Vancomycin-Resistant Enterococci and Vancomycin-Resistant Staphylococcus aureus: Heralding the end of the antibiotic era?

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The emergence of organisms resistant to commonly utilized antimicrobial agents has reached global epidemic proportions. In particular, nosocomial pathogens with antimicrobial resistant phenotypes, are presenting significant clinical difficulties. These difficulties arise due to limited efficacious antimicrobial agents available to treat patients infected with these organisms. Two organisms which currently represent major nosocomial pathogens include enterococci and Staphylococcus aureus. Both organisms exhibit antimicrobial resistant phenotypes which currently make clinical management difficult. Vancomycin-resistant enterococci (VRE) is endemic in many major US hospitals and outbreaks of this organism have been documented in Canada. More recently, isolates of vancomycin-resistant Staphylococcus aureus (VRSA) have been identified in Japan and the US. Vancomycin is often the last line antimicrobial available for treatment of infections caused by these organisms which have acquired resistance to virtually all other antimicrobials used. Therefore, infection control policies must be strengthened to contain the spread of these organisms. As well, these infection control policies must be utilized in conjunction with specific guidelines concerning antimicrobial usage to prevent the selection of new resistant organisms.

INTRODUCTION

The discovery and subsequent development of antimicrobial agents in the 1940s and 50s revolutionized medical care worldwide. For the first time, fatal infectious diseases such as tuberculosis and pneumonia could be treated effectively and countless lives were saved. However, the dawn of the antibiotic era was quickly accompanied by the emergence of microbes with resistant phenotypes to each of the antimicrobials used. Historically, combating antibiotic resistance was simple; use a different antimicrobial. The large number and variety of antimicrobial agents developed by pharmaceutical industry in the past 30 years overshadowed the potential impact of antibiotic resistance and resulted in a sense of complacency by clinicians and scientists. Increasingly however, the spread of antibiotic resistance is posing a significant obstacle to the successful treatment of infectious diseases worldwide.

Currently, resistance has been reported to nearly all classes of antimicrobials known. Furthermore, all the major bacterial pathogens have been shown to have antibiotic resistant variants and pathogens such as Mycobacterium tuberculosis, previously thought to be effectively controlled, are making successful comebacks (1). Intensive investigation into the basis for new resistant phenotypes has shown that bacteria have the ability to modify existing or acquire new genetic elements. The latter encode proteins which function to neutralize the effects of the various antimicrobial agents. Antimicrobial agents are classed by mechanism of action such as inhibition of cell wall synthesis, inhibition of cytoplasmic membrane synthesis, inhibition of nucleic acid synthesis, inhibition of protein synthesis and modification of energy metabolism (2). Remarkably, clinical bacterial isolates have exhibited resistant phenotypes to each of these classes by a variety of mechanisms including new chromosomal mutations, activation of latent genes or the acquisition of new genetic elements from the environment. Equally as

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disturbing as the ability of bacteria to rapidly develop new antibiotic resistance is their ability to effectively disseminate genetic resistance determinants throughout the bacterial populations. Gene dissemination has been traced throughout bacterial populations by a variety of molecular mechanisms which have demonstrated the role played by chromosomally encoded genes, extrachromosomal elements called plasmids, segments of DNA called transposons, and bacterial viruses in the spread of antibiotic resistance (3).

Both *Staphylococcus aureus* and *Enterococcus* species have acquired multiresistance to antimicrobials. These common pathogens are becoming increasingly more difficult to treat as they accumulate new antimicrobial resistance determinants (4,5).

**VANCOMYCIN-RESISTANT ENTEROCOCCI**

Enterococci are gram-positive, facultative anaerobic organisms which grow as singles, pairs or short chains (6). As human commensal organisms, the enterococci are well adapted to survival within the gastrointestinal tract. They are also found in a variety of niches including soil, food, water and living animals where they often represent a significant portion of normal gut flora (7). Although not particularly pathogenic, enterococci are the second most common cause of nosocomial infections in the United States and are responsible for a number of diseases ranging from urinary tract infections to life threatening bacteremia and endocarditis (8,9). Several additional clinical syndromes associated with enterococcal infection include intra-abdominal, biliary tract and indwelling foreign device infections (10,11).

