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Original Article

A Comparative Safety Assessment of Levosalbutamol and Salbutamol, with the Conventional Drug Delivery System, Metered-Dose Inhaler, in Mild Asthma; with a Pharmacovigilance Monologue

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Abstract

Introduction: Short-acting β2-agonists, such as salbutamol and levosalbutamol, are the most commonly used bronchodilators for the routine treatment of mild asthma. Occupation of β2 receptors by agonists results in the activation of the Gs-adenylyl cyclase-cAMP-PKA pathway, resulting in phosphorylative events, leading to bronchial smooth muscle relaxation. A metered-dose inhaler is a portable and a very convenient drug delivery system, conventionally used in the treatment of mild asthma.

Objective: The aim of this pharmacovigilance (PV) study was to compare the safety of levosalbutamol with salbutamol inhalation therapy, in the routine treatment of mild asthma, with a PV monologue.

Methods: Fifty patients, with mild asthma, were randomly allotted to Group A=25 and Group B=25. The patients in Group A and Group B were prescribed the inhalation treatment of levosalbutamol and salbutamol, respectively, two puffs in each nostril, with a metered-dose inhaler, once in the early evening, for 2.5 months. After the inhalation dose, the patients were monitored for 10 h, for adverse effects, such as headache, tremor, irritation in the oral cavity, and palpitation, with Adverse Event Case Report Forms; and the observations were statistically analyzed.

Results: In both Groups A and B, the adverse effects of levosalbutamol and salbutamol were not statistically significant; and both were equally safe and tolerable.

Conclusion: Inhaler administered levosalbutamol and salbutamol was equally safe, as the prevalent drug-through-the-device therapeutic system, for treating mild asthma.

Key words: Pharmacovigilance, levosalbutamol, salbutamol, metered-dose inhaler, asthma, drug safety.

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INTRODUCTION

Short-acting β2-agonists, such as salbutamol and levosalbutamol, are the most commonly used bronchodilators for the routine treatment of mild asthma.

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Occupation of β2 receptors by agonists results in the activation of the Gs-adenylyl cyclase-cAMP-PKA pathway, resulting in phosphorylative events, leading to bronchial smooth muscle relaxation.[1]

Salbutamol is a mixed dextro- and levo-rotatory racemate, and levosalbutamol is the purified enantiomer of racemic salbutamol that has a greater affinity for the β2 receptor as compared to salbutamol; both causing bronchodilatation, inhibition of inflammation, and baseline airway reversibility.[1,2]

A metered-dose inhaler is a topical drug delivery system, conventionally used in the treatment of mild asthma. It is portable, very convenient, cost effective, less time consuming, less energy resources consuming, requiring less maintenance and with lesser adverse effects like ororespiratory mucosal irritation.

Inhaled medications for asthma are available as pressurized metered-dose inhaler, metered-dose inhaler with spacer, breath-actuated metered-dose inhaler, dry powder inhalers, soft mist inhalers, and nebulized or wet aerosols.

Inhaler devices differ in their efficacy of drug delivery to the lower respiratory tract, depending on:
1. Form of devices
2. Formulation of medication
3. Particle size
4. Velocity of aerosol cloud or plume
5. Ease with which device can be used by majority of patients

Studies have shown no statistically significant differences on spirometric variables such as peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC, after giving bronchodilators, by metered-dose inhaler, nebulizer or dry powder inhaler.

Choice of an inhaler device depends on:
1. Patient's age
2. Cognitive status
3. Visual acuity
4. Manual dexterity and strength
5. Ability to coordinate inhaler actuation with inhalation
6. Disease severity
7. Convenient to use
8. Portability
9. Cost-effectiveness.[3]

Objectives

The objective of this comparative, multicenter, pharmacovigilance (PV) study was the safety assessment of levosalbutamol and salbutamol, administered with the familiar drug delivery system, a metered-dose inhaler, in the routine treatment of mild asthma; along with a PV monologue.

METHODS

Study Type

This was a multicenter, prospective, randomized, open-labeled, comparative PV study; and a PV monologue.

Study Population

The study participants consisted of 50 patients, suffering from mild asthma.

Study Place

The research study and the compilation of the study literature were conducted in the Departments of Pharmacology, Clinical Pharmacology, Rational Pharmacotherapeutics, PV, Respiratory Medicine and Chest Diseases, Medical Administration, in Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, J. J. M. Medical College, Bapuji Hospital, Chigateri General Hospital, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Raipur Institute of Medical Sciences, and Fortis Hospitals.

Study Period

The study period for the research study and the compilation of the study literature were 2.5 months, that is, December 2020–February 2021; and October 2021–November 2021.

