthma is a chronic disease characterized by chronic inflammation of airways and bronchial hypersensitivity that lead to bronchoconstriction, edema, cough, wheezing, dispnoea and hypersecretion of mucus.

We have studied five bronchodilators: three short-acting beta2-adrenergics (fenoterol, salbutamol, terbutaline) and two long-acting beta2-adrenergics (formoterol and salmeterol). The drugs were issued from the pharmacy as 13 pharmaceuticals. Except salbutamol, the short-acting bronchodilators have currently a low use in asthma therapy with the main indication for the treatment of asthma exacerbations. The long-acting bronchodilators are very effective in long-term treatment. Their efficiency is much higher in association with anti-inflammatory corticosteroids which decrease the airway inflammation. The multi-ingredient preparations such as salmeterol-fluticasone (Seretide) and formoterol-budesonide (Symbicort) combinations are most recommended in the maintenance treatment of asthma.

Key words: asthma, bronchoconstriction, wheezing, dispnoea, beta2-adrenergic bronchodilators, airways inflammation.

INTRODUCTION

Asthma is a chronic disease of the airways. According to American Thoracic Society and Global Initiative for Asthma (GINA), asthma is a syndrome characterized by chronic inflammation of airways and bronchial hypersensitivity that lead to bronchoconstriction, edema, cough, wheezing, dispnoea and hypersecretion of mucus (Sur G., 2004; GINA, 2009).

Asthma may occur in all age categories but usually begins in early childhood: half of the cases begins before the age of 10 years with a maximum at the age of 3 years. Asthma is more common in men until puberty and occurs more often in women between puberty and menopause. Studies show that some asthmatic children become asymptomatic at adolescence but the disease can return at adult age. Asthmatic adults, particularly those with onset in maturity, are usually symptomatic (Sur G., 2004; Neamțu M.L., 2003).

Asthma is a common illness worldwide. In the last 30 years, the incidence of asthma has increased to 10-15% in developed countries and the number of cases of asthma is increasing. In Romania, the prevalence of asthma is about 6%. In 2009, asthma affected about 300 million people and it caused 250,000 deaths globally. Currently, asthma affects 22 million

people in the United States being the most common chronic disease among children and a frequent cause of their hospitalization. Increased incidence of asthma is a consequence of air pollution (GINA, 2009; <http://emedicine.medscape.com>; Miller R.L., Ho S.M., 2008; <http://www.ncbi.nlm.nih.gov>; <http://www.nlm.nih.gov>; Cristea A.N., 2005; <http://www.emcb.ro>; <http://www.nowpublic.com/world>).

MATERIAL AND METHOD

Adequate asthma control is a major challenge today. According to current clinical criteria, a high number of patients remain uncontrolled or inadequately controlled despite the existence of effective therapies for asthma control (Chapman K.R. et al., 2008; van den Nieuwenhof L. et al., 2008).

Table 1

Short-acting beta2-adrenergic bronchodilators

Item No.	International common name	Proprietary name	Pharmaceutical presentation	Pharmaceutical company
1.	SALBUTAMOL	VENTOLIN INHALER 100 µg/dose	aerosol	GlaxoSmithKline
		VENTOLIN 5 mg/dose	inhalation solution	GlaxoSmithKline
		SALBUTAMOL 5 mg/2 ml	syrup	Eipico
2.	TERBUTALINE	BRICANYL 0.5 mg/dose	aerosol	AstraZeneca
		AIRONYL 1.5 mg/5 ml	syrup	Eipico
3.	FENOTEROL	BEROTEC N 200 µg/dose	aerosol	Boehringer Ingelheim Pharma GmbH & CoKg
4.	FENOTEROL + IPRATROPIUM BROMIDE	BERODUAL N 50 µg/20 µg/dose	aerosol	Boehringer Ingelheim Pharma GmbH & CoKg

Many patients do not know exactly what bronchodilator to use and show an overconfidence in short-acting beta2-adrenergic bronchodilators that treat only the symptoms but not the inflammation of airways, the major cause of asthma. According to clinical studies, the chronic administration of

large doses of short-acting beta2-bronchodilators increases the incidence of death from asthma (Crane J. et al., 1989; <http://www-archive.thoracic.org>).

The purpose of this paper was the study of some beta2-adrenergic bronchodilators issued by medical prescription between 2008-2013 in a community pharmacy in Oradea. Following the turnover of these products, we tried to make a determination of growth or decline in the consumption of these drugs for a period of six years. Because these products are released by medical prescriptions that remain at the pharmacy, we could determine exactly the quantity necessary to accomplish the pharmacological effect and not the marketing of these pharmaceutical products.

We have studied five bronchodilators: three short-acting beta2-adrenergics (fenoterol, salbutamol, terbutaline) and two long-acting beta2-adrenergics (formoterol and salmeterol). The drugs were issued from the pharmacy as 13 pharmaceuticals as can be seen in tables 1-2 (Paşcalău S., 2014).