The genus *Enterococcus* consists of at least 19 species of which *Enterococcus faecalis* and *Enterococcus faecium* represent the most clinically relevant organisms. *E. faecalis* is observed in approximately 80-90% of clinical isolates, while *E. faecium* accounts for 10-20% (7). These organisms possess virulence factors which facilitate attachment and colonization of host tissues, tissue invasion and immune modulation. Furthermore, the relative ease with which genetic material is horizontally transferred between members of the *Enterococcus* genus and between enterococci and other gram-positive organisms has long been observed (12). The promiscuity of the *Enterococcus* genus coupled with this organism’s extremely adept ability to horizontally shuffle genetic material, has facilitated the dissemination of antibiotic resistance traits throughout the genus, resulting in strains of *Enterococcus faecium* that are resistant to every useful antibiotic described (13). Accordingly, the emergence of enterococci as major nosocomial pathogens is due in part to the organism’s ability to survive and thrive in the hospital environment where antibiotic usage is high and therefore selection is heavy.

In 1988, the first evidence of a vancomycin-resistant enterococcus (VRE) was reported in Europe by Courvalin et al. in the *New England Journal of Medicine* (14). Detailed investigation of multiple subsequent isolates of vancomycin-resistant organisms in the following years resulted in the identification of three distinct antibiotic resistant phenotypes: VanA, VanB and VanC (15). Phenotypic characterisation of vancomycin-resistant enterococci is based on the susceptibility of the organism to both vancomycin and teicoplanin (a yet unlicensed glycopeptide antibiotic in North America). The VanA phenotype is characterised by a high level resistance to both vancomycin and teicoplanin [minimum inhibitory concentration (MIC) >64 μg/mL and MIC>16 mg/L, respectively]. Similarly, VanB phenotypic isolates are resistant to vancomycin of varying concentrations (MICs range from 4mg/L to >1000mg/L), but are susceptible to teicoplanin. Both the VanA and VanB phenotypes are inducible in the presence of vancomycin and both phenotypes are transferable by conjugation in certain strains. In contrast to VanA and VanB phenotypes, the enterococcal species *E. gallinarum* and *E. casseliflavus* are intrinsically resistant to low levels of vancomycin (MIC 4-32 mg/L), and susceptible to teicoplanin (15). These species of enterococci represent type VanC, a non-transferable phenotype. As will be discussed, each of the different phenotypic resistance mechanisms are due to the presence of specific genetic elements. Therefore more recent phenotypic classification schemes have been largely supplanted by genotypic mechanisms which function to identify the presence or absence of the specific genes.

**Resistance Mechanism**

Vancomycin, the prototype glycopeptide antibiotic, was first discovered in the 1950’s (17). Unlike β-lactam antibiotics, glycopeptides are inhibitors of cell wall synthesis which do not interact with cell wall biosynthesis enzymes. Rather, these large rigid molecules interact with peptidoglycan precursors at the outer cell membrane surface and thereby disrupt the cross-linking of glycan strands essential for the maintenance of cell wall integrity (18). Vancomycin is active against the majority of gram-positive bacteria. Possibly the most appealing feature of glycopeptides to physicians in the 1980’s was the belief that the development of resistance to a class of antibiotics with such a unique mechanism of action would be difficult, if not impossible. Such views were summarised in 1989 by P.E. Reynolds who wrote; "It is also difficult to envisage development of resistance arising from a change in the target site because of the complexity of the peptidoglycan biosynthetic pathway. Changes involving the complete refashioning of peptidoglycan synthesis could not be achieved rapidly, if at all" (18).

Biochemical characterisation of the mechanism of vancomycin resistance demonstrated that in fact enterococci were able to alter peptidoglycan synthesis. In both VanA and VanB clinical isolates, the normal target site for vancomycin binding, the peptidoglycan precursor peptidyl-D-alanyl-D-alanine is altered. In vancomycin-resistant cells the depsipeptide D-alanine-D-lactate, which has significantly reduced affinity for vancomycin, is preferentially synthesized (19). The presence of this novel structure within the bacterial cell wall reduces vancomycin binding and, therefore, confers vancomycin resistance.

**Epidemiology and Clinical Management**

In comparison with such organisms as *Staphylococcus aureus* or *Streptococcus pneumoniae*, enterococci are con-
sidered weakly virulent. However, the impact of this organism is significantly heightened by the acquisition of antimicrobial resistance including vancomycin resistance, as there are often no effective therapeutic agents commercially available for patients infected with VRE. The lack of efficacious therapeutic options for treatment of VRE, coupled with a growing number of world-wide nosocomial outbreaks of this organism (21-23), has resulted in severe medical and economic problems associated with control and eradication of this bacterium.

