Safety and Potential Side Effects of β_2-Agonists: A Still Debated Question

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Abstract: In the last years, the safety profile of β^2-agonists has been largely discussed as there are concerns about the adverse effects of their regular use. In this review, we analyze the main questions relating both morbidity and mortality of currently available β_2-agonists. Although questions still remain regarding the issue of safety, evidence from epidemiological studies is strongly suggestive that the use of β_2-agonists is not dangerous.

Keywords: Safety profile, β_2-agonists, therapy.

INTRODUCTION

The discussion on the safety of inhaled sympathomimetic drugs arose with the introduction of adrenaline about 60 years ago and is still nowdays a debating question [1-6]. The overuse of adrenaline was associated to death in asthmatic patients who used an adrenaline spray more than in those who did not use it [2]. Subsequently, agents such as isoproterenol, more selective for the β_1 and β_2-adrenoceptors, were proposed. However, similar warning were soon expressed about potential adverse effects, in particular the association between the overuse of isoproterenol and the development of refractory asthma [7-9]. Despite the subsequent development and widespread use of agents more selective for the β_2-adrenoceptor, similar concerns continues regarding their possible role in increasing mortality and morbidity. Consequently, the safety profile of β_2-agonists is still debated [10-12].

MATERIAL AND METHODS

We analyzed papers published in PubMed Medline and relating the safety profile of β_2-agonists till May 2012. We used the keywords "β_2-agonists" for the Medline search and we scanned the references of all included articles for additional studies. We reported evidence of morbidity and risk of mortality of currently available β_2-agonists.

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RESULTS

We reported evidence of morbidity and risk of mortality of currently available β_2-agonists.

a. Morbidity

Concerns about increased morbidity correlated to β_2-agonist drugs lead to numerous clinical trials. β_2-agonists can affect other muscles, as well as the lungs, leading to side effects. The most common side effects are summarized in Table **1**.

1. Asthma Severity

It has been reported that the regular use of β_2-agonists drugs is associated to the worsening of asthma through bronchial hyperresponsiveness, development of tolerance and reduced protection against provoking stimuli [13,14]. Nevertheless, the short-acting β_2-agonists (SABA) drugs albuterol and terbutaline and the long-acting β agonist (LABA) drugs salmeterol and formoterol have not been correlated to a worsened asthma control in some other reports [15,16]. Use of long-acting β_2-agonists such as salmeterol and formoterol has also been correlated to an increased asthma severity [13,17]. Moreover the regular use of fenoterol and isoproterenol had been associated with a worsening asthma control [16,18,19]. Other large clinical trials have evidenced that, differently from fenoterol, regular salbutamol does not cause a deterioration in asthma control neither asthma attacks [1,20]. Moreover, it has been demonstrated that the combination of LABA and inhaled corticosteroids may reduce exacerbations and hospitalizations for asthma. The regular administration of β_2-adrenergic

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Table 1: Potential Adverse Effects of β_2-Agonists

Adverse effect	Features
Electrolyte disturbances	Hypokalaemia, hypomagnesaemia
ECG changes	QTc interval prolongation, flat T waves, increased QRS amplitudes, tachycardias, arrhythmias
Cardiac effects	Palpitations, worsening of myocardial ischaemia, arrhythmias (ventricular and supraventricular), worsening of congestive heart failure
Tremor	normal resting tremor and normal postural tremor
Respiratory effects	Paradoxical bronchoconstriction, tolerance with long-term use, increased exacerbations,
Deaths	
Metabolic changes	Increased glucose and free fatty acid plasma levels
Central nervous system changes	Nervous tension, restlessness, headache, disturbances of sleep and behavior
Decreased blood pressure	
Addiction	Abuse of β_2-agonist
Hypersensitivity reaction	
others	Muscle cramps, coughing, irritated throat

agonists may contribute to the development of tolerance [15,21,22]. On the contrary, some other authors reported that a poor asthma control may be also due to a regular β_2-agonist use, which reduces bronchodilator responses due to down-regulation and desensitization of β-adrenoceptors [21-23]. Finally, a potential role for polymorphisms in the β_2-adrenergic receptor gene to regulate both short-and long-term responses to SABA has been studied [20, 24-28]. When SABA are used for long periods of time, patients who are Arg/Arg homozygotes at position 16 of the β_2-adrenergic receptor gene are at increased risk of deterioration in lung function and of asthma attacks compared with carriers of the other two genotypes at position 16 (Arg/Gly and Gly/Gly) [25]. Consequently, responses to long-term use of LABAs may be also regulated by polymorphisms in the β_2-adrenergic receptor gene.

