ORIGINAL CONTRIBUTION

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

Martin MacKinnon, BSc(Hon), MSc, MD'00

Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia

The emergence of organisms resistant to commonly utilized antimicrobial agents has reached global epidemic proportions. In particular, nosocomial pathogens with antimicrobial resistant pheno types, 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 nullify 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

Address correspondence to:

Martin MacKinnon, Box 47, Sir Charles Tupper Medical Building, Dalhousie University, Halifax, Nova Scotia, B3H 4H7

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 mg/L 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, wide spread 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 cellulitus (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, osteomyeletis 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 postoperative 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, the 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 increased 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, outpatient 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.

ACKNOWLEDGEMENTS

Special thanks to Dr. Claire Touchie, Department of Medicine (Division of Infectious Disease) for her helpful discussions and guidance in writing this paper.

REFERENCES

1. Frieden TR,Sherman LF, Maw KL et al. A multi-institutional outbreak of highly drug-resistant tuberculosis. Epidemiology and clinical outcomes. *JAMA* 1996; 276(15): 1229-35.
2. Neu H. The crisis in antibiotic resistance. *Science* 1992; 257 (21): 1064-1072.
3. Clewell DB. Movable genetic elements and antibiotic resistance in enterococcus. *Eur J Clin Microbiol Infect Dis* 1990; 9: 90-102.
4. Linden PK, Pasculle AN, Manez R, Kramer DJ, Fung JJ, Pinna AD, Kusne S. Differences in outcomes for patients with bacteremia due to vancomycin-resistant *Enterococcus faecium* or vancomycin-sensitive *E. faecium*. *Clin Infect Dis* 1996; 22: 663-70.
5. Williams D et al. Arrival of vancomycin resistance in *Staphylcoccus aureus*. *Antibiotics Chemotherapy* 1997; 7(2): 1.
6. Boseley GS, Facklam RR, Grossman D. Rapid identification of enterococci. *J Clin Microbiol* 1988; 18: 275-1277.
7. Murray BE: Life and times of the *Enterococcus*. *Clin. Microbiol. Rev* 1990; 3:46-65.
8. Felmingham D, Wilson APR, Quintana AI, Gruneberg RN. *Enterococcus* species in urinary tract infection. *Clin Infect Dis* 1992; 5: 295-301.
9. Emori TG, Gaynes RP. An overview of nosocomial infections including the role of the microbiological laboratory. *Clin Microbiol Rev* 1993; 6: 428-442.
10. Graninger W, Ragette R. Nosocomial bacteremia due to *Enterococcus faecalis* without endocarditis. *Clin Infect Dis* 1992; 15: 49-59.
11. Khardor N, Wong E, Carasco CH, Wallace S, Patt Y, Bodey GP. Infections associated with biliary drainage procedures in patients with cancer. *Rev Infect Dis* 1991; 13: 587-591.
12. Schaberg DR, Zervos MJ. Intergeneric and interspecies gene exchange in gram-positive cocci. *Antimicrob Agents Chemother* 1986; 30: 817-822.
13. Leclerq R. Enterococci aquire new kinds of resistance. *Clinical Infectious Diseases*. 1997; 24: 580-4.
14. Leclerq R, Derlot E, Duval J, Courvalin P. Plasmid mediated resistance to vacomycin and teicoplanin in *Enterococcus faecium*. *N Engl J Med* 1988; 319: 157-161.
15. Leclerq R, Courvalin P. Resistance to glycopeptides in entero cocci. *Clin Infect Dis* 1997;24: 545-56.
16. Tyrrell GJ, Bethune R, Willey B, Low D. Species identification of enterococci via intergenic ribosomal PCR. *J. Clinical Microbiol* 1997; 35: 1054-1060.
17. McCormick MH, Stark WM, Pittenger GE, Pittenger RC, McGuire JM. Vancomycin. a new antibiotic. *In Chemical and Biologic Properties: Antibiotics Annual*. 1956; pp. 606-611.
18. Reynolds PE. Structure, biochemistry, and mechanism of action glycopeptide antibiotics. *Eur J Clin Microbiol Infect Dis* 1989; 2: 943-950.
19. Evers S, Quintiliani R, Courvalin P. Genetics of glycopeptide re sistance in enterococci. *Microbial Drug Resistance* 1996; 2: 219-223.
20. Schaberg DR, Culver PA, Gaynes RP. Major trends in the microbial etiology of nosocomial infections. *Am J Med* 1991; 313 (Supp.): 3B-72S-3B-75S.
21. Papanicolaou G, Meyers B, Meyers J, Mendelson M, Lou W., Emre S, Sheiner P, Miller C. Nosocomial infections with vancomycin resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; 23: 760-766.
22. Suppola JP, Volin L, Valtonen V, Vaara M. Overgrowth of *Enterococcus faecium* in the feces of patients with hematologic malignancies. *Clin Infect Dis* 1996; 23: 694-697.
23. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Huang T, Sanford MP, Wenzel RP. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin Infect Dis* 1995; 20: 1126-33.
24. Livornese LL, Dias S, Samel C. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. *Ann Intern Med* 1992; 117: 112-116.
25. Centers for Disease Control and Prevention. Preventing the spread of vancomycin resistance - report from the hospital infection control practices advisory committee. *Federal Register* 1994; 59: 25757-25763.
26. Karafil LV, Murphy M, Josephson A. A cluster of vancomycin resistant *Enterococcus faecium* in an intensive care unit. *Infect Control Hosp Epidemiol* 1992; 13: 195-200.
27. Murray BE. What can we do about vancomycin-resistant enterococci. *Clin Infect Dis* 1995; 20: 1134-1144.
28. Poyart-C, Pierre C, Quesne G, Pron B, Berche P, Trieu-Cuot P. Emergence of vancomycin resistance in the genus Streptococcus: characterization of a vanB transferable determinant in *Streptococcus bovis*. *Antimicrob Agents Chemother* 1994; 41: 24-29.
29. Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett* 1992; 93: 195-198.
30. Musher DM, MacKenzie SO. Infections due to *Staphylococcus aureus Medicine* 1977; 56: 383.
31. Boyce JM. Nosocomial staphylococccal infections. *Ann Intern Med* 1981; 95: 241.
32. Iannini PB, Crossley K. Therapy of *Staphylococcus aureus* bacteremia associated with a removable focus of infection. *Ann Intern Med* 1976; 84: 558.
33. Hobby GL, Meyer K, Chaffee E: Activity of penicillin *in vitro* *Proc Soc Exp Biol Med* 1942; 50: 277.
34. Bondi A, Dietz CC: Penicillin resistant staphylococci. *Prec Soc Exp Biol Med* 1945; 60:55.
35. Panlilio AL, Culver DH, Gaynes RP et al. Methicillin-resistant *Staphylococcus aureas* in US Hospitals, 1975-1991. *Infect. Control Hosp Epidemiol*. 1992;13: 582.
36. Hiranastsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC.