Clusters of vancomycin resistant enterococcal infections were observed as early as 1988, and since then have been found with increasing frequency. Initially it was believed that enterococcal isolates causing infection originated endogenously. However, study of enterococcal isolates from outbreak situations by molecular typing mechanisms have demonstrated clonal dissemination of particular organisms throughout hospital wards (23,24). Between April and December 1993 an outbreak of vancomycin-resistant Enterococcus faecium occurred in an adult oncology unit in a community teaching hospital located on the east coast of the United States (23). VRE had not been previously identified as a cause of blood stream infection in this hospital. In the 9 month surveillance, 11 patients developed VRE bacteremia. Eight (73%) of the patients died on median post-infection day 8.5. Four deaths were directly attributable to VRE infection.

Outbreaks such as these have led to the introduction of infection control measures such as VRE screening in stool, isolation of colonized and infected individuals, educational programs and restrictions on the unnecessary use of vancomycin (25). Surveillance screening during outbreaks have isolated glycopeptide-resistant enterococci from the hands of health care workers, medication dispensers, pulse oximeters, electronic thermometers and stethoscopes (24,26), prompting the critical evaluation and revamping of infection control procedures.

Characterization of the patients involved in outbreak situations has identified several predisposing risk factors to VRE colonization. These include, severe underlying disease, hospitalisation for an extended period and prior multiple antibiotic treatments, particularly vancomycin medication (23). Outbreaks have been observed primarily within immunocompromised oncology and tissue transplantation patients where, despite the “second rate” pathogenicity exhibited by enterococci, they have caused severe life-threatening disease (21).

Currently, the spread of multidrug-resistant enterococci is presenting a challenge to physicians as treatment for these infections is limited to combined therapy utilizing a β-lactam antibiotic in conjunction with an aminoglycoside (15). However, the widespread resistance patterns to these antibiotics have forced clinicians to turn to experimental antimicrobial agents and combinations whose effectiveness have not yet been proven.

Of particular interest to clinicians and scientists worldwide is the possibility of the transfer of vancomycin resistance from enterococci to other gram-positive organisms as there appears to be no barrier preventing genetic exchange and expression of resistance determinants in such organisms as S. aureus, Streptococcus species and Listeria monocytogenes (27). The fear that the transfer of vancomycin resistance to a “first rate” pathogen such as S. aureus has only been heightened by the identification of a strain of Streptococcus bovis harboring a vanB related gene (28), and the demonstration of in vitro and in vivo transfer of glycopeptide resistance from E. faecalis to S. aureus under laboratory conditions (29).

**VANCOMYCIN-RESISTANT STAPHYLOCOCCUS AUREUS**

*Staphylococcus aureus* is a non-spore forming gram-positive ubiquitous bacterium which causes a wide spectrum of infections in both adults and children (30). *S. aureus* is isolated frequently as the causative agent of skin diseases such as impetigo, bullous impetigo and skin abscesses including furuncles, carbuncles and cellulitis (31). A variety of clinical syndromes are also associated with genetically encoded toxins which are released upon infection. Toxin mediated diseases include staphylococcal food poisoning, scalded skin syndrome and toxic shock syndrome. Finally, invasive disease associated with *S. aureus* bacteremia can be extremely serious and can be associated with the development of endocarditis, osteomyelitis or septic arthritis (32). *S. aureus* is one of the most frequently isolated nosocomial pathogens and in particular, this organism is an important cause of surgical wound infections (31).

Fatality estimates from *S. aureus* infection were as high as 90% in the pre-antibiotic era. Outcomes of *S. aureus* infection were dramatically improved with the introduction of penicillin G in the early 1940s. Shortly after the appearance of penicillin G, select clinical *S. aureus* isolates were observed with penicillin resistant phenotypes (33). The resistance phenotype was found to be due to a penicillinase, an enzyme responsible for the hydrolytic cleavage and thus inactivation of penicillin (34). The development of semisynthetic penicillin derivatives (e.g. methicillin) which were resistant to the hydrolytic action of penicillinases provided a temporary solution. The emergence of multi-drug resistant *Staphylococcus aureus* in the early 1980s severely limited treatment options for patients infected with this bacterium (35). Vancomycin has not only been the drug of choice, but in many cases the sole antimicrobial agent available for the treatment of methicillin-resistant *S. aureus* (MRSA). The appearance of vancomycin-resistant *Staphylococcus aureus* has been anticipated for a number of years. After 30 years of vancomycin use, resistance has emerged in clinical isolates of coagulase negative staphylococcus, and more recently several MRSA strains isolated from patients in the United States and Japan have also been vancomycin resistant (36,37).

