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PERSONALIZED MEDICINE FOR HIGH ALERT DRUGS IN RESPIRATORY DISEASES

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ABSTRACT

Background: Personalized medicine has significant potential for enhancing high-alert respiratory medication treatment, particularly emphasizing pharmacogenomics. Understanding the impact of genetic variations on drug responses can lead to improved patient care and minimized adverse reactions. This study reviews the current status and challenges of personalized medicine in high-alert respiratory drugs, exploring its potential to modify patient care and treatment outcomes. **The main body of the abstract:** This study aims to explore the application of personalized medicine in high-alert respiratory drugs by considering genetic factors and individual variations. The objective is to enhance patient safety and treatment efficacy while reducing the burden of respiratory diseases. The study discusses the genetic determinants of drug response in bronchodilator therapy (Albuterol, Salmeterol, and Formoterol), corticosteroid response (Fluticasone, Budesonide, and Prednisone), and anaesthesia (propofol) in respiratory problems. It highlights the role of pharmacogenomics in optimizing drug effectiveness and reducing adverse reactions. Additionally, the study emphasizes the significance of genetic variability and genotype-based therapies. **Conclusion:** Personalized medicine, especially pharmacogenomics, can change high-alert respiratory drug treatment by tailoring therapies based on individual genetic profiles. Despite challenges, implementing personalized medicine can improve patient care and treatment outcomes. Further research is essential to overcome barriers and integrate pharmacogenomics into routine healthcare for personalized respiratory drug therapy.

KEYWORDS: Personalized medicine, pharmacogenomics, high-alert respiratory drugs, genetic variability, and treatment efficacy.

INTRODUCTION

The study of pharmacogenomics, in particular, can change high-alert respiratory medication treatment. Despite challenges in implementation, understanding the impact of genetic variations on drug responses can optimize treatment outcomes and minimize adverse reactions, ultimately improving patient care.[1-4] This study reviews the current status, challenges, and prospects of personalized medicine for high-alert respiratory drugs, aiming to offer valuable insights and recommendations for effective implementation. By tailoring treatments based on genetic factors, personalized medicine can revolutionize patient care, particularly in complex diseases like cancer, leading to improved outcomes and reduced adverse reactions.[5, 6]

High-alert respiratory drugs are bronchodilators (Albuterol, salmeterol, and formoterol), corticosteroids (Fluticasone, budesonide, and prednisone), anaesthesia (Propofol), and oxygen therapy, which pose significant risks if not used properly. If these drugs are overused or given in excess amounts, side effects such as tachycardia, hyperglycemia, and neuropsychiatric events may happen, but respiratory depression is a significant adverse effect.[7,8] Personalized medicine holds promise in optimizing the use of high-alert respiratory drugs by considering genetic factors and individual variations, enhancing patient safety and treatment outcomes.[9] This study explores the potential of personalized medicine in improving medication safety and addressing the challenges associated with high-alert respiratory drugs, emphasizing the importance of patient monitoring and education.[10-12]

Respiratory diseases like Asthma and Chronic obstructive pulmonary disease (COPD), cystitis fibrosis,

and lung cancer (many diseases) have a significant global impact, contributing to a substantial number of deaths worldwide. The long-term use of respiratory drugs is necessary for disease management, but these medications can carry significant side effects.[13] Implementing personalized medicine in respiratory drug therapy becomes crucial for optimizing treatment outcomes and minimizing adverse reactions.[14,15] The current study explores the potential of personalized medicine in improving respiratory drug therapy by considering individual genetic variations and response patterns, aiming to enhance patient care and reduce the burden of respiratory diseases.[15,16]

Pharmacogenomics, the study of how genetic factors influence drug responses, holds great potential for personalized medicine.[17] Understanding patients' genetic profiles allows healthcare providers to customize treatment plans, maximizing effectiveness and minimizing adverse reactions, particularly in the context of respiratory drug prescriptions. The current review article explores the application of personalized medicine and pharmacogenomics in optimizing patient care and treatment efficacy for high-alert respiratory drugs, highlighting the importance of genetic variability and genotype-based therapies.[18] Patient care and reduce the burden of respiratory diseases.[15,16]

Personalized medicine has significant implications for personalized medicine in high-alert respiratory drugs, as it identifies genetic variations impacting drug response and allows tailored treatment plans. Analysis of genetic information reduces adverse reactions and improves treatment effectiveness by identifying variations in drug response. This review explores the application of pharmacogenomics in high-alert respiratory drugs, emphasizing personalized treatments and minimized risks through genetic testing. Integrating genetic information into prescribing enables optimal outcomes and reduced adverse reactions.[19] The study aims to enhance patient care and treatment efficacy through personalized medicine in high-alert respiratory drugs.