Methicillin-resistant *Staphylococcus aureas* clinical strain with reduced vancomycin susceptibility. *Journal of Antimicrobial Chemotherapy* 1997; 40: 135-146.
37. CDC Update. *Staphlycoccus aureus* with reduced susceptibility to vancomycin - United States , 1997. *MMWR* 1997; 46: 813.
38. Struelens MJ, Merten R. Groupment pour le despitage, l'etude et al prevention des infections hospitalieres: National survey of methicillin-resistant *Staphylococcus aureas* in Belgian hospitals: Detection methods, prevalence trends, and infection control measures. *Eur J Clin Microbiol Infect Dis* 1994; 13:56.
39. Ayliffe GA. The progressive intercontinent spread of methicillin-resistant *Staphylcoccus aureas. Clinical Infectious Diseases* 1997; 24, (sup 1): 574-9.
40. Barrett FF, McGee RF, Finland M. Methicillin-resistant *Staphylcoccus aureus* at Boston City Hospital. Bacteriologic and epidemiologic observations. *N Engl J Med* 1968; 279: 441-8.
41. Sreedharam S, Peterson LR, Fisher LM. Ciprofloxacin resistance in coagulase-positive and negative staphlycocci: Role of mutations at serine d4 in the DNA gyrase A protein of *Staphylococcus aureus* and *Staphylcoccus epidermidis. Antimicrob Agents Chemother* 1991; 35: 2151.
42. American Society for Microbiology (ASM). Report of the ASM task force on antibiotic resistance. *Antimicrob Agents Chemother* 1995; (sup 1).
43. Shales DM, Gerding DN, John JF et al. SHEA/IDSA Joint committee on the prevention of antimicrobial resistance: Guidelines for the prevention of the antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol* (In press).