In May 1996 in Japan, a 4 month old infant who had undergone heart surgery for pulmonary atresia developed post-operative fever (37). The surgical incision site developed purulent discharge yielding MRSA. Treatment was commenced with vancomycin for 29 days, but fever and discharge of pus continued. Only when the treatment regimen was changed to
a combination of vancomycin and arbekacin (an aminoglycoside recommended for treatment of MRSA) did the purulent discharge subside and the wound begin to heal. Twelve days later the surgical site appeared inflamed and developed a subcutaneous abscess accompanied by a sudden onset of fever. Therapy was resumed with the combination of arbekacin and ampicillin/sulbactam. After six days, the patient’s fever subsided. The MRSA strain which was isolated from the purulent discharge at the sternal incision site and from the debridement sample was found to be vancomycin-resistant (MIC: 8 mg/L).

**Resistance Mechanisms**

The exact mechanism of the intermediate resistance phenotype exhibited by several MRSA strains has yet to be elucidated. Laboratory experimentation has demonstrated the possibility of the transfer of vancomycin resistance from enterococci to other gram positive organisms as there appears to be no barrier preventing genetic exchange and expression of resistance determinants in *S. aureus*. However, PCR analysis of the vancomycin-resistant MRSA strains demonstrated that they did not carry either vanA or vanB genes (36). Rather it appears that alterations in the cell wall integrity of the organism may play a role in resistance. Electron microscopy indicates that the cell wall is twice as thick as the walls of control strains. There was also a three-fold increase in the production of both penicillin-binding protein PBP2 and PBP2' as measured by Western blotting, and finally a three-fold increase in the production of cell wall murein precursors compared with vancomycin-susceptible MRSA strains (36).

**Epidemiology and Clinical Management**

The most common method of spread of *S. aureus* is directly from person to person, often on the hands of hospital staff (38). However, other modes of transport, i.e. aerosolization, can occur. As the second leading cause of nosocomial infections and hospital deaths worldwide, it is not surprising that clinical infections are most common in patients in intensive care units and in other high risk wards. Colonization frequently occurs in elderly patients in long-term facilities or in patients with prolonged hospital stays, with previous antimicrobial treatment or in those with surgical wounds and lesions such as pressure sores and burns (39). Although MRSA has not been shown to be more virulent than its methicillin-susceptible counterpart, its spread within hospitals worldwide has been rapid, undoubtedly influenced by widespread antibiotic pressure. The first strains of MRSA were reported in the United Kingdom in 1961 soon after the introduction of methicillin. The first outbreak in the U.S. was reported in 1968 (40) and major interhospital spread has occurred since then. Unfortunately, it is not unrealistic to believe that the spread of vancomycin-resistant *S. aureus*, under the influence of vancomycin use, would undertake similar if not more rapid dissemination dynamics. Equally as disturbing has been the fact that rapid increases in *S. aureus* resistance rates have been documented in institutions utilizing non-β-lactam antimicrobials as front line agents. Resistance to extensively utilized fluoroquinolones (e.g. ciprofloxacin) has increased exponentially in a few short years, attributable to substantial increases in the usage of these agents (41). As vancomycin usage increases, selective pressure will only increase the appearance and dissemination of more VRSA isolates. Fortunately, the isolates of VRSA which have been isolated thus far have been susceptible to antimicrobial agents other than vancomycin or methicillin. Although treatment to date has been successful, the ability of these bacteria to horizontally shuffle genetic resistant determinants suggests the likelihood that a time may come when no antimicrobials will be effective against this organism.

