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Original Research Article

Safety profile differences between salbutamol and levosalbutamol: Results from the FDA Adverse Event Reporting System

Wenzhong Peng[1], Jia Chen[2], Ruoxi He[1], Yongjun Tang[1], Juan Jiang[1], Ling Ouyang[3], Dandan Zhao[3], Ying Li[1]*

[1]Department of Respiratory Medicine, National Key Clinical Specialty, Xiangya Hospital, Central South University, Hunan 410078, [2]The Second Department of Respiratory Medicine, Third People's Hospital of Pingxiang City, Jiangxi Province, [3]Joincare Pharmaceutical Group Industry Co. Ltd, Shenzhen, China

For correspondence:* ***Email:* *liying971@163.com*

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Abstract

Purpose: *To examine the safety profiles of salbutamol and levosalbutamol reported in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.*
Methods: *Retrospective pharmacovigilance disproportionality analysis for drug-related ADRs reported in the FAERS database was performed from October 1, 2003 to March 31, 2020. The proportion of report ratio (PRR), proportional reporting ratio (PRR), and reporting odds ratio (ROR) were calculated and used for the determination of safety signals. The definition was based on system organ class (SOCs) and Standardized Medical Dictionary for Regulatory Activities Queries (SMQ) by the Medical Dictionary for Regulatory Activities (MedDRA).*
Results: *A total of 83,166 and 3,133 adverse event reports were identified for albuterol and levalbuterol, respectively, and were linked mainly with 12 SOCs, i.e., cardiac, vascular disorders, respiratory, thoracic, mediastinal disorders, and immune system disorders. The largest ROR among the 20 most frequent SMQs was asthma/bronchospasm for reports both in salbutamol group (ROR: 13.585, 95% CI: 13.254, 13.923) and levosalbutamol group (ROR: 16.225, 95% CI: 14.575, 18.063).*
Conclusion: *Data mining of the FAERS may be considered a useful approach for identifying salbutamol and levosalbutamol-related adverse events, which might provide additional information to guide their use in clinical practice.*

Keywords: *Salbutamol, Levosalbutamol, Safety profile, Drug-related ADRs*

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INTRODUCTION

Salbutamol, a short-acting β_2-agonist, is widely used for symptomatic relief of asthma and chronic obstructive pulmonary disease, and salbutamol preparation consists of a racemic 50:50 mixture of its R- and S-isomers [1]. The R-isomer has been reported to play a predominant role in the bronchodilator effect and potential adverse events of tachycardia, tremor, and nervousness [2]. Furthermore, the S-isomers exert proinflammatory effects which affect

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cytokine production, production of histamine, and release of immune cells and nitric oxide [3]. Studies have indicated that salbutamol is widely used for prevention and treatment of bronchospasm in patients with reversible obstructive airway disease and that salbutamol should be kept on hand, to prevent catastrophic asphyxiation for patients suffering recurring obstructive airway symptoms [4,5].

Levosalbutamol has been introduced in clinical practice for chronic inflammation caused by the S-isomer [6]. However, the safety profiles of salbutamol and levosalbutamol in the real world are not fully understood. There is a wealth of public information regarding ADRs in the FDAAERS database, which supports the safety monitoring for specific agents through using the ADRs reported from healthcare professionals, consumers and manufacturers [7]. This study investigates ADRs reported for salbutamol and levosalbutamol, using the FAERS database in a real-world practice setting.

METHODS

Data source

The FAERS files published by FDA quarterly include data on demography and administration, drug, unwanted toxic effects, treatment outcomes, and information on report sources [8]. Open Vigil FDA was applied for interrogating FAERS data using Open Vigil FDA API to access FDA data repository [9,10]. All quarterly data from FAERS between October 1, 2003 and March 31were extracted, and missing data on outcome were excluded by Open Vigil FDA.

ADR categorization and identification

The reported adverse drug reactions (ADRs) in the FAERS database were coded using Preferred Terms (PTs) from the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries v22.0. Moreover, a combination of various PTs was sued to categorize a specific illness or focal interest via Standardized MDRA Queries (SMQs).

Data mining

All ADRs listings were extracted for salbutamol and levosalbutamol, when the signal was detected. Due to the arbitrary nature of drug names reported in FAERS database, all drug names were unified into generic names (albuterol or salbutamol, and levalbuterol or levosalbutamol) through DrugBank, a reliable drug database used as a reference in pharmacovigilance analyses, prior to analysis. Evaluation was carried out only on the primary drug of interest, and only on 1 peculiar identification report. In order to prevent duplications, a report with several ADRs in the same MedDRA hierarchy was treated only once. Moreover, the “errors in medication” and “absence of effectiveness” were removed owing to the fact that the reports were not directly related to drugs.