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.

Tupper Link Beautification Project

A project is currently underway in an effort to improve the aesthetic appearance of the medical school. We aim to display historic photos of interest and artwork by faculty, alumni & students. If you are interested in displaying artwork, please contact:
Barbara O'Neil (Class of 2000) [boneil@tupmcms1.med.dal.ca 464-0135] or
Dr. Gita Sinha [494-7059, gsinha@is.dal.ca].

Zachary A.
Pneumonia
Taking up gymnastics

Bill F.
PAT
Scuba diving again

Marlene R.
Asthma
Buil[illegible] vacation home

Alan D.
Elevated blood pressure
Quit smoking

Chuck S.
SVT
Working two jobs

Dennis D.
Asthma
[illegible]ree softball teams

[illegible] H.
[illegible]diabetes
Wa[illegible]old grandson

Stanley L.
Angina
Singing in a choir

Nancy L.
Constrictive pericarditis
Teaches 28 ten-year-olds

Jim W.
Acute indigestion
Quit eating squid and onions

Vicki [illegible]
Mitral valve pr[illegible]
Expecting second c[illegible]

Nam T.
Chest wall pains
[illegible]acticing tennis backhand

Hannah P.
Ventricular septal
Outgrew it

Melody K.
Palpitations
[illegible]lots her own plane

Kenny [illegible]
Stills murm[illegible]
Playing socce[illegible]

Harpreet K.
Pulmonary edema
Traveled to Hong Kong

Thanks for listening.

Successful outcomes begin with careful listening. That's why, for over 25 years, more health care providers have counted on the reliability and superior acoustics of 3M™ Littmann™ Stethoscopes than any other brand. To hear more, call 3M Health Care at 1-800-3M HELPS (364-3577), or visit our website at http://www.3M.com/Littmann.

3M Health Care

* For long-term, twice daily (morning and evening) administration in maintenance treatment of asthma patients 12 years of age and older who are receiving optimal corticosteroid treatment, and, experiencing regular or frequent breakthrough symptoms requiring the use of a short-acting bronchodilator. Oxeze® Turbuhaler® should not be initiated or increased in patients with significantly worsening or deteriorating asthma, or in patients whose asthma can be managed by occasional use of short-acting β_2-agonists, and should not be used to treat acute symptoms.

** Formoterol and Corticosteroids Establishing Therapy. 1 year, double-blind, randomized, parallel study of 852 patients in 71 centres. Terbutaline (250 µg per inhalation) was used as needed.

‡ Requiring treatment with oral glucocorticosteroid, or decrease in PEF in morning >30% of baseline on two consecutive days

† PEF >20% below baseline values; three additional uses of rescue medications/24 hours; awakenings at night due to asthma

Tremor, palpitations, and headache occurred with a frequency between 1 and 10%

Please see full prescribing information for safety and dosing guidelines.

P Oxeze® Patients Show Up In The Most Amazing Places

*Add New Oxeze® Turbuhaler® to optimal inhaled corticosteroid therapy, to take your patients farther.**

Today, inhaled corticosteroid therapy is the single best way of bringing and keeping asthma under control. Yet many patients experience breakthrough symptoms that prevent them from doing all they want to, from sleeping comfortably to hiking that extra mile.[1,2]

Now there's new Oxeze® Turbuhaler®. The first long-acting β_2–agonist proven to reduce both mild and severe exacerbations of asthma.[1] A landmark asthma trial, The FACET** Study, has demonstrated that the addition of Oxeze® Turbuhaler® to either low or high dose P Pulmicort® (budesonide) Turbuhaler® produced remarkable reductions in the rates of severe‡ and mild exacerbations.† The combination of Oxeze® and high dose Pulmicort® resulted in the greatest reductions.

For improved control, add Oxeze® Turbuhaler® to an optimal dose of inhaled corticosteroid.* Because there's a big world waiting for her.

Formoterol fumarate dihydrate

P Oxeze®
Turbuhaler®
Going Farther

A proud sponsor of the Canadian Medical Association's online collection of clinical practice guidelines.

CMA CPG Infobase www.cma.ca/cpgs

Association Médicale Canadienne / Canadian Medical Association

ASTRA
Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

Formoterol fumarate dihydrate

Oxeze® Turbuhaler®

(formoterol fumarate dihydrate)

6 µg/Metered Dose and 12 µg/ Metered Dose
Dry powdered inhalers for oral inhalation

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS AND CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Formoterol produces bronchodilation by stimulation of the β_2 adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of smooth muscle fibres.