Ethical Approval

At first, the clearance and the approval from the Institutional Ethics Committee were obtained. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the regulatory requirements. Informed consent was obtained from each patient.

Selection Criteria of the Patients

Inclusion criteria

The following criteria were included in the study:
(a) Age >18 years, of any gender;
(b) British Thoracic Society definition of asthma grades;[4]
(c Ability to perform spirometry maneuvers;
(d) Cooperative and conscious patients.

Exclusion criteria

The following criteria were excluded from the study:
(a) Uncooperative and unconscious patients;

(b) Patients presenting with acute severe or acute life-threatening or near-fatal asthma;
(c) History of hypersensitivity to the study drugs;
(d) Pregnant or lactating women;
(e) Other associated medical illness having impact on study results;
(f) Children or very old patients.

Study Procedure

Fifty patients, with mild asthma, were randomly allotted to Group A = 25 and Group B = 25. The demographic characteristics of the patients, and the details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory and cardiopulmonary examinations, were recorded. Pulse rate, oxygen saturation of arterial hemoglobin (SpO2), and respiratory rate were recorded.

Spirometric variables such as PEFR, FEV1, FVC, and FEV1/FVC were recorded, after giving bronchodilators, by metered-dose inhaler. The patients in Group A and Group B were prescribed the inhalation treatment of levosalbutamol and salbutamol, respectively, two puffs in each nostril, with a metered-dose inhaler, once in the early evening, for 2.5 months. After the inhalation dose, the patients were monitored for 10 h, for adverse effects, such as headache, tremor, irritation in the oral cavity, and palpitation, with adverse event (AE) case report forms; and the observations were statistically analyzed with the test of significance with p values, with subsequent tabular representations.

RESULTS

The demographic characteristics of the study participants were comparable.

In both Groups A and B, the adverse effects of levosalbutamol and salbutamol were not statistically significant; and both were equally safe and tolerable, as depicted in Table 1.

DISCUSSION

PV plays a key role in assessing, monitoring, and preventing adverse drug reactions (ADRs). In recent years, national legislative bodies and national regulatory authorities (NRAs) across the world have issued a significant amount of legislation and guidance enforcing the obligation to perform PV activities. In countries where the NRA is a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), safety management requirements are generally consistent with ICH guidelines. In a number of countries beyond this scope, requirements may deviate from internationally agreed standards, adding a substantial complexity and increasing burden on the stakeholders involved, while the benefit for patients' safety may not be evident. Committed to fulfilling safety regulatory obligations in any country for a medicinal product license, global pharmaceutical companies have accumulated a broad and deep experience acquired while meeting the expectations of a large array of diverse PV systems across the world. These range from suboptimal frameworks, according to the World Health Organization (WHO) Global Benchmarking Tool, to highly effective resource-optimized PV systems. To support countries creating or further developing their PV systems, especially where infrastructure and resources are limited, the European Federation of Pharmaceutical Industries and Associations International PV Group (IPVG) has developed consensus recommendations consistent with harmonized standards for the development and step-wise implementation of key PV system components.

Table 1: Adverse effects of levosalbutamol and salbutamol, with their frequency of occurrence

Adverse effects	Levosalbutamol (*n*=25)	Salbutamol (*n*=25)	*P*-value
Headache	0	0	ns
Tremor	0	1	ns
Irritation in oral cavity	0	1	ns
Palpitations	0	0	ns

ns: Non-significant

The ability to oversee suspected ADRs and information on medicinal product use in special situations is fundamental to the detection, assessment, understanding, and mitigation of medicinal product risks. Various collection tools for such information are available depending on local needs and preferences, for example, telephone hotlines, paper forms, websites, and mobile applications such as the WEBRADR Mobile App. Suspected ADRs need to be maintained in a safety database. To maximize the use of limited resources, the IPVG recommends the use of the WHO's VigiFlow when not setting up a specific national database.

Further elements of a national PV system may include:

- Requirements for the submission of periodic safety reports,
- Requirements for the submission of risk management plans,
- Requirements for a written description of the key stakeholders' PV system,
- Establishment of a local safety responsible,

The priority and the order in which each element may be added will depend on local needs, available resources, and preferences in relying on outputs from other regulators, and the choice to use own or NGO-offered safety systems either temporally or permanently.