Statistical analysis

To identify an association between a drug and an ADR, disproportionality analysis (DPA) and Bayesian analysis were performed at SMO level, while ROR, PRR, and Bayesian confidence propagation neural network (BCPNN) were used to identify signals of DPA and Bayesian analysis, respectively, with higher scores indicating firmer correlation between adverse effects and drugs [11,12]. Table 1 provides the calculation formulas and criteria for the above three algorithms. The ADRs were said to be drug-related if both algorithms satisfied these criteria.

Table 1: Summary of major indices used for signal detection

Algorithm	Calculation formulas of major indices	Criterion
ROR	$ROR = ad/c/b$, 95% $CI = e^{ln(ROR) \pm 1.96\sqrt{1/a+1/b+1/c+1/d}}$	Lower bound of 95% CI > 1, a ≥ 2
PRR	$PRR = a(c + d)/c/(a + b)$, $\chi^2 = \{(ad-bc-(a+b+c+d)/2)^2\}(a+b+c+d)/\{(a+c)(a+b)(b+d)(c+d)\}$	PRR ≥ 2, a ≥ 3, $\chi^2 \geq 4$

Key: a = no. of reports on ADRs of drug of interest; b = no. reports on ADRs of other drugs; c = no. of reports on other ADRs of drug of interest; d = no. of reports on other drug ADRs. ROR = reporting odds ratio; PRR, proportional reporting ratio; χ^2 chi-squared

The clinical features of subjects with salbutamol and levosalbutamol-linked ADRs collected from the FAERS database were presented using descriptions. Distribution of baseline demographic and clinical information were compared between albuterol and levalbuterol regimens using Chi-squared test. Statistical significance was assumed at $p < 0.05$. Data mining and all statistical analyses were performed with SPSS, version 23.0 (SPSS Institute, Inc., Chicago, IL, United States) and Microsoft EXCEL 2010.

RESULTS

Descriptive analysis

After data cleaning, a total of 18,606,922 ADR reports were identified from October 1, 2003 to March 31, 2020 from the FAERS databases. Out of these, a total of 86,299 ADR reports were for salbutamol (n = 83,166) and levosalbutamol (n = 3,133) as the first suspected drugs. Table 2 shows numbers of ADR reports and patient demographic characteristics. Ranked on the basis of gender, 29,928 articles were associated with males, which accounted for 34.68 %. Serious adverse events accounted for 36.32%, with the most frequently reported cases being hospitalization or prolonged hospitalization.

Signal detection for salbutamol and levosalbutamol

The total numbers of positive signals in salbutamol and levosalbutamol-associated ADRs reports were 77 and 81, respectively, as elaborated using SOC.

All the detected ADRs were mainly associated with 12 SOCs such as cardiac and vascular disorders, respiratory, thoracic and mediastinal disorders, and immune system disorders, as shown in Table 3. The most frequent ADRs in salbutamol-associated reports displayed according to SOC were cardiac and vascular disorders (50,005 reports), respiratory, thoracic, and mediastinal disorders (47,609 reports) and immune system disorders (43,883 reports), while in levosalbutamol-associated reports, the most frequent ADRs were cardiac and vascular disorders (3,103 reports), nervous system disorders (2,988 reports), and gastrointestinal, hepatobiliary and endocrine disorders (2,520 reports).

The most common adverse incidents were subjected to analysis using OR so as to ascertain therapy-specific variations. Values of OR > 1 indicated the possibility of salbutamol-associated toxic effects, while OR < 1 indicated the most likelihood of toxic side effects from levosalbutamol. The findings indicated that salbutamol had a higher likelihood than levosalbutamol, with respect to producing cardiac and vascular disorders (OR = 1.11), ear and labyrinth disorders (OR = 1.39), immune system disorders (OR = 1.32), infections and infestations (OR = 6.24), metabolic and nutritional disorders (OR = 1.29), psychiatric disorders (OR = 1.42); respiratory, thoracic and mediastinal disorders (OR = 1.35) and surgical and medical procedures (OR = 1.44), as shown in Table 4.

The largest ROR among the 20 most frequent SMQs was asthma/bronchospasm, for reports both in salbutamol group (ROR: 13.585, 95 % CI: 13.254, 13.923) and levosalbutamol group (ROR: 16.225, 95 % CI: 14.575, 18.063). The results showed that 11 and 10 signals were not listed within salbutamol pharmacy leaflet and levsalbutamol pharmacy leaflet.

