

Sales of Medication for Obstructive Pulmonary Diseases and Asthma Mortality in Argentina for the Last 40 Years

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Abstract

Introduction: Global asthma mortality is still an unresolved issue, despite the existence of highly effective treatments. This occurs in Argentina, where there are also some effective treatments, but there is few information about the relationship between asthma mortality and sales of inhaled medication. The purpose of this study was to analyze sales in pharmacies of medication for obstructive respiratory diseases and asthma deaths, before and after the appearance of inhaled corticosteroids (ICSs) and their combinations.

Materials and Methods: An official bulletin was the source document for data about asthma mortality in Argentina between 1983 and 2018. All data on pharmacy sales were provided by the same source (IQVIA Solutions Argentina), but there are no sales data from 1990 to 1999.

Results: The mean \pm standard deviation of the ratio between total sales of short-acting β_2 -adrenergic agonist bronchodilators (SABAs) over total sales of ICS and their combinations was 13.68 ± 2.85 between 1983-1988 and 1.03 ± 0.12 between 2010-2019 ($p < 0.0001$). There was a significant correlation between the SABA/ICS ratios and the number of asthma deaths from 1983 to 2018 (Pearson correlation: $r = 0.977$, $p < 0.0001$). During the period from 2010 to 2018 there was a significant decrease in the number of deaths compared to 1980-1989 (145.9 ± 28.58 vs. 43.1 ± 5.2 ; $p < 0.0001$). Since 2016, SABA sales started to decrease and were overtaken in 2019 by the combinations of ICS/long-acting β_2 -agonist bronchodilators (LABAs).

Conclusions: The significant correlation between the SABA/ICS sales ratio and asthma deaths would make us rethink the long-established treatment stereotype of SABAs for the management of asthma.

Key words: Sales of medication; Mortality, asthma; Argentina

Introduction

The marketing department of pharmaceutical industry is usually in charge of the information regarding the sales of drugs. This information is very expensive and used for purposes other than epidemiology and public health. Also, mortality rates are studied by epidemiologists and public health physicians who have no access to the sales of drugs. Only on rare occasions the sales of drugs and mortality rates are analyzed jointly. The epidemic outbreaks that caused asthma deaths associated with isoproterenol in the United Kingdom and fenoterol in New Zealand are clear examples of the importance of analyzing the mortality and drug sales variables jointly¹.

The increased knowledge of asthma inflammation and the availability of inhaled corticosteroids produced an important decrease in the global asthma mortality rate since the 1990s²⁻⁵. Despite these achievements in the treatment of asthma, global asthma mortality has been stalled since 2006^{1, 2, 4}. Short-acting β_2 -adrenergic agonist bronchodilators (SABAs) are still a deeply rooted stereotype of the asthma treatment on a global scale, regardless of the positive correlation between SABA use and

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Abbreviations

SABA	short-acting β 2-agonist bronchodilator.
ICS	inhaled corticosteroid.
LABA	long-acting β 2-agonist bronchodilator.
LAMA	long-acting muscarinic antagonist.
ICD	International Classification of Diseases.
GDP	Gross Domestic Product.
COPD	chronic obstructive pulmonary disease.

the increase in asthma mortality³. In the case of salbutamol, the initial scientific evidence was only a 300-minutes study carried out in 24 patients to observe the bronchodilating action⁶. The SABAs do not have an anti-inflammatory action, and subjects with asthma may develop overreliance on SABA, thus promoting the withdrawal of the controller medication⁷.

The purpose of this study was to analyze sales in pharmacies of medication for obstructive respiratory diseases and asthma deaths, before and after the appearance of inhaled corticosteroids (ICSs) and their combinations.

Materials and Methods

Since the beginning of 2020 we began to gather data for this descriptive, retrospective study. We started to analyze the trend of sales in pharmacies of medication for obstructive respiratory diseases and on the other hand the deaths from asthma. Two different periods of time were taken into account. The first stage, between 1983 and 1989, where effective ICSs weren't still available (there were low doses of beclomethasone and disodium cromoglycate), and the other stage between 2000 and 2019, with optimum doses of ICSs and ICSs in combination with long-acting β 2-agonist bronchodilators (LABAs).