2. Paradoxical Bronchoconstriction

A paradoxical bronchoconstriction may occur with β_2-agonists, with a decrease of 20% in FEV1 [10,29]. This phenomenon has been evidenced in about 8% of patients using salbutamol and is transient but severe. It generally increases with the age of patients. The underlying mechanism is still unknown [30].

3. Cardiovascular Effects

β_2-agonists can affect cardiac function as β_2-adrenoceptors are present in the heart [13, 31-33]. In obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease, the initiation of β_2-agonists therapy has been correlated to a significant increase in heart rate and a reduction in potassium concentration [10,11]. The stimulation of cardiac receptors may be responsible of positive chronotropic (increased heart rate) and inotropic (increased force of cardiac contraction) consequences, so that patients may experience palpitations [32]. When the treatment is continuative, the rate of cardiovascular events is increased. In fact, through β_2-adrenergic stimulation, a regular treatment with β_2-agonists can facilitate arrhythmias, ischemia, and congestive heart failure [13, 21, 31, 34-37]. Some reports suggest the presence of an association between β_2-agonists and the risk of chronic heart failure [35]. A chronic β-adrenergic stimulation may induce myocardial pro-inflammatory cytokine expression, which plays a a key-role in the pathophysiology of congestive heart failure [32,38]. On the other hand, some other studies reported that SABA in any form do not increase the risk of an acute myocardial infarction. In particular, first-time use does not increase the risk of myocardial damnage [39]. Moreover, the Asthma b-agonists and Development of Congestive Heart Failure (ABCHF) study failed to confirm an association between asthma, β_2-agonist use, and the later development of idiopathic dilated cardiomyopathy [40].

4. Tremor

Tremor associated with β_2-adrenergic agonists is a well-studied adverse effect, even if difficult to quantify [10, 21,41]. It affects 2-4% of patients with asthma assuming a regular β_2-adrenergic agonist and 2-14% of patients with acute bronchitis without underlying pulmonary disease [42,43]. The mechanism underlying

the tremor induction by β_2-adrenergic agonists is still unknown. It has been reported that β_2-adrenergic agonists may act directly on muscle, provoking both normal resting tremor and normal postural tremor [41,44]. Recent studies demonstrated that stimulation of β_2-adrenoceptors causes tremor due to potassium entry into skeletal muscle and that there is a direct correlation tremor-hypokalemia [45]. Beta-adrenergic effects on postural tremor are more clinically relevant than those of resting tremor because they are much greater in magnitude. Tremor associated with SABAs and LABAs is dose-related. Moreover, it is likely to occur with oral administration and with high doses delivered *via* a nebulizer. In detail, orally salbutamol and terbutaline are likely to provoke an increase in physiological tremor [46,47]. Terbutaline, but not salbutamol, elicited a dose-related response [48]. Fenoterol causes tremor, with a dose-dependent increase in tremor, but with a short duration. Salmeterol has shown a similar effect on tremor than salbutamol, but with a less rapid onset [42,49]. When these bronchodilators are administered by inhalation at therapeutic doses, tremor is not significant, rapidly decreases in intensity and disappears when the patient is under regular treatment [41, 49]. Finally, tremor response to suspension aerosol is higher than that to solution aerosol, due to a likely difference in systemic absorption [41]. Suspensions produce particles of 3.5 to 4.0 mm in diameter and typically deliver no more than 15% of the inhaled dose to the lungs. On the contrary, solutions produce an extrafine aerosol with a mass median aerodynamic diameter of 1.1 mm. The smaller particle size are much more likely to been deposited in the lung than the larger ones, particularly in the small airway [41].

5. Central Nervous System (CNS) Disturbances

In literature, salbutamol has been reported to cause appetite suppression, agitation, nausea and sleep disturbances and to reactivate delusions in psychotic patients [10, 50, 51]. β_2-agonists can cause systemic peripheral vasodilation, which may facilitate headaches and a reduction in blood pressure. Terbutaline and fenoterol have been also associated to mild CNS disturbances [30, 52-56].

6. Decreased Blood Pressure

A reduction in blood pressure has been reported in some susceptible asthmatics using β_2-agonists. However, this side effect is considered infrequent or of a mild degree and is generally outweighed by the good control of asthma produced by β_2-agonists [57]. Moreover, a standard dose of salbutamol and formoterol does not cause haemodynamic disorder. In fact, patients with severe asthma had normal systolic and diastolic blood pressure after short and long acting β_2-agonist [58].

7. Addiction

Rare cases have been reported of asthma suffers who developed an apparent addiction to salbutamol inhalers [50, 59,60]. Such abuse of inhaled salbutamol may be primarily related to the fluorocarbon propellents, although other evidence suggests that dependence also develops to salbutamol itself [50, 59,60].