These included eosinophilic pneumonia, cardiomyopathy, and pulmonary hypertension, as presented in Table 5 and Table 6).

Table 2: Baseline demographic and clinical information

Variable	Total (n=86,299)	Salbutamol (n=83,166)	Levosalbutamol (n=3,133)	*P*-value
Gender				
Female	51,376 (59.53%)	49,404 (59.40%)	1,972 (62.94%)	
Male	29,928 (34.68%)	28,899 (34.75%)	1,029 (32.84%)	<0.001
Unknown or missing	4,995 (5.79%)	4,863 (5.85%)	132 (4.2%)	
Age (years)				
< 18.0	5,693 (6.60%)	5,181 (6.23%)	512 (16.34%)	
18.0-44.0	9,632 (11.16%)	9,315 (11.20%)	317 (10.12%)	
45.0-64.0	16,179 (18.75%)	15,617 (18.78%)	562 (17.94%)	<0.001
65.0-74.0	8,522 (9.87%)	8,155 (9.81%)	367 (11.71%)	
≥ 75.0	6,612 (7.66%)	6,309 (7.59%)	303 (9.67%)	
Unknown or missing	39,661 (45.96%)	38,589 (46.40%)	1,072 (34.22%)	
Serious outcomes	31,346 (36.32%)	29,910 (35.96%)	1,436 (45.83%)	
Hospitalization or prolonged hospitalization	20,923 (66.75%)	19,892 (66.51%)	1,031 (71.80%)	
Disability	2,382 (7.60%)	2,316 (7.74%)	66 (4.60%)	<0.001
Life-threatening	2,790 (8.90%)	2,676 (8.95%)	114 (7.94%)	
Death	5,251 (16.75%)	5,026 (16.80%)	225 (15.67%)	
Reporter country				
USA	64,452 (74.68%)	61,709 (74.20%)	2,743 (87.55%)	<0.001
Other countries	21,847 (25.32%)	21,457 (25.80%)	390 (12.45%)	

Table 3: Frequencies of adverse events classified by reactions groups

Outcome	Salbutamol	Levosalbutamol	*P*-value
Cardiac and vascular disorders	50,005	3,103	< 0.001
Ear and labyrinth disorders	8,332	408	< 0.001
Eye disorders	1,802	216	< 0.001
Gastrointestinal, hepatobiliary, and endocrine disorders	11,795	2,520	< 0.001
General disorders and administration site conditions	5,265	776	< 0.001
Immune system disorders	43,883	2,344	< 0.001
Infections and infestations	4,918	54	< 0.001
Metabolism and nutrition disorders	11,106	585	< 0.001
Nervous system disorders	33,260	2,988	< 0.001
Psychiatric disorders	20,823	1,012	< 0.001
Respiratory, thoracic, and mediastinal disorders	47,609	2,502	< 0.001
Surgical and medical procedures	10,756	509	< 0.001
Others	11,060	561	< 0.001

Table 4: Treatment differences in adverse events

SOC	Report	OR (95% CI)
Cardiac and vascular disorders	53,108	1.11 (1.06, 1.15)
Ear and labyrinth disorders	8,740	1.39 (1.26, 1.54)
Eye disorders	2,018	0.56 (0.49, 0.55)
Gastrointestinal, hepatobiliary, and endocrine disorders	14,315	0.28 (0.27, 0.30)
General disorders and administration site conditions	6,041	0.45 (0.41, 0.48)
Immune system disorders	46,227	1.32 (1.26, 1.38)
Infections and infestations	4,972	6.24 (4.77, 8.17)
Metabolism and nutrition disorders	11,691	1.29 (1.19, 1.41)
Nervous system disorders	36,248	0.71 (0.69, 0.74)
Psychiatric disorders	21,835	1.42 (1.33, 1.52)
Respiratory, thoracic, and mediastinal disorders	50,111	1.35 (11.29, 1.41)
Surgical and medical procedures	11,265	1.44 (1.32, 1.58)
Others	53,521	1.33 (1.22, 1.45)

Table 5: Reported positive signals for salbutamol at the SMQ level in FAERS for twenty most common toxic effects