**CONTROL OF NOSOCOMIAL SPREAD OF VRE AND VRSA**

VARIOUS PROGRAMS HAVE ADDRESSED THE INCREASING PROBLEM OF ANTIMICROBIAL RESISTANCE. CONTROLLING THE SPREAD OF VANCOMYCIN RESISTANCE HAS BEEN THE GOAL OF THE HOSPITAL INFECTION CONTROL PRACTICES ADVISORY COMMITTEE (HICPAC) WHO HAVE WORKED IN COLLABORATION WITH THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) TO FORMULATE RECOMMENDATIONS FOR PREVENTING THE SPREAD OF THESE RESISTANT PHENOTYPES. HICPAC LISTED FOUR ELEMENTS WHICH MUST BE ADDRESSED BY HOSPITAL DEPARTMENTS TO ACHIEVE THE PREVENTION AND CONTROL OF VANCOMYCIN RESISTANCE (25). FIRSTLY, TO AVOID COLONIZATION WITH VRE, THE PRUDENT USE OF VANCOMYCIN BY CLINICIANS IS CRUCIAL. SECONDLY, HOSPITAL STAFF MUST BE EDUCATED IN THE PROBLEM AND CONSEQUENCE OF VANCOMYCIN RESISTANCE. THIRDLY, RESISTANT MICRO-ORGANISMS MUST BE IDENTIFIED AND REPORTED PROMPTLY. FINALLY, APPROPRIATE INFECTION CONTROL PROCEDURES MUST BE IMPLEMENTED TO PREVENT PATIENT TO PATIENT SPREAD OF INFECTION (25).

The development of resistance is correlated with the level of antimicrobial use. Overuse of antibiotics has therefore decreased the number of resistance-conferring mutations. The Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Centers for Disease Control and Prevention (CDC), and the American Society for Microbiology (ASM) have drafted guideline programs that address the proper use of antimicrobials agents (25,42,43). In particular, guidelines to improve the prescribing of antimicrobials in the management of pneumonia, urinary tract infection, outinant upper respiratory tract infections, prophylaxis for opportunistic infections in AIDS patients and intravascular device infections are currently being introduced and monitored.

Surveillance for antimicrobial resistance allows prompt recognition of particular phenotypes and makes control more likely. Many combinations of surveillance and control measures have been developed and adopted with varying success. Molecular epidemiologic analysis of clinical isolates involved in outbreaks have also proved helpful in the investigation and control of outbreaks, and have identified patterns of transmission in specific hospital settings. Finally, strict hand washing procedures by health care workers, contact isolation, and antimicrobial treatment of the carrier state in health care workers and patients have had an impact on the spread of antibiotic resistance bacteria.
CONCLUSION

As antimicrobial resistance continues to increase, worldwide novel strategies must be adopted to stem the flow of untreatable bacterial infections. Currently at the forefront of these approaches is surveillance for antimicrobial resistant bacteria on a local and global scale. Although vancomycin-resistant enterococci are endemic within numerous U.S. hospitals, only limited outbreaks have been observed in Canada. In conjunction with surveillance, infection control policies to reduce the risk of nosocomial transmission of VRE and the reduction of antimicrobial use to decrease the selection of antibiotic resistance clones have impacted upon the transmission of this organism in Canada. Although it is yet unclear whether vancomycin-resistance in staphylococci is prevalent worldwide, lessons learned from dealing with VRE will impact on strategies to control such an eventuality. In the short term, non-essential vancomycin usage should stop. Laboratories should screen S. aureus strains isolated from patients on vancomycin therapy and patients from whom vancomycin-resistant staphylococcus has been isolated should be isolated to prevent spread of the organism.

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**Author Biography**

Martin MacKinnon is presently entering his third year of study at Dalhousie University’s Faculty of Medicine. Previously Martin has been granted the degree of Bachelor of Science and in May 1998 he was conferred with the degree of Master of Science in Microbiology and Immunology. Martin’s graduate work focused on the study of vancomycin resistant enterococcus (VRE), specifically the characterization of variant VRE isolates. In the future Martin plans to continue work in broad research areas as he completes his medical education.
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** Emended and edited with consultation. Therapy 1 year, double-blind, placebo-controlled, parallel study of 832 patients in 71 centers. Terbutaline (250 μg per inhalation) was used as needed.

1. Requires treatment withdrawal if not well tolerated, or decrease in PEF in morning of >30% of baseline on two consecutive days

2. PEF >90% of baseline value, above additional use of rescue medication/24 hours, awakenings at night due to asthma

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Treatment of Acute Symptoms

OXEZE TURBUHALER should not be used to treat acute symptoms. It is crucial to advise patients accordingly and prescribe a short-acting, inhaled bronchodilator for this purpose. Medical attention should be sought if patients find that short-acting inhaled bronchodilators become less effective or that they need more inhalations than usual (see PRECAUTIONS).