A successful reporting system requires public awareness. The IPVG recommends that global public awareness tools such as those provided by the Strengthening Collaboration for Operating PV in Europe initiative and by the Uppsala Monitoring Center (UMC) are used to increase public awareness and importance of ADR reporting. Educational material for health-care professionals (HCPs) is also available through SCOPE and may be used for training of HCPs in university courses and beyond. It is recommended that public health campaigns center around a specific public health initiative, for example, a vaccination program or an emergency medicine.

The foundation of any national PV system is a national reporting system. Such a system facilitates the collection of AEs and information on medicinal product use in special situations from HCPs and consumers/patients, and the expedited reporting of suspected ADRs as individual case safety reports (ICSRs). ICSR data form the basis of a national dataset for medicinal products. This dataset is constantly evolving based on the information received. ICSR data also serve as the basis for the detection of safety signals, the review of the benefit–risk relationship in periodic safety reports, and risk management planning. NRAs receiving ICSRs in an expedited manner, that is, within specific timelines, should assess individual reports soon after receipt. If a significant public health concern is identified, the NRA should quickly take regulatory action to mitigate risks to patients. The most accepted standards for PV come from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), which have set many of the founding principles for PV, including the CIOMS form for reporting suspected ADRs. In addition to the collection of AEs, collection of information on medicinal product use in special situations is required by many regulators for systematic safety surveillance. This information can be collected in the same way as AEs. ICSRs should be considered valid for expedited reporting only if the report contains the four minimal criteria as described in the ICH E2D guidance. The minimum criteria for ICSRs valid for regulatory reporting are as follows:

1. An identifiable reporter,
2. A single identifiable patient,
3. A suspect medicinal product,
4. A suspect adverse reaction.

To support their national PV database, NRA members of the WHO Programme for International Drug Monitoring (WHO-PIDM) are entitled to use the VigiFlow system made available by the UMC, the WHO-associated center for international drug monitoring. VigiFlow is an online platform, structured according to country-specific ICSR containers owned, and controlled by the respective NRAs. VigiFlow includes functionality to let NRAs forward ICSRs to VigiBase (the global WHO PV database). In addition, any NRA contributing to the WHO-PIDM (using VigiFlow or not) has access to VigiBase to search for signals at country, regional, or global levels, using VigiLyze, an advanced online analytic tool supplied by the UMC. VigiLyze also allows a NRA to view foreign ICSRs as they relate to a search topic.

The IPVG recommends that NRAs request marketing authorization holder (MAHs) to collect information on all domestic AEs as well as cases of parent–child exposure even if no AE occurred. Other domestic cases of exposure in special situations lacking the occurrence of any AE do not require expedited reporting, but should be compiled by the MAH and reported in the Periodic Benefit Risk Evaluation Report (PBRER). For expedited reporting, the following reporting timelines are recommended:

- 15 calendar days for serious ICSRs as per ICH E2D guidance.
- 90 calendar days for non-serious ICSRs as per European Union (EU) Good Vigilance Practice (GVP)

For access to foreign ICSRs, the IPVG recommends considering accessing the WHO's VigiBase, the largest global PV database, currently containing over 20 million ICSRs, using the WHO's VigiLyze software. VigiLyze is exclusively reserved for NRAs contributing to the WHO-PIDM, free of charge, and represents a powerful and resource-efficient alternative to the receipt of foreign ICSRs from MAHs. In addition, the VigiLyze data analytic tool can be used to perform signal detection and other analytic investigations at the country, regional, or global level.

A medicinal product is authorized for marketing if the applicant can demonstrate sufficient evidence for quality, safety, and efficacy in the specified indication(s) and target population(s). As the investigated clinical trial population is usually limited in size and duration of drug exposure, as well as selective for criteria such as age, gender, genetic variants, concomitant diseases, and comedication, not all ADRs and risks will be known at the time of the initial marketing authorization. In fact, certain ADRs and risks can only be discovered or further characterized post-authorization. According to internally accepted standards and regulations, MAHs should, therefore, have continuous safety monitoring and signal management systems in place that permits early detection of potential new risks or potentially changed characteristics of known risks. Signal management is defined as a set of activities performed to determine whether, based on an examination of ICSRs, aggregated data from active surveillance systems or studies,