The implementation of pharmacogenomics in respiratory drug therapy faces challenges and limitations, such as cost, availability, interpretation of genetic data, and integration into routine healthcare. Overcoming these barriers is crucial for the widespread adoption of personalized medicine in respiratory drug prescriptions.[19] Improved research and development efforts are needed to address these challenges and effectively integrate pharmacogenomics into standard clinical practice for personalized respiratory drug therapy.

The review summarizes the current knowledge on pharmacogenomics for high-alert respiratory drugs, including genetic variants and their impact on drug metabolism, response, and adverse reactions. It evaluates clinical evidence, identifies research gaps, and provides guidance for implementing pharmacogenomics in respiratory medicine to enhance patient care and treatment outcomes.[20]

PERSONALIZED APPROACHES IN BRONCHODILATOR THERAPY

Bronchodilators, essential in the management of respiratory disorders like asthma and COPD, exhibit interindividual variability in efficacy and safety. Pharmacogenomics studies have identified specific genes, including ADRB2 (beta-2 adrenergic receptor gene) and GSTP1 (glutathione S-transferase gene), that influence drug metabolism, response, and potential adverse reactions. Albuterol, salmeterol, and formoterol (Fig. 1) are a few examples of bronchodilators metabolized by the ADRB2 and GSTP1 enzyme system.

Fig. 1: Understanding the Significance of High-Risk drugs in Respiratory Pharmacotherapy.

ALBUTEROL

Albuterol is classified as a short-acting beta agonist (SABA) that functions by binding to the beta-2 adrenergic receptor. Albuterol, a short-acting β2-agonist, exerts its effects through binding to ADRB2 on airway smooth muscle cells.[21] This leads to bronchodilation and significantly improves breathing for individuals who have asthma. The ADRB2 gene is associated with the response to albuterol treatment in asthma patients since it encodes the beta-2 adrenergic receptor. Studies have revealed that genetic variations in this gene can impact the effectiveness of albuterol treatment. Specifically, individuals with the arginine-16 (Arg16) homozygous genotype exhibit a more acute response to SABA bronchodilation when compared to those with the Gly16 homozygous genotype.[22-26] The ADRB2 gene exhibits significant polymorphism, with multiple single nucleotide polymorphisms (SNPs) reported[27], some of which result in amino acid changes and impact protein structure.[28] Studies indicate that specific variants, such as Ile164, lead to reduced receptor activation duration.[29, 30], while the glycine-16 (Gly16) allele is associated with enhanced ADRB2 down-regulation.[31] In a multi-ethnic asthma population, it has been observed that rare genetic variants in the ADRB2 gene can influence the likelihood of experiencing severe exacerbations and the level of symptom control during long-acting beta-agonist treatment. These genetic variations have been found to impact the risk and effectiveness of long-acting beta-agonist treatment in individuals with asthma.[32] In an Indian asthmatic population, individuals with the Arg16 homozygous genotype showed a lower response to albuterol.[33]

SALMETEROL

Salmeterol, similar to albuterol, acts as a beta-2 adrenergic receptor agonist, resulting in bronchodilation for individuals with asthma. However, the gene associated with the response to salmeterol differs from that of albuterol. In patients treated with formoterol and salmeterol, those with the Arg16 homozygous genotype have been observed to exhibit bronchoprotective subsensitivity. Furthermore, studies indicated that the Arg16 genotype was linked to a more favourable response to personalized second-line therapy in children with asthma.[34-36]

FORMOTEROL

A long-acting beta-2 adrenergic receptor agonist is a type of medication formoterol. It is commonly used to induce bronchodilation in patients with asthma. By binding to the β2 adrenergic receptor, formoterol initiates a cascade of events within the G-protein coupled receptor pathway. This activation ultimately triggers the production of cyclic AMP, resulting in the relaxation of smooth muscles.[37-41] While administered formoterol and salmeterol, the Arg16 homozygous genotype has been shown to have bronchoprotective subsensitivity.