OXEZE TURBUHALER and the Management of Asthma

The management of asthma should normally follow a stepwise programme, with patient response monitored clinically and by lung function tests. Current asthma management guidelines recommend the following for long-acting β₂-agonists:

• Oral or intravenous corticosteroids should not be stopped.
• Adequate education should be provided to the patient regarding the use of long-acting β₂-agonists and the acute treatment of asthma, with close follow-up to ensure compliance.
• Long-acting β₂-agonists should not be introduced in significantly worsening or acutely deteriorating asthma.
• Long-acting β₂-agonists should never be used as rescue medication.

Increasing use of short-acting inhaled β₂-agonists to control symptoms indicates deterioration of asthma control and the need to reassess the patient’s therapy.

Sudden or rapid deterioration in asthma control is potentially life-threatening; the treatment plan must be re-evaluated, and consideration be given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring with the addition of options for acceptable variation limits should be considered.

Cardiovascular and Hypotensive Effects

Potentially serious ECG changes (such as increased QTC interval) and hypokalaemia have been reported following OXEZE TURBUHALER therapy. Although clinically not significant, a small increase in QTC interval and/or decrease in serum potassium has been reported at therapeutic doses of formoterol. Particular caution is advised in susceptible patients who are at risk of cardiac arrhythmias. Close monitoring is therefore recommended (see PRECAUTIONS). It is recommended that serum potassium levels be monitored in such situations.

Therefore, OXEZE TURBUHALER, like all inhaled β₂-agonists, should not be used with caution in patients with cardiovascular disorders, arrhythmias and hypertension.

Other Diseases

Symptomatic bronchodilators should be administered cautiously to patients who are unlikely to respond to symptomatic amines, e.g., in patients with hyperthyroidism not yet under adequate control. Since β₂-agonists may increase the blood glucose level, additional blood glucose controls are recommended when asthmatic patients with concomitant diabetes are started on OXEZE TURBUHALER.

Paracutaneous Effect

As with other inhaled asthma medication, the potential for paracutaneous bronchoscopy should be kept in mind. If it occurs, treatment with OXEZE TURBUHALER should be discontinued immediately and therapy institution.

Postmarketing Experience

The postmarketing experience with OXEZE TURBUHALER is limited. Postmarketing experience with other long-acting β₂-agonists (formoterol and salmeterol) have reported serious exacerbations of asthma including some that have been fatal. In most cases, these have occurred in patients with severe asthma and/or in some patients whose asthma has been acutely deteriorating (see WARNINGS), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether long-acting β₂-agonists contributed to the events or simply failed to relieve the deteriorating asthma.

PRECAUTIONS

Do Not Introduce OXEZE TURBUHALER AS A Treatment For Acutely Deteriorating Asthma

OXEZE TURBUHALER (formoterol fumarate dihydrate) is intended for the maintenance treatment of asthma (see INDICATIONS AND CLINICAL USE) and should not be introduced in patients with acutely deteriorating asthma, who may have a potentially life-threatening condition. In patients with worsening asthma, there are no data demonstrating that long-acting β₂-agonists provide any additional benefits to short-acting, inhaled β₂-agonists. In patients with, e.g., exacerbations of short-acting β₂-agonists, serious acute respiratory events, including fatalities, have been reported, some of which have occurred in patients with severe asthma and some of whom asthma has been acutely deteriorating. Although it is not possible from these reports to determine the causal relationship between long-acting β₂-agonists and these adverse events, the introduction or increased use of a long-acting β₂-agonist in patients with acutely deteriorating asthma is inappropriate.

Do Not Use OXEZE TURBUHALER as a Substitute for Oral or Inhaled Corticosteroids

Patients who require therapy with OXEZE TURBUHALER should also receive optimal anti-inflammatory therapy with corticosteroids. Patients are advised to continue their current anti-inflammatory therapy even when symptoms decrease. Any change in corticosteroid dosage should be made ONLY after clinical consultation.

Do Not Use OXEZE TURBUHALER to Treat Acute Symptoms

OXEZE TURBUHALER should only be used in patients requiring long-term regular bronchodilator therapy and NOT as an alternative to short-acting β₂-agonists used on-demand or in the event of an acute attack.

OXEZE TURBUHALER should NOT be used to relieve acute asthma symptoms. When prescribing OXEZE TURBUHALER, the physician must also provide the patient with a short-acting inhaled β₂-agonist (e.g., terbutaline or salbutamol) for treatment of symptoms that occur acutely, despite regular twice-daily use of OXEZE TURBUHALER.