scientific literature information, or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications, and tracking. Depending on the size of the dataset, different signal detection methodologies or combinations of methodologies may be used. Review of global safety data should reside with experienced staff of the MAH that owns the global safety database for the medicinal product and who are in the position to oversee and analyze signals from all sources from the totality of the globally available dataset relevant to a given safety issue. If a MAH does not own or have access to the global safety database or lacks the expertise to conduct signal detection and analysis, the MAH may delegate some or all activity to the global safety database-owning organization. Review of national safety data for local signals by NRAs/national PV centers may contribute to understanding a medicinal product's safety profile in the local market and may focus on, for example, medication errors, off-label use, misuse, abuse, or potential risks described in RMPs. Regional and/or global data may supplement local data as appropriate. For example, identified similarities of national data with regional or global data will further strengthen a local signal, whereas differences between national and regional/global data may help in identifying factors that are specific to a country/region and need to be considered when discussing appropriate local risk minimization measures. For reviewing pools of individual safety data, the IPVG recommends using VigiLyze for searching into the WHO PV database (VigiBase) to detect signals at the country level compared to searches at the regional or global levels. NRAs may also consider networking with stakeholders or other NRAs for confirmation of their signal detection finding and/or use signal detection outcomes from established NRAs as surrogates for their own analyses.

Signal reporting from the MAH to NRAs should be proportionate to the information arising from the signal analysis. The IPVG proposes a risk appropriate approach to signal reporting similar to recommendations made by the Swiss medic and that those signals that require in-market action (e.g., product information update, direct market communication, and marketing authorization suspension/revocation/withdrawal for safety reasons) should be notified to an NRA.

The IPVG also recommends using common terminology such as the terminology proposed by the CIOMS or EU-GVP to avoid misunderstandings in reportability of signals to NRAs. The term "emerging safety issue" should only be used for the most serious risks where an immediate in-market action is required to protect patients and public health.

Periodic safety reports such as the EU Periodic Safety Update Report (PSUR) provide a review of the current benefit–risk profile of a medicinal product, taking into account, all available worldwide data including:

- Safety, efficacy, and effectiveness data
- Use of the medicinal product in authorized and non-authorized ("off-label") indications
- Missing data (e.g., data in special populations)

For a consistent global approach to the periodic evaluation of a medicinal product's benefit–risk profile, the IPVG recommends the use of the PBRER format as outlined by the ICH E2C guidance. The PBRER is very comprehensive, describing post-marketing data, data from completed and ongoing clinical trials, relevant non-interventional studies and other activities, cumulatively, and for the specified report period, at a global level. The document also presents a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product in the context of its benefits, taking into account new information from the last reporting period and cumulative information. The analysis of the risks is based on the reference safety information. The International Birth Date (IBD) is the date of the first marketing authorization for any medicinal product containing the active substance granted to an applicant in any country in the world. Using a single birth date such as the IBD and aligned review periods/data lock points (DLPs) for periodic safety reports worldwide is recommended, not only for harmonization purposes and reduction of administrative burden but also to facilitate true global periodic benefit–risk assessment for the medicinal product. In addition, the IPVG recommends aligning the periodicities of existing country-specific periodic safety reports with the periodicities of the global benefit–risk assessments in the PBRERs to allow for direct comparability of local data with global data and the interpretation of local data in the context of available global data from all sources. The PBRER should preferably be written in a commonly understood technical language, that is, English, to allow for consistency and avoid translation errors. Should translations into national languages be required, a translation of the executive summary could be an effective approach, as it contains a summary of the key information contained in the document. The frequency of report submission to NRAs depends on factors such as the length of time the medicinal product has been on the market, product-specific risks, and the extent of knowledge regarding the product's benefit–risk profile. In general, PBRER periodicities and submission frequencies for newly authorized medicinal products in a country should follow ICH E2C and/or EU-GVP recommendations and be based on the DLP calculated from the IBD, that is, 6-month periodicity the first 2 years after approval, then annually for the subsequent 3 years. When a newly authorized medicinal product in a country already has a marketing authorization in

a reference country, the IPVG recommends alignment with the periodicity and submission frequency for the medicinal product in the reference country or alignment with the periodicity and submission frequency as described in the EU Reference Dates list. The IPVG recommends harmonized timelines for PBRER preparation and submission according to internationally acceptable timelines such as:

- Within 70 calendar days of the DLP for PBRERs covering intervals up to 12 months.
- Within 90 calendar days of the DLP for PBRERs covering intervals in excess of 12 months.

Furthermore, the IPVG would like to mention that the European Medicines Agency (EMA) has an EU-GVP for PSUR assessment report (PSUSA) in place where one EU member state ensures a coordinated single assessment for medicinal products that contain the same active substance or combination of active substances. The PSUSA procedure is an excellent example of resource-effective regulatory reliance advocated earlier.[5]

CONCLUSION

Inhaler administered levosalbutamol and salbutamol was equally safe, as the prevalent drug-through-the-device therapeutic system, for treating mild asthma. Therefore, this PV research study rendered an elaborate medical treatise regarding the algorithmic logistics of ADRs monitoring mechanisms.

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