Table 2

Long-acting beta2-adrenergic bronchodilators

Item No.	International common name	Proprietary name	Pharmaceutical presentation	Pharmaceutical company
1.	FORMOTEROL + BUDESONIDE	SYMBICORT TURBUHALER 4.5 µg/80 µg/dose	aerosol	AstraZeneca
		SYMBICORT TURBUHALER 4.5 µg/160 µg/dose	aerosol	AstraZeneca
		SYMBICORT TURBUHALER 9 µg/320 µg/dose	aerosol	AstraZeneca
2.	SALMETEROL XINAFOATE + FLUTICASONE PROPIONAT	SERETIDE DISKUS 50 µg/100 µg/dose	aerosol	GlaxoSmithKline
		SERETIDE DISKUS 50 µg/250 µg/dose	aerosol	GlaxoSmithKline
		SERETIDE DISKUS 50 µg/500 µg/dose	aerosol	GlaxoSmithKline

RESULTS AND DISCUSSION

From the studied data we found that the pharmaceutical products containing short-acting bronchodilators have currently a low use in therapy (Table 3). For instance, there is not any drug containing terbutaline and the fenoterol products (Berotec and Berodual) were released in very low amounts. Even if the drugs in these pharmaceuticals are selective beta-bronchodilators, their short duration of action gives them the main indication in the asthma exacerbation therapy. In addition, some first generation selective beta-adrenergics present severe side effects. A very convincing example is fenoterol which was suspected to be the cause of death of some patients who have used this drug (Paşcalău S., 2014).

Table 3

The amount of pharmaceuticals containing short-acting beta2-bronchodilators issued during the years 2008-2013

Item No.	Proprietary name	2008 boxes	2009 boxes	2010 boxes	2011 boxes	2012 boxes	2013 boxes
1.	VENTOLIN Inhaler CFC-Free	299	271	258	249	202	175
2.	VENTOLIN inhal. sol.	4	13	26	30	29	37
3.	SALBUTAMOL syrup	186	144	91	27	52	68
4.	BEROTEC N aerosol	18	12	5	6	10	15
5.	BERODUAL N aerosol	0	2	13	13	13	4

The exception in this class is represented by salbutamol (Fig. 1, Table 3) which is very efficient and selective and the most frequently used. More of this, lower price of salbutamol preparations compared to modern long-acting bronchodilators make this drug accessible to a large number of patients.

Salbutamol is administered as pressurized aerosols (Ventolin Inhaler), by inhalation (Ventolin inhal sol) or orally as a syrup (Salbutamol syrup). Inhaled administration has the advantage of high bronchodilator effect and reduced systemic effects compared to oral administration which explains the high percentage of Ventolin Inhaler release. Even so its short duration of

action influences the frequency of use, the drug registering currently a decline. Compared to 2008, its release decreased about 50%.

Products for children, such as Salbutamol syrup, recorded also a decrease of 50% in 2010 compared to 2008. A sudden decrease was recorded in 2011 due to blocked imports from Egypt (Egyptian revolution). Slight increases were recorded in the next years with no return to 2008 values. Oral administration has a slow onset but prolonged action and is useful for asthma crisis prevention or when inhalation is not possible (children under 2-3 years). Because of the higher plasma level, the side effects are more frequently compared when inhaled.

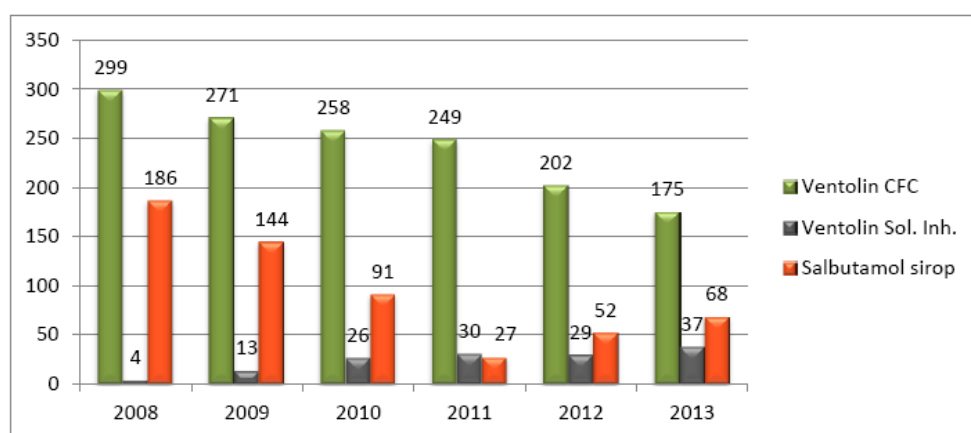


Fig. 1. The pharmaceuticals containing short-acting beta2-bronchodilators issued during the years 2008-2013

Ventolin inhal. sol. showed a significant increase (about 10 times) in 2013 compared to 2008. This growth is due to the absence of syrups and the occurrence of aerosol devices on the market in Romania. Aerosol versus syrup administration of salbutamol to children has the advantage of rapid absorption and reduced side effects (e.g. diarrhea, very common in the case of oral administration).