Mortality data in Argentina were collected from an official report published by the *Instituto Nacional de Enfermedades Respiratorias "Emilio Coni"* (National Institute of Respiratory Diseases "Emilio Coni") and the National Administration of Laboratories and Health Institutions, Ministry of Health (Argentine Republic)⁸. This report about asthma mortality shows the absolute values between 1980 and 2018 and the crude and age-adjusted asthma mortality rate curves per 100,000 inhabitants in Argentina within the 5-39 age group (ICD 9: 493 and ICD 10: J45-J46)⁸. The official site for the national asthma mortality data has been unavailable since October 2020.

The source of data about the sales in pharmacies of drugs for obstructive respiratory diseases in Argentina was the same for both periods. The data used from 1983 to 1990 had been already published by IQVIA Solutions Argentina (former IMS HealthInc), available in Table 1 of the Molfino et al article⁹, and from 2000 to 2019, unpublished data were used, obtained by courtesy of IQVIA. There are no sales records between 1990 and 1999.

In order to obtain the SABA/ICS ratio, all the short-acting inhaled bronchodilators of every year were added and then divided by the sales of beclomethasone for the 1983-1988 period. From 2000 to 2019, the sales of short-acting inhaled bronchodilators were added year after year, and the denominator of the SABA/ICS ratio was the sum of all the ICSs used for monotherapy plus all the ICS/LABA combinations (Table 1). Oral theophylline and montelukast were considered separately.

Results are shown as mean \pm standard deviation (SD). In order to analyze if two variables are related (SABA/ICS sales ratio and asthma deaths), we applied the Pearson correlation coefficient as a measure of linear dependence between two quantitative variables. The result of the analysis is a correlation coefficient with values between -1 and +1. The Independent Sample Student T Test was used to evaluate if there was a significant difference between the mean number of deaths and the SABA/ICS ratios in the

two groups (both decades), after checking if there was normal distribution with the F test. A p-value < 0.05 was considered significant. We used the InStat-Graphpad program.

Results

Table 1 shows annual sales of SABAs and ICS/LABA, the ratios between both and finally asthma deaths in individuals between 5 and 39 years. The mean SABA/ICS sales ratio between 1983 and 1988 was 13.68 ± 2.85 (mean \pm SD). This means that for every sold unit of ICSs, 13.68 units of SABAs were sold (see **Table 1**). The SABA/ICS sales ratio of the period 2010-2019 was 1.03 ± 0.12 , significantly lower than the 1983-1988 ratio ($p < 0.0001$; Table 1).

A correlation was found between the SABA/ICS sales ratio and the number of asthma deaths ($r = 0.97$; $p < 0.0001$) according to the Pearson Correlation (Figure 1). Deaths from asthma showed a significant decrease in the 5-39 age group, when average deaths from the 1980-1989 decade were compared to those of the 2020-2018 period (mean 145.9 ± 28.58 vs. 43.1 ± 5.2 ; unpaired T Test; $p < 0.0001$).

Discussion

The most important finding of this study was to show for the first time in Argentina, a correlation between the SABA/ICS sales ratio and asthma deaths so that the lower the ratio (because the ICS sales ratio is higher) the lower the number of deaths. A greater number of ICS sales would suggest that the inflammatory aspect of asthma is being treated without distractions as with bronchodilators. Encouraging the treatment of the inflammation should be the keystone of every health policy on asthma.