Although formoterol has a rapid onset of action (1 to 3 minutes), current asthma management guidelines recommend that long-acting inhaled bronchodilators should be used only as twice-daily maintenance bronchodilator therapy.

Watch for Increased Need for Short-Acting, Inhaled β₂-Agonists

Bronchodilators of the short-acting adrenergic stimulant type may be used for relief of breakthrough symptoms while using OXEZE TURBUHALER. Asthma may deteriorate during treatment if a period of hours or slowly over several days or longer. Should symptoms persist or treatment with short-acting inhaled β₂-agonist become less effective or a patient needs inhaled β₂-agonists more than usual, this indicates a worsening of the underlying asthma and warrants reassessment of the treatment regimen and consideration given to increasing corticosteroid therapy. Increasing the daily dosage of OXEZE TURBUHALER in this situation is not appropriate. Patients requiring increasing doses or inhalations of short-acting β₂-agonists for relief of symptoms should be advised to consult a physician for reassessment.

Do Not Exceed Recommended Dosage

OXEZE TURBUHALER should not be used more frequently than twice daily or at higher doses than recommended. Failures have been reported in association with excessive use of inhaled sympathomimetic drugs (see below).

Cardiovascular and Other Medical Conditions

Usually no effect on the cardiovascular or central nervous system has been seen after the administration of formoterol at recommended doses. In contrast, the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased heart rate, cardiac contractility, tremor) can occur while using OXEZE TURBUHALER. Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving OXEZE TURBUHALER when the following conditions may exist: ischecmic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, severe hypertension, hypertrophic obstructive cardiomyopathy, thyrotoxicosis or severe heart failure.

Use with caution in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle. Caution should be observed when treating patients with known or suspected prolongation of the QTC-interval. Formoterol itself may induce prolongation of the QTC-interval.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of OXEZE TURBUHALER. OXEZE TURBUHALER contains lactose (600 μg per metered dose) and is contraindicated in patients with hypersensitivity to lactose or formoterol. The amount of lactose in OXEZE TURBUHALER does not normally cause problems in lactase intolerant people (see CONTRAINDICATIONS).

Metabolic Effects

Due to the reversible hyperglycaemic effect of β₂-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Use in Women

Pregnant Women

The use of OXEZE TURBUHALER during pregnancy has not yet been established (see Use in Labour and Delivery).

Lactating Women

Formoterol was found to be excreted in the milk of lactating rats after administration to the mother. It is not known whether OXEZE TURBUHALER in nursing mothers, its use in such circumstances should only be considered if the expected benefit to the mother is greater than the risk to the infant.
Use in Laboratory and Delivery

There are no well-controlled human studies that have investigated the effects of oxetene on preterm labour or labour at term. Because of the potential for B2-agonist interference with placental blood flow, use of B2-agonists, such as OXETENE TURBUHALER, during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Use in Geriatrics

No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment, at the recommended normal doses. (See also WARNINGS and PRECAUTIONS for patients with cardiovascular disorders).

Use in Pediatrics

OXETENE TURBUHALER is not currently recommended for use in children younger than 12 years of age due to limited clinical data in this age group.

Use in Adults with Patients and Asthma Severity Reassessment

In adults patients the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with OXETENE TURBUHALER is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting B2-agonists, should be carefully monitored in adults receiving long-acting B2-agonists.

Drug Interactions

Beta-Receptor Blocking Agents

Beta receptor blocking agents, especially non-selective ones, may partly or totally inhibit the effect of beta-stimulants.

Should a patient be receiving OXETENE TURBUHALER also require concurrent treatment with a beta-blocker, it is recommended that a beta-blocker (e.g., metoprolol) with less predominant B2-blocking effects should be used. Should concurrent treatment be necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug.

Xanthine Derivatives, Steroids and Diuretics

Concurrent treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalemic effect of B2-agonists. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digoxin, digoxin-like substances.

Other Drugs

Diuretics: Use with caution in patients with cardiac failure, especially those with renal failure, and the elderly.

Information to be Provided to the Patient

See illustrated INFORMATION FOR THE CONSUMER section. It is important that patients understand how to use OXETENE TURBUHALER and how it should be used in relation to other asthma medications they are taking. They should be given the following information:

1. The recommended dosage, as follows:

   Adults: The usual dose is 6 or 12 g twice daily, at 12 hour intervals. Some adults may need 24 g twice daily. The maximum daily dosage for adults, 48 g, should not be exceeded.