Furthermore, a study revealed that asthmatic children with the Gly16 genotype demonstrated a more favourable response to formoterol. Extensive research has focused on the ADRB2 gene, which encodes the β2 adrenergic receptor, particularly in asthma pharmacogenetics. Various genetic variations within the ADRB2 gene have been identified and linked to the response individuals have to beta-2 agonists, including formoterol.[42-45]

GENETIC DETERMINANTS OF CORTICOSTEROID RESPONSE IN RESPIRATORY PROBLEMS

Glucocorticoids are crucial in a biological pathway involving biosynthetic hormones that bind and activate a cytosolic chaperone-receptor heterocomplex, which subsequently translocates into the nucleus. This process leads to the repression of proinflammatory gene transcription and the enhancement of anti-inflammatory gene transcription.[46, 47] The response to systemic glucocorticoids, such as corticosteroids, in respiratory conditions like asthma can vary among individuals. Genetic factors, including variants in genes such as NR3C1 (glucocorticoid receptor), FKBP5 (glucocorticoid receptor co-chaperone protein), and CRHR1 (corticotropin-releasing hormone receptor 1), have been associated with the response to systemic glucocorticoids in asthma patients. Understanding the genetic basis of individual responses to corticosteroids (Fluticasone, Budesonide, Prednisone) (Fig. 1) can contribute to the development of personalized medicine approaches for respiratory problems, optimizing treatment outcomes and patient safety.[48, 49]

FLUTICASONE

Fluticasone, an inhaled glucocorticoid, functions as an anti-inflammatory agent within the lungs of individuals with asthma. It achieves this by binding to the glucocorticoid receptor, which results in the activation of anti-inflammatory genes and the inhibition of proinflammatory genes. The response to inhaled glucocorticoids involves multiple genes, including CRHR1, STIP1, and GLCCI1 (glucocorticoid-induced 1), which have been associated with the effectiveness of this treatment.[48-53] A specific study has identified that sequence variants in the CRHR1 gene are linked to enhanced lung function in individuals with asthma who are undergoing treatment with inhaled corticosteroids. These genetic variations have been found to influence the respiratory capacity and improvement observed in asthmatic patients receiving inhaled corticosteroid therapy. Similarly, the gene STIP1, which encodes the glucocorticoid receptor heterocomplex, has been linked to enhanced lung function in individuals with asthma who receive treatment with inhaled corticosteroids. Conversely, a genome-wide association study (GWAS) revealed that a variant in the GLCCI1 gene was associated with a reduced response to inhaled glucocorticoids.[48, 49, 54] These genes CRHR1, STIP1, TBX21(T-box transcription factor 21), and GLCCI1 to

fluticasone response. These studies encompassed candidate gene approaches, and GWAS and the response phenotypes evaluated included FEV1(forced expiratory volume 1) response and broncho protection.[32]

BUDESONIDE

Budesonide is an inhaled glucocorticoid used as an anti-inflammatory agent in asthma patients. It functions by binding to the glucocorticoid receptor, thereby activating anti-inflammatory genes and suppressing proinflammatory genes in the lungs. Notably, specific genes such as CRHR1, STIP1, and GLCCI1 have been linked to the response to inhaled glucocorticoids. In a GWAS, researchers identified a variant in the GLCCI1 gene associated with a reduced response to inhaled glucocorticoids. These findings provide valuable insights into the genetic factors influencing the efficacy of budesonide in asthma treatment.[55-58] Glucocorticoids exert their therapeutic effects by targeting a biological pathway involving biosynthetic hormones. These hormones bind to and activate a cytosolic chaperone-receptor heterocomplex in the cytosol. The activated complex then translocates into the nucleus, where it represses the transcription of proinflammatory genes while enhancing the transcription of anti-inflammatory genes. Notably, specific sequence variants in CRHR1 have been linked to improved lung function in asthmatic patients treated with inhaled corticosteroids. Similarly, the gene STIP1, which encodes the glucocorticoid receptor heterocomplex, has also been associated with improved lung function in subjects with asthma undergoing inhaled corticosteroid treatment. These findings highlight the significance of genetic factors in modulating the response to glucocorticoid therapy in asthma management.[48-53]

PREDNISONE

Prednisone is a systemic glucocorticoid utilized for treating asthma exacerbations and as a chronic controller therapy. By binding to the glucocorticoid receptor, it initiates the activation of anti-inflammatory genes and concurrently suppresses proinflammatory genes. This dual mechanism of action enables prednisone to mitigate inflammation in asthma patients effectively. Its role as both an acute treatment for exacerbations and a long-term controller therapy highlights its significance in managing asthma.[46,47]