Very effective in the treatment of asthma are the drugs containing a long-acting beta2-bronchodilator and an inhaled corticosteroid such as salmeterol-fluticasone (Seretide) and formoterol-budesonide (Salmeterol) combinations. Due to the complementary effects of the components, multi-ingredient preparations manifest fast effect at low doses and give good results in the maintenance treatment of asthma (Table 4, Fig. 2).

Seretide Diskus 50/100 was very rarely recommended by doctors. Although the low doses would result in reduced side effects, the therapeutic effect is probably not achieved in many patients. The same situation is found in the case of Symbicort 80/4.5.

Table 4

The amount of pharmaceuticals containing long-acting beta2-bronchodilators issued during the years 2008-2013

Item No.	Proprietary name	2008 boxes	2009 boxes	2010 boxes	2011 boxes	2012 boxes	2013 boxes
1.	SERETIDE 50/100	6	3	0	0	0	0
2.	SERETIDE 50/250	27	44	47	25	19	16
3.	SERETIDE 50/500	67	69	74	39	53	37
4.	SYMBICORT 80/4.5	0	3	4	0	0	0
5.	SYMBICORT 160/4.5	0	7	20	35	30	8
6.	SYMBICORT 320/9	0	4	11	17	11	8

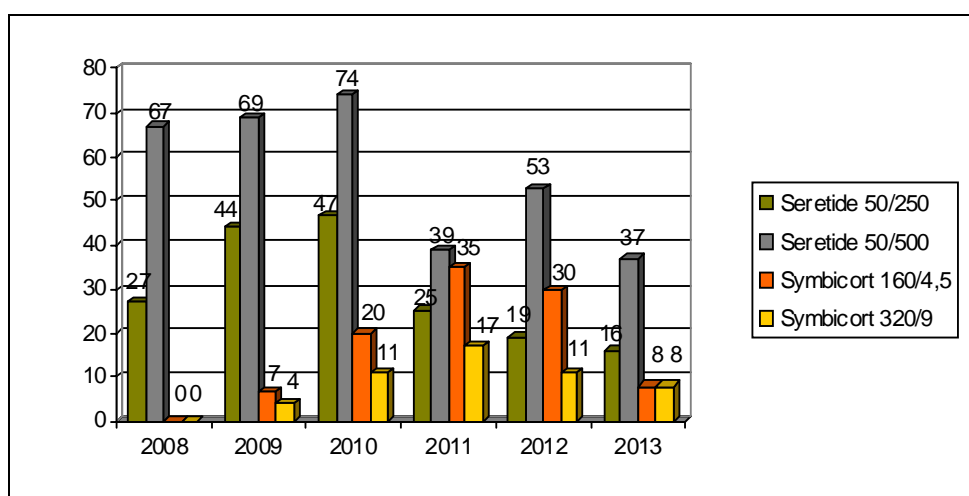


Fig. 2. The pharmaceuticals containing long-acting beta2-bronchodilators issued as multi-ingredient preparations during the years 2008-2013

The most recommended product was Seretide Diskus 50/500. Therapeutic use of this drug increased slightly in 2008-2010 and declined in 2011-2013. The minimum was recorded in 2013 when the Glaxo cards program stopped at July 1st, 2013. Based on a national program established between the Ministry of Health, National House for Health Insurance and

Glaxo Pharmaceutical Company, the company supported some part of the drug's price as a discount for patients until July 2013. Seretide Diskus 50/250 shows a variation similar to Seretide Diskus 50/500 but at lower values.

Among the medicines containing formoterol, the most recommended was Symbicort 160/4.5 with high values in 2011-2012 but lower than Seretide Diskus 50/500. In 2013, in order to support the patients, the Ministry of Health and AstraZeneca Pharmaceutical Company established together the program called "patient on the first". The purpose of this program is to increase the patients' accessibility to this drug.

CONCLUSIONS

The study of five bronchodilators with different duration of action showed that the pharmaceutical products containing short-acting beta2-adrenergic bronchodilators (salbutamol, terbutaline, fenoterol) have currently a low use in asthma therapy. Their short duration of action associated to some severe side effects indicate these compounds in the treatment of asthma exacerbations.

On the other side are the bronchodilators manifesting long duration of action. Taking into account that asthma is a chronic disease, such drugs are very effective in long-term treatment. Their efficiency is much higher in association with anti-inflammatory corticosteroids which decrease the airway inflammation as one of the disease causes. The multi-ingredient preparations such as salmeterol-fluticasone and formoterol-budesonide combinations are most recommended in the maintenance treatment of asthma.

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