In 2019, the sum of all ICS/LABA combinations without the ICSs used for monotherapy was able to surpass the sales of SABAs, for the first time in history (Figure 2). Due to the appearance of the SARS-CoV2 pandemic, it will be very difficult to analyze data from year 2020. The first ICSs was beclomethasone, which reached peak sales in 1987 with 165,000 units, even though it represented less than 2% of the total sales of that year⁹. The concentration of beclomethasone was $50 \mu\text{g}$ as metered-dose inhaler and the minimum anti-inflammatory dose is $400 \mu\text{g}/\text{day}$. An individual had to inhale 8 daily doses. Between 2010 and 2019, the ICSs plus their combinations always sold over 3 million units. The SABA/ICS sales ratio started to decrease at the end of the 1980s (not taking into account the sales of oral bronchodilators); but since 2010, the constant increase in the sales of ICSs and their combinations achieved a SABA/ICS ratio close to one. Such decrease in the ratio was produced only by an increase in the denominator until 2016; since that year the numerator (SABA sales) began a slow decrease together with the continuous increase in the denominator (ICS sales). As the ratio decreased, asthma deaths started to decline⁸ (see **Figure 1**) and both variables (ratio and deaths) showed a significant correlation from 1983 to 2018 (Pearson correlation, $r = 0.97$; $p < 0.0001$). Beyond the objections to death certificates¹⁰; by excluding individuals under 5 years old, deaths from bronchiolitis are not counted, and by excluding individuals older than 39 years, COPD deaths are discarded. Thus, the 5-39 age group provides more accuracy to the data obtained from death certificates.

With the arrival of very effective ICSs and the promotion activities performed by some organizations such as GINA¹¹ a deceleration in the asthma mortality rate in Argentina could be achieved¹². This auspicious phenomenon occurred on a global level; but reached a plateau in 2006 that is still sustained². The high consumption of SABAs between 1983 and 1989 could be related to deaths from asthma, as has happened in other countries¹. We can't say that the high consumption of SABAs over mortality is a matter of causality, nevertheless, the correlation found between the SABA/ICS sales ratio and the deaths ($r = 0.97$; $p < 0.0001$) supports the hypothesis of a relationship. This correlation emphasizes the need to insist on treating inflammation.

In order to place the Argentinian situation within the world context, we can observe the Finland phenomenon, where a successful 10-year program was implemented from 1994 to 2004 based on the anti-inflammatory intervention from the outset¹³. In 1987, one third of asthma patients in Finland were

TABLA 1. Sales in units and asthma deaths in individuals between 5 and 39 years from 1983 to 2018

YEARS	SOLD UNITS			
	SABAs	ICS+ICS/LABA	Sales ratio SABA/ICS	Deaths asthma (5-39 años)
1983	1869100	147400	12.68	119
1984	2377000	148800	15.97	153
1985	2693200	177800	15.15	182
1986	2900000		15.42	173
1987	3021000	190500	15.86	188
1988	3284400	235400	13.95	151
1989	3300000		11.5	120
2000	3370930	786427	4.29	48
2001	3248589	1108129	2.93	65
2002	2651312	906165	2.93	55
2003	3197783	1197493	2.67	62
2004	3091582	1378495	2.24	50
2005	3141758	1627754	1.93	66
2006	3220957	1866024	1.73	56
2007	3666501	2199072	1.67	53
2008	3538784	2404154	1.47	49
2009	3536681	2576681	1.37	50
2010	3755919	2940229	1.28	48
2011	3685486	3349005	1.10	33
2012	3681856	3353191	1.10	38
2013	3807905	3672374	1.04	44
2014	3600276	3499781	1.03	46
2015	3857276	3945762	0.98	44
2016	4045570	4142997	0.99	41
2017	3967111	4169743	0.98	50
2018	3507025	4017760	0.91	44
2019	3245502	4819198	0.85	

SABA: units of inhaled bronchodilators sold in pharmacies in Argentina. ICS+ICS/LABA: sales in units of inhaled corticosteroids plus combinations of corticosteroids and long-acting bronchodilators. SABA/ICS ratio: result of the division between the total sales of SABAs/total sales of ICSs+ICSs/LABAs. Asthma deaths reported by the "Emilio Coni" Institute within the 5-39 years age group. Correlation between asthma deaths and the SABA/ICS ratio: $r = 0.977$; $p < 0.0001$ according to the Pearson Correlation Test. The mean values of the SABA/ICS sales ratios between 1983 and 1988 were 13.68 ± 2.85 (mean \pm SD) versus the 2010-2019 period (1.03 ± 0.12 ; unpaired T Test: $p < 0.0001$).