Bentley et al. conducted a study investigating how prednisolone treatment impacts gene expression in the bronchial mucosa of individuals with asthma. The results of the study demonstrated that prednisolone treatment led to a decrease in the expression of genes related to inflammation, such as IL-4, IL-5 (interleukins), and interferon-gamma.[59-61]

PERSONALIZED MEDICINE IN ANAESTHESIA: INTEGRATING GENETIC FACTORS FOR ENHANCED PATIENT MANAGEMENT

Anaesthesia, as a critical component of perioperative care, is an area where personalized medicine has the potential to revolutionize patient management. By considering an individual's genetic profile, anaesthesiologists can optimize drug selection, dosage, and administration techniques to enhance efficacy and minimize adverse effects.[62]

According to a study by *Smith et al.* (2018), respiratory factors are crucial in individualized anaesthesia management. Factors such as lung function, respiratory comorbidities, and airway anatomy contribute to the variability in drug response and ventilation requirements during anaesthesia. Furthermore, genetic variations associated with respiratory function and drug metabolism can impact the efficacy and safety of anaesthetic agents.[63]

PROPOFOL

Propofol is an essential drug with potential pharmacodynamic and pharmacokinetic variability. The pharmacodynamic variability of Propofol may be linked to the genes that encode the epsilon subunit of the GABA A receptor (GABRE). On the other hand, the pharmacokinetic variability of Propofol is potentially associated with the cytochrome P450 2B6 (CYP2B6) gene.[64]

Propofol is an agonist for GABA receptors and inhibits glycine, nicotinic, and M1 muscarinic receptors. It undergoes metabolism by human UDP Glucuronosyltransferase family one member A9 (UGT1A9) and intestinal or liver microsomes. Additionally, it can be metabolized by cytochrome P450 3A4 (CYP3A4), primarily by CYP2B6 and cytochrome P450 2C9 (CYP2C9) (Table 1).[65-68]

The results of Iohom and colleagues investigated the genetic determinants of propofol requirements and recovery from anaesthesia.[69-75]

Table 1: Drugs and gene interaction and their response.

DRUGS	GENES	RESPONSES
Albuterol	ADRB2	Improved bronchodilation
	Arg16Gly, Arg19Cys, Glu27Gln, Val34Met, and Thr164Ile	Variable response
Salmeterol, Formoterol	Arg16	Bronchoprotective sensitivity
Fluticasone, Budesonide	CRHR1, STIP1 and GLCCI1	Inflammatory modulation, Lung function
Prednisone	IL-4, IL-5, and Interferon-gamma	↓inflammatory response
Propofol	UGT1A9, CYP 3A4, CYP 2B6 and CYP 2C9	Metabolism variation

CONCLUSION

Personalized medicine, focused explicitly on pharmacogenomics, shows significant potential in improving patient care and treatment outcomes for high-alert respiratory drugs. Utilizing individual genetic variations and response patterns enables healthcare providers to customize treatment plans, optimizing their effectiveness while minimizing adverse reactions. However, the successful integration of pharmacogenomics into respiratory drug therapy faces various challenges, including cost, availability, data interpretation, and routine healthcare integration. Despite these obstacles, personalized medicine remains vital for enhancing medication safety and addressing the complexities of high-alert respiratory drugs. Further research and dedicated efforts are necessary to advance the implementation of personalized medicine in respiratory medicine and ensure its widespread application for optimal patient care.

Abbreviations

Arginine-16 (Arg16)
Beta-2 adrenergic receptor gene (ADRB2)
Corticotropin-releasing hormone receptor 1 (CRHR1)
Cytochrome P450 2B6 (CYP2B6)
Cytochrome P450 2C9 (CYP2C9)
Cytochrome P450 3A4 (CYP3A4)
Forced expiratory volume 1(FEV1)
Glucocorticoid receptor co-chaperone protein (FKBP5)
GABA A receptor (GABRE)
Glucocorticoid induced 1 (GLCCI1)
Glycine-16 (Gly16)
Glutathione S-transferase gene (GSTP1)
Genome-wide association study (GWAS)
Glucocorticoid receptor (NR3C1)
Interleukins (I.L.)
Short-acting beta agonist (SABA)
Single nucleotide polymorphisms (SNPs)
Stress-Induced Phosphoprotein-1 (STIP1)
TBX21 (T-box transcription factor 21)
UDP Glucuronosyltransferase family 1member A9 (UGT1A9)

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