Following inhalation of formoterol, a marked improvement in pulmonary function is observed within 1-3 minutes and lasts for a mean duration of 12 hours after a single dose.

Pharmacokinetic Properties

Absorption

Inhaled formoterol is rapidly absorbed. Peak plasma concentration is reached about 15 minutes after inhalation.

In studies the mean lung deposition of formoterol after inhalation via TURBUHALER ranged from 21-37% of the metered dose. The total systemic availability for the higher lung deposition was approximately 46% of the metered dose.

Distribution and Metabolism

Plasma protein binding is approximately 50%.

Formoterol is metabolized via direct glucuronidation and O-demethylation. The enzyme responsible for O-demethylation has not been identified. Total plasma clearance and volume of distribution has not been determined.

Elimination

The major part of the dose of formoterol is eliminated via metabolism. After inhalation 6-10% of the metered dose of formoterol is excreted unmetabolized in the urine. About 20% of an intravenous dose is excreted unchanged in the urine. The terminal half-life after inhalation is estimated to be 8 hours.

INDICATIONS AND CLINICAL USE

OXEZE TURBUHALER (formoterol fumarate dihydrate) is indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of asthma in patients 12 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who are using optimal corticosteroid treatment and experiencing regular or frequent breakthrough symptoms requiring regular use of a short-acting bronchodilator. OXEZE TURBUHALER should not be used in patients whose asthma can be managed by occasional use of short-acting inhaled β_2-agonists.

Corticosteroids should not be stopped because formoterol is prescribed.

Formoterol is a long-acting β_2-agonist and should not be used as a rescue medication. To relieve acute asthmatic symptoms a short-acting inhaled bronchodilator (e.g., terbutaline or salbutamol) should be used.

CONTRAINDICATIONS

OXEZE TURBUHALER (formoterol fumarate dihydrate) is contraindicated when there is known hypersensitivity to formoterol or inhaled lactose. Like other sympathomimetic amines, OXEZE TURBUHALER should not be used in patients with tachyarrhythmias.

WARNINGS

Acutely Deteriorating Asthma

OXEZE TURBUHALER (formoterol fumarate dihydrate) should not be initiated or increased in patients with significantly worsening or acutely deteriorating asthma (see PRECAUTIONS).

Use of Anti-Inflammatory Agents

Patients should be receiving optimal anti-inflammatory therapy with corticosteroids before starting OXEZE TURBUHALER. Formoterol is not a substitute for inhaled or oral corticosteroids; its use is complementary to them. Corticosteroids should not be stopped when OXEZE TURBUHALER is initiated. Patients must be advised not to stop or reduce corticosteroid therapy without medical advice (see PRECAUTIONS).

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 relief bronchodilator treatment becomes 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 β_2-agonists:

- Oral or inhaled corticosteroids should not be stopped.
- Adequate education should be provided to the patient regarding the use of long-acting β_2-agonists and the acute treatment of asthma, with close follow-up to ensure compliance.
- Long-acting β_2-agonists should not be introduced in significantly worsening or acutely deteriorating asthma.
- Long-acting β_2-agonists should never be used as rescue medication.

Increasing use of short-acting inhaled β_2-agonists to control symptoms indicates deterioration of asthma control and the need to reassess the patient's therapy.

Sudden or progressive 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 precise instructions for acceptable variation limits should be considered.

Cardiovascular and Hypokalemic Effects

Potentially serious ECG changes (such as increased QTc interval) and hypokalemia may result from β_2-agonist 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 severe asthma as these effects may be potentiated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics. Hypokalemia will increase the susceptibility of digitalis patients to cardiac arrhythmias (see PRECAUTIONS). It is recommended that serum potassium levels be monitored in such situations. Therefore, OXEZE TURBUHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, arrhythmias and hypertension.

Other Diseases

Sympathomimetic bronchodilators should be administered cautiously to patients who are unusually responsive to sympathomimetic amines, e.g., in patients with hyperthyroidism not yet under adequate control. Since β_2-agonists may increase the blood glucose level, additional blood glucose controls are recommended when asthmatic patients with concomitant diabetes are started on OXEZE TURBUHALER.

Paradoxical Bronchospasm

As with other inhaled asthma medication, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, treatment with OXEZE TURBUHALER should be discontinued immediately and alternative therapy instituted.