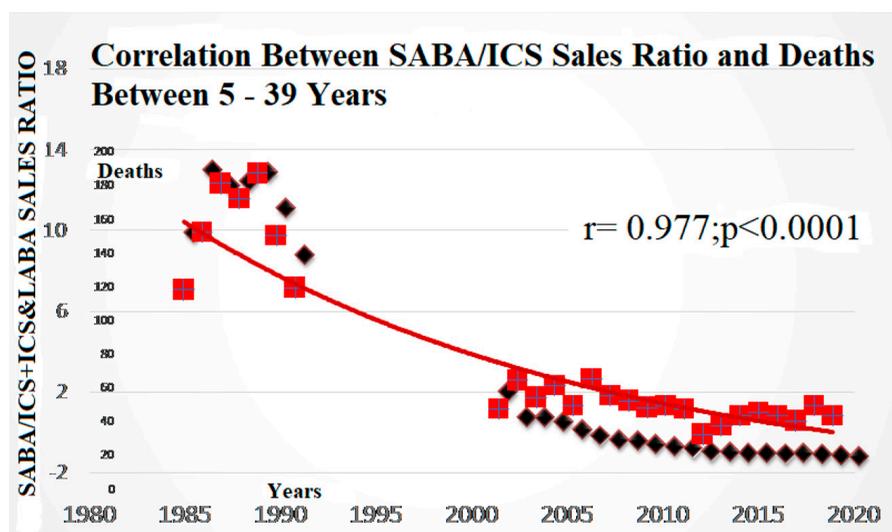


Figure 1. SABA total sales ratio over ICS+ICS/LABA sales (black rhombus) from 1983 to 2019. Asthma deaths between 5 and 39 years (red squares) per year from 1983 to 2018. Pearson correlation test between the SABA/ICS ratio and the number of asthma deaths in individuals from 5 to 39 years ($r = 0.977$; $p < 0.0001$). Solid red line: Trend in the number of deaths.

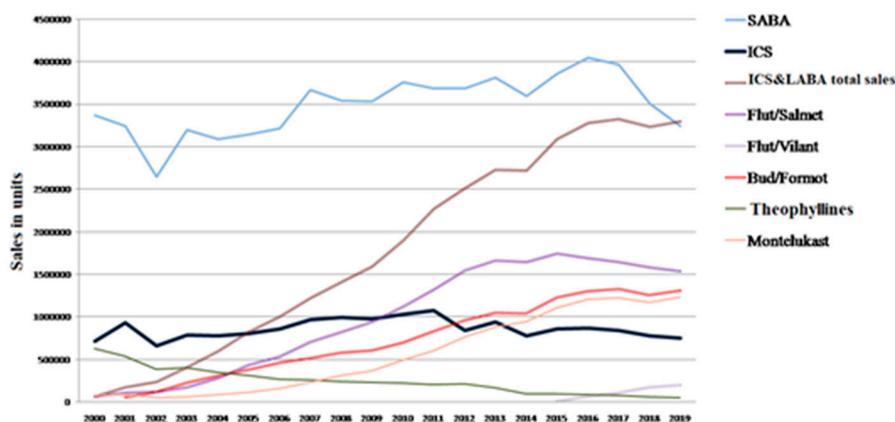


Figure 2. Trends in the total amount of annual sales for 8 groups of drugs in absolute values from 2000 to 2019 in Argentina.

under treatment with ICSs (in Argentina less than 2% of sales) and in 2004 more than 85% of patients who purchased medication for asthma at the pharmacy were using ICSs on a daily basis¹³. In 2005 Finland achieved a ratio of 1 of daily doses of ICS/SABA and during the period from 1990 to 2003 there were only 10 deaths from asthma in individuals under 20. However, with the Finnish program, 72% of patients were using SABAs almost every day, 35% used a course of oral corticosteroids, there were 18% of asthma hospitalizations and to its advantage, asthma deaths of patients of all ages decreased from 123 to 85 seven years after the program had begun¹⁴. The SABAs were part of the program because there weren't any alternatives. Not eradicating the SABAs from the program may have influenced the fact that the results weren't more categorical.

With a much different data processing, this study shows that it was only in 2015 that Argentina took the SABA/ICS consumption ratio to 1; but Finland calculated the ratio in doses, and in Argentina it was calculated per units sold, where one unit may contain between 200 and 250 doses and between 30 and 200 ICS and their combinations. This would mean that treatments with ICSs wouldn't be available for most of the asthmatic population in Argentina.