   Adolescent Children (12-16 years): The usual dose is 6 g twice daily, at 12 hour intervals. Some children may need 12 g twice daily. The maximum daily dosage for adolescent children, 24 g, should not be exceeded.

OXETENE TURBUHALER is not recommended to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting B2-agonist, such as terbutaline or salbutamol, such as OXETENE TURBUHALER (the physician should provide the patient with such medication and instruct the patient in how it should be used).

6. The physician should be notified immediately if any of the following symptoms occur, which may be a sign of seriously worsening asthma:

   - Decreased effectiveness of short-acting, inhaled B2-agonist
   - Need for more medications than usual of short-acting, inhaled B2-agonist

OXETENE TURBUHALER should not be used as a substitute for oral inhaled corticosteroids. Patients must be advised to continue taking their corticosteroid therapy after the introduction of OXETENE TURBUHALER even when symptoms decrease.

7. Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain.

Long-Term Twice Daily Maintenance Therapy

The dose of OXETENE TURBUHALER should be individualized to the patient's needs and should be the lowest possible dose that keeps the patient symptom free or fulfills the therapeutic objective.

Adults:

The usual dose is 6 or 12 g, twice daily, at 12 hour intervals. Some adults may need 24 g, twice daily. The maximum daily dosage for adults, 48 g, should not be exceeded.

Adolescent Children (12-16 years):

The usual dose is 6 g twice daily, at 12 hour intervals. Some children may need 12 g twice daily. The maximum daily dosage for adolescent children, 24 g, should not be exceeded.

In adolescent patients, the severity of asthma may be variable with age and periodic reassessment should be considered to identify the lowest dose required to maintain control and to determine if continued maintenance therapy with OXETENE TURBUHALER is still indicated (see PRECAUTIONS). OXETENE TURBUHALER is available in two strengths, 6 or 12 g per inhalation. Use of the higher strength is recommended for patients requiring 12 g or more, twice daily OXETENE TURBUHALER is not currently recommended for children younger than 12 years of age due to the limited clinical data in this age group.

It is important to instruct patients to avoid inhaling into the device and to always replace the cover after using OXETENE TURBUHALER.

**NOTE:** The medication from OXETENE TURBUHALER is delivered to the lung by the patient inhaled and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication with OXETENE TURBUHALER due to the small amount of drug dispersed.

**PHARMACOLOGICAL INFORMATION**

**Drug Substance:** Formoterol fumarate dihydrate

**Chemical Structure:**

- Molecular formula: C_{32}H_{40}N_{2}O_{8}
- Molecular weight: 616.8

**Chemical Name:** (R, R)-1-[(2-[(2R, 5R)-dihydropyrimidin-4-yl]-3-[4-(4-methylphenyl)-1-methylpyrazolyl]phenyl]ethyl)phényl)for- mamide, (E)-2-butoxydiacetate(2:1), dihydrate

**Description:** Formoterol fumarate dihydrate is a white to off-white or slightly yellow non-hygrosopic crystalline powder.

**Disposal:** The pAug of formoterol fumarate dihydrate at 25°C is 7.9 for the pAug of the glucopyranose and 9.2 for the gluco spoil.

**Partition Coefficient:** The octanol-water partition coefficient of the dihydrate is 2.9.

**Composition:**

Active: Formoterol fumarate dihydrate 6 or 12 g/halation.

Non-Medicinal: Lactose monohydrate.

**Stability and Storage Recommendations:**

OXETENE TURBUHALER should be stored at room temperature between 15°C and 30°C with the cover tightened, away from moisture.

**AVAILABILITY OF DOSAGE FORMS**

OXETENE TURBUHALER (formoterol fumarate dihydrate) is supplied in two strengths: 6 µg/metered dose (60 doses) and 12 µg/metered dose (60 doses).

The strength of OXETENE TURBUHALER can be identified by the colour of the turning ring. The 6 µg/metered dose strength has a light greenish-blue turning ring, and the 12 µg/metered dose strength has a dark greenish-blue turning ring.

OXETENE TURBUHALER and capsule lactose (600 µg per metered dose). This amount does not normally cause problems in lactose-intolerant people.

OXETENE TURBUHALER cannot be refilled and should be discarded when empty.

**References:**

3. Oxet® TURBUHALER® Product Monograph

**Product Monograph available upon request**

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