Postmarketing Experience

The postmarketing experience with OXEZE TURBUHALER is limited. Postmarketing experience with other long-acting β_2-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 β_2-agonists contributed to these 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 or increased in acutely deteriorating asthma, which is a potentially life threatening condition. In patients with worsening asthma, there are no data demonstrating that long-acting β_2-agonists provide greater efficacy than or additional efficacy to short-acting, inhaled β_2-agonists. With other long-acting β_2-agonists, serious acute respiratory events, including fatalities, have been reported, some of which have occurred in patients with severe asthma and/or patients in whom asthma has been acutely deteriorating. Although it is not possible from these reports to determine the causal relationship between long-acting β_2-agonists and these adverse events, the introduction or increased use of a long-acting β_2-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 must be advised to continue taking their anti-inflammatory therapy after the introduction of OXEZE TURBUHALER even when symptoms decrease. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

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 beta-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 β_2-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 β_2-Agonists

Bronchodilators of the short-acting adrenergic stimulant type may be used for relief of breakthrough symptoms while using formoterol. Asthma may deteriorate acutely over a period of hours or slowly over several days or longer. Should symptoms persist, or treatment with short-acting inhaled β_2-agonist become less effective or a patient needs more inhalations than usual, this indicates a worsening of the underlying condition 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 β_2-agonists for relief of symptoms should be advised to consult a physician for re-evaluation.

Do Not Exceed Recommended Dosage

OXEZE TURBUHALER should NOT be used more frequently than twice daily or at higher doses than recommended. Fatalities 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 is seen after the administration of formoterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased heart rate, cardiac contractility, tremor) can occur while using formoterol. Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving OXEZE TURBUHALER when the following conditions may exist: ischemic 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 inhaled lactose or formoterol. The amount of lactose in OXEZE TURBUHALER does not normally cause problems in lactose intolerant people (see CONTRAINDICATIONS).

Metabolic Effects

Due to the reversible hyperglycemic effect of β_2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Use in Women

Pregnant Women

The safety 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 oral administration. Since there is no experience in the use of 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 Labour and Delivery

There are no well-controlled human studies that have investigated the effects of formoterol on preterm labour or labour at term. Because of the potential for ß-agonist interference with uterine contractibility, use of $ß_2$-agonists, such as OXEZE 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

OXEZE 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 Adolescent Patients and Asthma Severity Reassessment

In adolescent patients the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with OXEZE TURBUHALER is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting $ß_2$-agonists, should be carefully followed in adolescents receiving long-acting $ß_2$-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 treated with OXEZE TURBUHALER also require concomitant treatment with a beta-blocker, it is recommended that a beta-blocker (e.g., metoprolol) with less predominant $ß_2$-blocking effects be considered. If concomitant treatment is 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

Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalemic effect of $ß_2$-agonists. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Other Drugs

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $ß_2$-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Information to be Provided to the Patient

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

i. The recommended dosage, as follows:

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

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

OXEZE TURBUHALER is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting, inhaled $ß_2$-agonist such as terbutaline or salbutamol (the physician should provide the patient with such medication and instruct the patient in how it should be used).

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

- Decreased effectiveness of short-acting, inhaled $ß_2$-agonist
- Need for more inhalations than usual of short-acting, inhaled $ß_2$-agonist.

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

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

v. In patients receiving OXEZE TURBUHALER other inhaled medications should be used only as directed by the physician.

vi. Parents/guardians of adolescent children who have been prescribed OXEZE TURBUHALER should be alerted to the general concern regarding asthma therapy compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting $ß_2$-agonists.

ADVERSE REACTIONS

Pharmacologically predictable side-effects of $ß_2$-agonist therapy, such as tremor and palpitations, may occur but tend to be transient and reduced with regular therapy. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. The following adverse reactions can be classified as common (i.e. frequency ≥1% and <10%): tremor, palpitations and headache; uncommon (frequency ≥0.1% and <1%): muscle cramps, tachycardia, agitation, restlessness and sleep disturbances; very rare (frequency <0.01%): bronchospasm, exanthema, urticaria, pruritus and hypokalemia.

The clinical program conducted with OXEZE TURBUHALER, has involved more than 1,800 patients. The incidence of adverse events, irrespective of causality towards the drug, from four controlled trials (duration 1, 3, 3 and 6 months respectively) with OXEZE TURBUHALER is presented in the following table.