8. Hypersensitivity Reactions

In rare cases, patients may develop hypersensitivity reactions to a beta-agonist, to its metabolites or to one of the filler ingredients [61].

9. Metabolic Consequences

Hyperglycemia and increase in ketone bodies have been reported among acute metabolic consequences of β_2-adrenergic agonists, mainly in diabetics [10, 21, 62-64]. β_2-adrenergic agonists can cause hyperglycemia *via* a β_2-adrenoreceptor mediated increase in glycogenolysis [62]. Moreover, β_2-adrenoceptors may facilitate the degradation of stored triglycerides to fatty acid and glycerol [62,63].

10. Electrolyte Disturbances

Electrolyte disturbances, such as hypokaliema, are very rare. In literature they have been reported in case of clenbuterol overdose in unresponsive asthma attacks or in case of albuterol abuse [66-67].

11. Electrocardiogram Changes

Electrocardiogram (ECG) alterations have been rarely reported in literature. They are in most cases associated to overdose of drugs, such as an albuterole abuse or a clenbuterol overdose resulting in supraventricular tachycardia and atrial fibrillation [66,67]. In clinical studies on LABA-treated patients, there was no evidence of an association between LABA and increased incidence of ECG alterations [68,69].

12. Other Side Effects

Other side effects have been very rarely reported. Out of them, muscle cramps have been associated to continuous nebulization of beta 2 agonists [70].

b. Mortality

Concerns about the safety of regular use of β_2-adrenergic agonists first arose in the occasion of two epidemics of deaths from asthma in which patients were using dispensers delivering high doses of β_2-adrenergic agonists [71-74]. The first of these epidemics, happened in the United Kingdom in the late 1950s, was associated to isoproterenol. The second epidemic event was in New Zealand in the late 1970s and was connected with the use of fenoterol [71-74]. Since then, available evidence indicates that the use of the high-dose preparations of isoproterenol and fenoterol were connected to an increased mortality. A possible explanation was the result of both long-term effects with their regular use, leading to a worsened asthma control, and acute effects relating to their overuse in severe attack of asthma [6, 21, 75-82]. Researches analyzed the relationship between LABA therapy and the worsening of disease or the respiratory deaths. Some studies showed an incremented mortality among patients who used salmeterol or formoterol [13, 31, 83,84]. The conclusion on the dangerous consequence of regular treatment with salmeterol was not confirmed and was opposed by the results of other studies [15,21, 34, 85]. By the way, large retrospective case-control studies of asthma attacks and mortality failed to include LABA use among risk factors for hospitalization, intensive care unit admissions, or mortality [21]. Moreover, the association between fenoterol and the epidemic deaths in New Zealand was reexamined. An analysis of β-agonist prescribing patterns in Saskatchewan, Canada, revealed that there was preferred prescribing of fenoterol among users of albuterol who showed signs of increased severity or uncontrolled asthma [86]. A prospective study in 653 patients in New Zealand underlined that fenoterol was more often used by patients with severe asthma and that its use did not increase the risk of severe life-threatening asthma [18]. Further analysis of the New Zealand epidemic revealed that the increase in asthma-related deaths occurred in the lowest and poorest socioeconomic areas, while sparing the economically advantaged areas, in a period of dramatic increase in unemployment. The use of albuterol and terbutaline are not been recognized to be associated with an increased risk of mortality [1]. Although this lack of risk may also apply to formoterol and salmeterol, in the absence of sufficient studies specifically addressing the risk of death, this remains uncertain [1].

DISCUSSION

In literature, morbidity and mortality have been associated to β_2-agonists use [87,88]. In particular, concern about a possible association of LABA and increased risk of cardiovascular events and deaths, especially in patients with asthma, is still discussed [87]. Indeed most of the reports are single case reports and the intensity of the adverse effects may be related to the dose and to the intrinsic efficacy of the agent used [65,66, 89]. On the contrary, in recent large clinical studies on LABA-treated patients, an association between LABA and either increased incidence of cardiac arrhythmias or cardiac hearth rate alterations failed to be demonstrated [69].

Although questions still remain open on safety, epidemiological studies may help us in concluding that the use of β_2-agonists is not dangerous. In fact, most observational studies, systematic reviews, and meta-analyses of β_2-agonist safety have shown no increased risk of cardiovascular events or mortality [87]. Among agents, recent data show that indacaterol has a high bronchodilator efficacy, with an excellent safety profile comparable with that of placebo [90].

In conclusion, even if caution is warrented in potentially vulnerable groups, such as those with particular genotypes for the β-receptor who might be prone to adverse effects or patients with cardiovascular diseases, the prescription of β-agonist is generally safe. Factors like age, LABA choice and duration of treatment may be considered when evaluating risks of side effects and adverse outcomes.

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