Outcome	Report	ROR (95% CI)	PRR	Chi-squared	Listed in drug labels
Anaphylactic reaction	23,940	3.008 (2.963,3.054)	2.43	22314.67	Yes
Hypersensitivity	16,196	1.905 (1.872,1.938)	1.729	5511.525	Yes
Cardiomyopathy	14,431	2.833 (2.782,2.885)	2.515	13789.369	Yes
Acute central respiratory depression	12,898	4.068 (3.992,4.147)	3.593	24314.43	Yes
Eosinophilic pneumonia	11,310	4.21(4.126,4.296)	3.774	23012.87	No
Pulmonary hypertension	10,999	4.901 (4.802,5.002)	4.385	28336.756	No
Anticholinergic syndrome	9,913	1.066 (1.043,1.088)	1.058	34.704	No
Hypoglycemia	9,537	1.109 (1.085,1.133)	1.096	89.289	No
Neuroleptic malignant syndrome	8,749	1.194 (1.167,1.221)	1.173	242.844	No
Noninfectious encephalopathy/delirium	8,523	1.069 (1.046,1.094)	1.062	34.025	No
Angioedema	7,990	1.736 (1.696,1.777)	1.665	2214.086	Yes
Asthma/bronchospasm	7,849	13.585 (13.254,13.923)	12.397	73228.875	Yes
Guillain-Barre syndrome	6,154	1.047 (1.02,1.074)	1.043	11.75	No
Cardiac arrhythmias	5,984	1.562 (1.521,1.604)	1.522	1104.598	Yes
Depression and suicide/self-injury	5,491	1.037 (1.008,1.065)	1.034	6.509	No
Extrapyramidal syndrome	4,998	1.231 (1.196,1.267)	1.217	200.815	No
Depression	4,891	1.164 (1.13,1.198)	1.154	104.646	No
Oropharyngeal disorders	4,797	1.878 (1.823,1.934)	1.827	1819.334	Yes
Infections and allergies	3,921	2.052 (1.987,2.12)	2.003	1973.016	Yes
Respiratory failure	3,816	2.203 (2.131,2.276)	2.147	2336.182	No

Table 6: Reported positive signals for levosalbutamol at the SMQ level in FAERS for twenty most common toxic effects

Outcome	Report	ROR (95%, CI)	PRR	Chi-squared	Listed in drug labels
Anaphylactic reaction	1208	4.595 (4.276, 4.938)	3.209	2082.803	Yes
Hypersensitivity	884	3.072 (2.842,3.32)	2.487	884.244	Yes
Toxic effect linked to eosinophilia/systemic symptom syndrome	776	1.468 (1.353,1.592)	1.352	86.576	No
Cardiomyopathy	671	3.618 (3.322,3.941)	3.058	995.751	Yes
Acute central respiratory depression	644	5.583 (5.12, 6.089)	4.641	1917.735	Yes
Eosinophilic pneumonia	558	5.634 (5.141, 6.174)	4.808	1740.722	No
Hypoglycemia	543	1.793 (1.635, 1.967)	1.656	156.752	Yes
Pulmonary hypertension	507	5.997 (5.453, 6.596)	5.189	1761.733	No
Anticholinergic syndrome	488	1.452 (1.318, 1.599)	1.382	57.493	No
Gastrointestinal, non-localized inflammatory dysfunction	481	1.458 (1.323, 1.607)	1.388	58.074	Yes
Non-infectious encephalopathy/delirium	478	1.685 (1.529, 1.858)	1.581	112.199	No
Neuroleptic malignant syndrome	472	1.798 (1.63, 1.983)	1.678	141.113	No
Angioedema	401	2.381 (2.144, 2.644)	2.204	278.501	Yes
Asthma/bronchospasm	382	16.225 (14.575, 18.063)	14.369	4751.657	Yes
Noninfectious encephalitis	377	1.451 (1.303, 1.616)	1.397	46.086	No
Cardiac arrhythmias	330	2.359 (2.105, 2.645)	2.216	229.767	Yes
Guillain-Barre syndrome	330	1.542 (1.376, 1.728)	1.485	55.663	No
Acute pancreatitis	301	1.384 (1.229, 1.559)	1.347	28.633	No
Hyperglycemia/new onset diabetes mellitus	285	1.337 (1.184, 1.51)	1.306	21.669	Yes
Noninfectious meningitis	275	1.418 (1.253, 1.605)	1.381	30.484	No

These included eosinophilic pneumonia, cardiomyopathy, and pulmonary hypertension, as presented in Table 5 and Table 6).