Table 1.

Incidence of adverse events (irrespective of causality) with frequency higher than placebo in four controlled trials of duration 1, 3, 3 and 6 months respectively.

	OXEZE TURBUHALER			Placebo TURBUHALER
	Total No. (%)	6 µg b.i.d. No. (%)	12 µg b.i.d. No. (%)	No. (%)
Total Number of Evaluable Patients	359	190	169	412
Headache	66 (18%)	15 (8%)	51 (30%)	84 (20%)
Tremor	11 (3%)	4 (2%)	7 (4%)	2 (0%)
Pharynx Disorder	18 (5%)	3 (2%)	15 (9%)	10 (2%)
Cramps	10 (3%)	3 (2%)	7 (4%)	3 (1%)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of $ß_2$-adrenergic agonists: tremor, headache, palpitations and tachycardia. Hypotension, metabolic acidosis, hypokalemia and hyperglycemia may also occur. Supportive and symptomatic treatment may be indicated.

DOSAGE AND ADMINISTRATION

OXEZE TURBUHALER (formoterol fumarate dihydrate) should NOT be initiated or increased in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition (see PRECAUTIONS).

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

OXEZE TURBUHALER SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe a short-acting, inhaled $ß_2$-agonist for this purpose.

OXEZE TURBUHALER SHOULD NOT BE USED MORE FREQUENTLY THAN TWICE DAILY WITH A TWELVE-HOUR INTERVAL BETWEEN DOSES OR AT HIGHER DOSES THAN RECOMMENDED. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting inhaled $ß_2$-agonist becomes less effective or a patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reassessment of the treatment regimen. Increasing the daily dosage of OXEZE TURBUHALER in this situation is not appropriate (see PRECAUTIONS).

Bronchodilators should not be the only or the main treatment in patients with moderate to severe or unstable asthma. Patients with severe asthma may require regular medical assessment. These patients will require high dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroids dosage which should be administered under medical supervision.

Since there may be serious adverse effects associated with excessive dosing, the dosage or frequency of administration should not be increased.

As a twice daily regular treatment, OXEZE TURBUHALER provides 24-hour bronchodilation and can replace regular use of a fast-acting, short duration inhaled bronchodilator (e.g., salbutamol or terbutaline), when used concurrently with corticosteroid therapy.

Dosage should be individualized and patient response should be monitored by the prescribing physician on an ongoing basis.

Long-Term Twice Daily Maintenance Therapy

The dose of OXEZE 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 µg, twice daily, at 12 hour intervals. Some adults may need 24 µg, twice daily. The maximum daily dosage for adults, 48 µg, should not be exceeded.

Adolescent Children (12-16 years):

The usual dose is 6 µg, twice daily, at 12 hour intervals. Some children may need 12 µg, twice daily. The maximum daily dosage for adolescent children, 24 µg, 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 OXEZE TURBUHALER is still indicated (see PRECAUTIONS).

OXEZE TURBUHALER is available in two strengths, 6 or 12 µg per inhalation. Use of the higher strength is recommended for patients requiring 12 µg or more, twice daily. OXEZE 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 exhaling into the device and to always replace the cover after using OXEZE TURBUHALER.

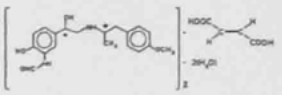
NOTE: The medication from OXEZE TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication when using OXEZE TURBUHALER due to the small amount of drug dispensed.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: formoterol fumarate dihydrate

Chemical Structure:



Molecular Formula: $C_{42}H_{56}N_4O_{14}$

Molecular Weight: 840.9

Chemical Name: (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate

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

Dissociation Constant: The pK_a of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

Partition Coefficient: The octanol-water partition coefficient at 25°C is 2.6.

Composition

Active: Formoterol fumarate dihydrate 6 or 12 µg/inhalation.
Non-Medicinal: Lactose monohydrate.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

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

OXEZE TURBUHALER also contains lactose (600 µg per metered dose). This amount does not normally cause problems in lactose-intolerant people.

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

References:
1. Canadian Respiratory Journal 1996;3(2):89-100.
2. Pauwels R, et al. New England Journal of Medicine 1997;337:1405-1411.
3. Oxeze® Turbuhaler® Product Monograph.

Product Monograph available upon request

A DMJ Special Focus on the Medical Humanities