Since 2015 the sales growth of ICSs used as monotherapy has stalled, but ICS/LABA combinations began to increase. The use of SABAs started to decrease in 2016 (Figure 2). Since 2015, the SABA/ICS ratio has remained under 1. This doesn't imply that the SABA hegemony was over in 2015; but the descending trend has been maintained for 4 uninterrupted years and for the first time the SABAs were surpassed by another drug category in 2019. We will have to wait a few years to know if that trend is consolidated.

If we analyze the sales of fluticasone/salmeterol separately (Figure 2), we can observe that with 12 commercial brands a very mild decrease has started since 2016. The ICSs used as monotherapy showed a similar trend with 28 commercial brands. On the other hand, an ascending trend can be observed since 2014 with budesonide/formoterol (with 8 brands), montelukast (14 commercial brands) and fluticasone/vilanterol, which appeared in 2015.

Most asthmatic patients use controller and rescue medication but are unaware of the advantages of controller medications¹⁵ and loose adherence, because they rely on the immediate bronchodilating effect of the SABAs⁷. Budesonide/formoterol is the exception because it can also be used as rescue agent¹⁶. In this regard we could say that the decrease in the sales of SABAs, ICSs and fluticasone/salmeterol could be explained by the growing use of the anti-inflammatory rescue strategy with budesonide/formoterol that substitutes both the SABAs and other controller drugs. Every patient using SABAs could develop an overreliance that could increment the risk of death and asthma attacks with life-threatening risk^{3,7}. This overreliance and the increasing use of SABAs was the strongest characteristic both in patients who died from asthma^{7,10} and in patients with life-threatening attacks^{7,17}. We published a document with information about these SABA-related risks¹⁸ in order to warn the scientific community in Latin America.

Monotherapy with LABAs for asthma is prohibited by all the regulatory entities and international recommendations¹⁶ for much less evidence against them than the SABAs. Monotherapy with SABAs should have the same recommendation. Additionally, the essential study of salbutamol with 24 patients lasted 5 hours⁶, and any regulatory entity would approve it at present for chronic asthma. Evidence regarding the deleterious effect on asthma⁷, and more importantly the dose-response relationship in mortality³ justify the warning about the use of SABAs in asthma¹⁸.

The 2018-2019 negative trends for SABAs, ICSs and fluticasone/salmeterol could be related to the decline in Argentina's GDP¹⁹; but budesonide/formoterol, fluticasone/vilanterol and montelukast continued rising and their prices are much higher than those of the SABAs. Also, the total sales are not related to the natural growth of the Argentinian population that has been dropping since 1960, though it has always been positive. In the 1980-1991 census, the average annual growth rate was 14.7 per thousand (1.47%); in the 1991-2001 decade, 10.1 per thousand (1.01%); and between 2001 and 2010, 11.4 per thousand (1.14%)²⁰.

Among the limitations of this study, there is the fact of not being able to identify the recipients of the sales, since there are many indications to prescribe the SABAs, such as COPD, respiratory infections and other obstructive diseases besides asthma. Given that it is not possible to effectively know if the asthmatic population in Argentina are the recipients of such sales, we could refute the relationship between the high asthma mortality in Argentina during the eighties and the large amount of SABA sales. However, epidemiological studies of large databases such as Canada found a relationship between risk of death from asthma and SABA consumption because, among other important aspects, they could evaluate asthma-only prescriptions³.

The other limitation of this study is the fact that sales correspond to pharmacies and don't include purchases made by official entities for public health plans of free distribution, hospital purchases and direct purchases, such as biological therapies.

To conclude, asthma mortality in Argentina for the 5-39 age group continues to plateau and, on the other hand, the SABAs were top-selling medications for obstructive respiratory diseases until 2018. Finding a significant correlation between the SABA/ICS sales ratio and deaths from asthma should warn the authorities and the scientific community. If the descending trend in SABA sales is sustained with an increase in the ICS or ICS/LABA sales, the asthma mortality rate plateau could finally break in a few years.

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