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ORIGINAL ARTICLE

Menadione (vitamin K) enhances the antibiotic activity of drugs by cell membrane permeabilization mechanism

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KEYWORDS

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Abstract Menadione, vitamin K3, belongs to the class of lipid-soluble vitamins and lipophilic substances as menadione cause disturbances in the bacterial membrane, resulting in damage to the fundamental elements for the integrity of the membrane, thus allowing increased permeability. Accordingly, the aim of this study was to evaluate in vitro the antibiotic-modifying activity of menadione in multiresistant strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*, with a gradual increase in its subinhibitory concentration. In addition, menadione was compared with cholesterol and ergosterol for similarity in mechanism of drug modulatory action. Antibiotic-modifying activity and antibacterial effect were determined by the broth microdilution assay. Menadione, cholesterol and ergosterol showed modulatory activity at clinically relevant concentrations, characterizing them as modifiers of bacterial drug resistance, since they lowered the MIC of the antibiotics tested. This is the first report of the antibacterial activity of menadione and its potentiation of aminoglycosides against multiresistant bacteria.

1. Introduction

Menadione, vitamin K3, is a synthetic compound that belongs to the class of lipid-soluble vitamins, which is converted to vitamin K2 in the gut (Klack and Carvalho, 2006). Lipid-soluble vitamins are organic substances present in small amounts in foods, and they are essential to the functioning of the body as co-factors (Paixão and Stamford, 2004). Vitamin K is a biologically active substance found in functional foods, which is required particularly in the mechanism of

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blood coagulation, where it is essential for the synthesis of prothrombin, besides being involved in the synthesis of proteins present in plasma, kidney and perhaps other tissues. Some studies on vitamin K2 have demonstrated growth inhibitory effects against various neoplastic cells and reduced risk of mutagenic events in rapid cell proliferation in the fetus and newborn (Klack and Carvalho, 2006). Some studies report that lipid-soluble compounds modulate plasma membrane permeability in bacteria (Pretto et al., 2004; Gibbons, 2004; Nicolson et al., 1999). Therefore, menadione with its lipid-soluble nature may cause changes in the fluidity of the bacterial membrane, making it more permeable to substances, including antibiotics.

Cholesterol is a lipid component that is necessary for normal functioning of the body, and it plays an important role in the structure and function of the plasma membrane as well as organelle membranes. Also, it is involved in the synthesis of bile acids required for the absorption of lipids and lipid-soluble vitamins from the intestine, and participates in the synthesis of steroid hormones and vitamin E (Ludke and López, 1999; Leança et al., 2010).

Bacteria do not have cholesterol as part of their cytoplasmic membrane, nor ergosterol, a cholesterol derivative and lipid component of fungal membranes. Both sterols were used as complex lipid substances (Santos and Carvalho, 2001; Thevissen et al., 2003; Loguercio-Leite et al., 2006) that can act on the fluid mosaic of the bacterial membrane, modifying its fluidity, for comparison with menadione with regard to effect on the bacterial plasma membrane.

Bacteria are simple organisms found in most natural environments, where the bacterial cell has several structures, some present only in certain species. An essential structure is the cytoplasmic membrane, which is responsible for numerous functions including DNA replication, enzyme secretion, biosynthesis of components, solute transport and energy production (Schaechter et al., 2002). The cell wall is a structure that gives rigidity to many bacteria, and according to its constitution, bacteria are divided into two classes, Gram-positive and Gram-negative bacteria, the difference being mainly due to their permeability properties and surface components (Tortora et al., 2008; Schaechter et al., 2002; Pretto et al., 2005).

Bacterial infections are currently the focus of public health, mainly due to the significant growth of bacterial resistance. Infections caused by *Staphylococcus aureus* are the most common, showing a greater difficulty in treatment due to its resistance to various antibiotics (Tortora et al., 2008). The species *Pseudomonas aeruginosa* is the leading cause of nosocomial infections, attacking the skin, urinary tract, ear, and eye (Murray et al., 2004). *Escherichia coli* are the most common species of the genus *Escherichia*, associated with severe urinary tract infections, meningitis and gastroenteritis (Murray et al., 2004; Tortora et al., 2008).

The aim of this study was to evaluate in vitro the antibiotic-modifying activity of menadione in multiresistant strains of *S. aureus*, *P. aeruginosa* and *E. coli*, with gradual increase in its subinhibitory concentration. Also, menadione was compared to cholesterol and ergosterol with regard to mechanism of modulating action (see Figs. 1 and 2).

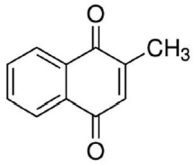

Figure 1 Structural formulae of menadione.

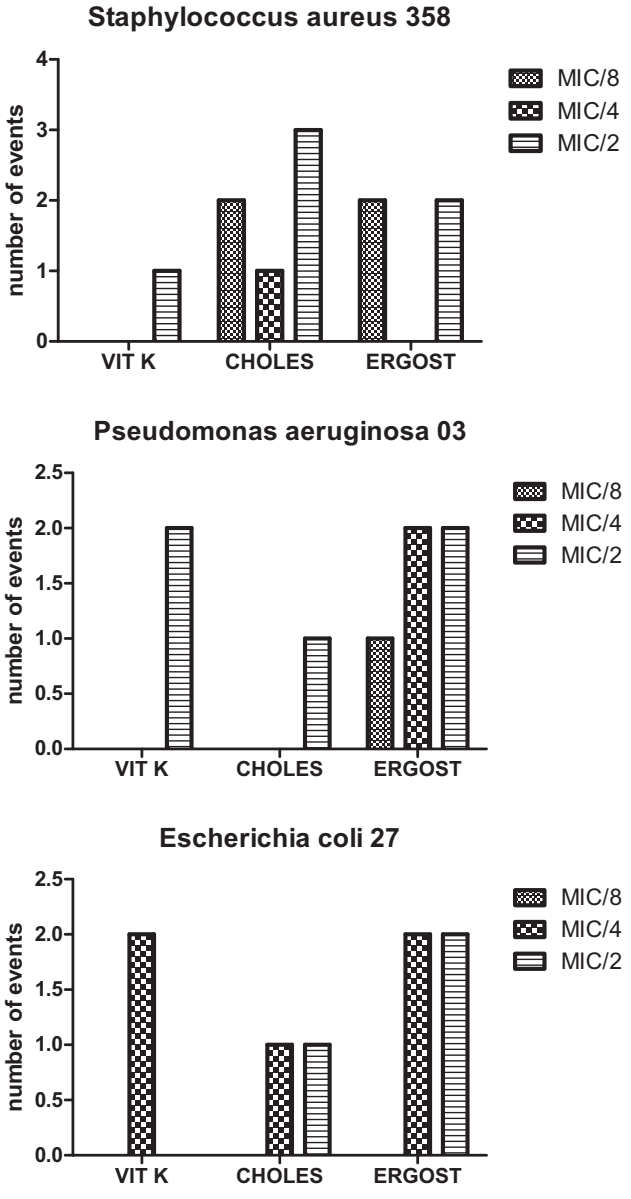

Figure 2 Comparison of the number of events modulator concentrations subinhibitory MIC/8, MIC/4, MIC/2 between the solutions of menadione, cholesterol and ergosterol. *MIC: minimum inhibitory concentration, VIT K: vitamin K.