DISCUSSION

This study was based on FAERS database, and it identified potential safety profiles regarding the use of salbutamol and levosalbutamol. A total of 83,166 and 3,133 ADR reports for salbutamol and levosalbutamol, respectively, were identified across a wide range of individual characteristics from 18,606,922 reports in FAERS database. A total of 77 and 81 positive ADR signals were detected for salbutamol and levosalbutamol, respectively. The most common ADR for salbutamol included cardiac and vascular disorders, respiratory, thoracic and mediastinal disorders, and immune system disorders, while the ADRs for levosalbutamol were mainly manifested in cardiac and vascular disorders, nervous system disorders, and gastrointestinal, hepatobiliary and endocrine disorders. Moreover, it was observed that the incidence of cardiac, vascular, ear and labyrinth disorders; immune system disorders, infections and infestations, metabolic and nutritional disorders, psychiatric disorders; respiratory, thoracic and mediastinal disorders; surgical and medical procedures were higher in salbutamol than in levosalbutamol. Conversely, the use of salbutamol was associated with lower proportion of ADRs manifested in eye disorders, gastrointestinal, hepatobiliary, and endocrine, general disorders and administration site conditions, and nervous system disorders, when compared with levosalbutamol. This study identified 83,166 ADR reports related to salbutamol and 3,133 ADR reports related to levosalbutamol, and found more reports from females than from males. The most common age stages were 45.0 - 64.0 years for salbutamol, while for levosalbutamol, the most common age stages were 45.0 - 64.0 years and < 18.0 years. A total of 29,910 (35.96 %) and 1,436 (45.83 %) ADR reports were on the serious outcomes for salbutamol and levosalbutamol, respectively. The most serious levosalbutamol-associated outcome was hospitalization, which could be due to the high proportion of individuals aged 18.0 years or younger. Most ADRs were from USA, irrespective the drug type (salbutamol or levosalbutamol). This may be due to the fact that the FAERS databases were prepared in USA, and most clinicians in USA were involved. The number of ADR reports related to salbutamol was larger than that for levosalbutamol, which could be explained by the fact that salbutamol was marketed earlier than levosalbutamol, and more people used salbutamol than levosalbutamol. Moreover, the population of users from 2016 to 2020 was stable, while the ADR reports were increased. Therefore, the use of levosalbutamol should be recommended in

clinical practice to prevent these potential adverse events.

This study found that the proportions of ADRs which occurred as ear and labyrinth disorders, infections and infestations, metabolic and nutritional disorders, psychiatric disorders, and surgical and medical procedures for salbutamol were higher than the corresponding proportions for levosalbutamol. However, the use of salbutamol caused less proportion of ADRs in form of eye disorders, and general and administration site lesions, when compared with levosalbutamol. Several reasons could explain the above results: (1) the components of ADRs in the reports on salbutamol and levosalbutamol were not consistent, and this could affect the proportion of positive ADR signals; (2) the characteristics of individuals were not balanced; and (3) the proinflammatory effects differed between salbutamol and levosalbutamol, which could affect subsequent positive ADR signals [3].

Although the strength of disproportionality analysis was intrinsic to the FAERS database [14,15], several limitations of this study should be acknowledged. Firstly, the ADR reports in spontaneous reporting systems were underestimated, and not all of ADRs related to the investigated drugs were available from FAERS [16]. Secondly, duplicate ADR reports for the same event and person, misspelling and miswording might have occurred, which could have affected the effect estimated for specific ADR signal. The causal relationship between pharmacological agent and ADR could not be obtained, owing to the retrospective design of the study. Finally, the analysis of disproportionality was based on univariable results, and the characteristics of individuals were not adjusted, which might affect the risk of ADR related to each pharmacological agent.

CONCLUSION

To the best of our knowledge, this study is the first reported ADR profiles of salbutamol and levosalbutamol using the FAERS database. The proportions of ADRs for salbutamol manifested as cardiac, vascular, ear and labyrinth disorders, immune system disorders, infections and infestations, metabolic and nutritional disorders, psychiatric disorders; respiratory, thoracic and mediastinal disorders, and surgical and medical procedures, were higher than those of levosalbutamol. The ADRs of salbutamol which resulted in eye disorders, gastrointestinal, hepatobiliary, and endocrine disorders, general disorders, administration site lesions, and nervous system disorders, were less than those of levosalbutamol. Further pharmacovigilance studies should be conducted to verify the findings of this study, and determine whether individual characteristics s could affect the positive ADR signals related to salbutamol and levosalbutamol.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Wenzhong Peng and Ying Li conceived and designed the study, and drafted the manuscript. Wenzhong Peng, Jia Chen, Ruoxi He, Yongjun Tang, Juan Jiang, Ling Ouyang and Dandan Zhao collected, analyzed and interpreted the data. Jia Chen and Ruoxi He revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

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