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Review article

Interactions of Antibacterial Antibiotics with Magnesium and Zinc

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Abstract

The action of antibacterial antibiotics on bacteria but also on the cells of the human body is dependent on many factors. An important place is the interactions with magnesium and zinc. The aim of this narrative review is to highlight the complexity of interactions between these two cations and some antibacterial antibiotics. The review presents pharmacokinetic, pharmacodynamic interactions and the influence of magnesium and zinc on some adverse effects of antibiotics. The influences of some antibiotics on plasma concentrations of magnesium and zinc are also discussed. The interactions take place before the contact of the antibiotic with the pathogenic bacteria, during the action on bacteria but also after this action. Some adverse effects of antibiotics are produced by their direct action on human cells and plasma and tissue concentrations of magnesium and zinc are important for reducing these effects. These two biometals play multiple and complex roles in the human body. Some antibiotics such as aminoglycosides and polymyxins greatly increase the renal excretion of magnesium and significantly decrease the plasma concentration of this cation. Zinc increases the bacterial sensitivity to the action of beta-lactams. The polymerization of vancomycin dimers increases the antibacterial activity and it is dependent of zinc. Zinc oxide nanoparticles have a significant antibiofilm action. On the other hand, magnesium and zinc salts greatly reduce the digestive absorption of many antibiotics and decrease their bioavailability. Regarding adverse effects, there are situations were magnesium and zinc can reduce some of these effects. A low magnesium level aggravates the cartilage damage produced by quinolones. This cation reduces nephrotoxicity of Aminoglycosides and vancomycin and hepatotoxicity of some antituberculosis drugs. Determination of zinc and magnesium concentration is strictly necessary for patients receiving antibiotics and in the case of abnormal levels, correction must be made immediately.

Keywords: ***antibiotics, magnesium, zinc, adverse effects.***

Introduction

Antibacterial antibiotics are one of the most used drug groups in current medical practice [1]. The correct use of this group of drugs has saved and continues to save millions of lives every year.

Unfortunately, the rapid development of bacterial resistance to antibiotics has greatly limited the use of some of the known antibiotics and has even made some antibiotics practically obsolete. In addition to bacterial resistance to antibiotics and ways to limit its development, there are many other less studied problems related to the use of antibiotics. One of these problems is the complex interaction between these drugs and the bivalent cations in the plasma and in the cells. Two of the most important biometals in the human and animal body are magnesium and zinc.

Disturbances in the concentration of the two biometals are involved in the pathogenesis of numerous diseases [2-5] and influence the action of some drugs [6,7].

Interactions between magnesium, zinc and antibacterial antibiotics

The interactions between these two bivalent cations and antibacterial antibiotics are complex. Antibacterial antibiotics act not only on bacterial organisms but also on the cells of the human body. In both actions, there can be various interactions with zinc and magnesium.

The following types of interactions exist between antibiotics and zinc and magnesium:

a) Antibiotics influence on plasma and tissue concentration of magnesium and zinc
b) Influence of these two cations on the pharmacodynamic action of antibiotics
c) Influence of zinc and magnesium on the pharmacokinetics of antibiotics
d) Zinc and magnesium influence on some adverse effects of antibiotics.

a) Influence of antibiotics on magnesium and zinc plasma concentration

Aminoglycoside antibiotics (gentamycin, kanamycin, amikacin and others) induce chronic hypomagnesemia by increasing the renal elimination of magnesium. Aminoglycosides reduce the paracellular reabsorption of magnesium at the renal level and increase the urinary elimination of this cation. The effect is very strong. A dose of 5mg/kg of gentamicin can cause an increase of about four times in the renal elimination of magnesium. This effect sometimes persists even after stopping the administration of aminoglycosides. Neomycin and tobramycin also increase the urinary excretion of magnesium [8] Polypeptide hormones (glucagon, calcitonin, and arginine vasopressin) stimulate the reabsorption of magnesium at the level of the distal convoluted tubule. Aminoglycoside antibiotics inhibit this hormone-stimulated Mg^{2+} absorption [9]. Some authors proposed to consider fractional excretion of magnesium as a biomarker for aminoglycoside nephrotoxicity and primarily for tubular injuries [10].

Polymyxin B also increases the renal elimination of magnesium and causes hypomagnesemia [11]. The daily level of magnesium decreases by more than 70% in the case of the administration of polymyxins. Ethambutol and isoniazid, frequently used in tuberculosis therapy, produce hypomagnesemia both alone and in combination. In experimental studies on rabbits, metronidazole (45 mg/kg per os) and tinidazole (40mg/kg per os) increased the urinary excretion of zinc and significantly reduced the serum level of this bivalent cation [12].

b) Zinc and magnesium influence on antibiotics antibacterial activity

The interaction between transitional metals (zinc, magnesium and others) and antibacterial antibiotics is complex. This complexity is primarily due to the fact that these transition metals have multiple roles both in the human and animal body and in the bacterial cell. These roles can sometimes be different. There are big differences still incompletely explained regarding the influence of magnesium and zinc (and other bivalent metals) on the antibacterial action of different antibiotics used clinically.

Fluoroquinolones

In the mechanism of quinolones action, the presence of the Mg^{2+} ion is important. It has been shown that the action of fluoroquinolones on topoisomerase IV from *B. anthracis* is dependent on Mg^{2+}. Some mutations produced at the level of this enzyme increased the Mg^{2+} concentration required to produce maximal quinolone-induced DNA cleavage. The binding of fluoroquinolones to topoisomerase IV is dependent on the existence of this water-metal ion bridge. Its absence is a cause of the lack of effect of fluoroquinolones and a mechanism by which resistance to these antibiotics develops [13].

Quinolones form complexes with plasmatic magnesium. Magnesium interacts with the COO^- and ketone CO groups from the structure of quinolones. In the case of these complexes, the MIC (minimal inhibitory concentration) is higher than when the antibiotic is free. The increase in MIC is due to the fact that an interaction of the quinolone-Mg^{2+} complex with DNA gyrase occurs in the bacterial cell.

The penetration of quinolones into the bacterial cell is reduced when the amount of magnesium is higher. The effect is more pronounced in the case of hydrophobic quinolones such as pefloxacin and sparfloxacin [14].

Beta-lactam antibiotics

The poisoning of the bacterial cell with zinc also increases the sensitivity to the action of beta-lactam antibiotics. Zinc oxide nanoparticles (ZnO NPs) have an important action against Gram negative bacteria (such as *K. pneumoniae*, *E.coli*, *P. aeruginosa*, *S. typhi*, *P. mirabilis* and others) producing beta lactamase and resistant to the action of beta lactam antibiotics [15].

Two main mechanisms of antibacterial action for zinc oxide nanoparticles have been studied: **a)** The production of bacterial membrane lesions following the direct interaction between these nanoparticles and the bacterial membrane [16]. **b)** the bactericidal action through the generation of hydrogen peroxide.

The effect of zinc sulfide nanoparticles is non-identical in relation to the action of all antibiotics, nor in relation to all pathogenic bacteria. The antibacterial action of zinc sulfide nanoparticles 150 µg/mL is greater in the case of *A.baumannii* compared to the action on *S. pyogenes* [17].

On the other hand, zinc is necessary for the synthesis of peptidoglycans in the structure of the bacterial wall in the structure of some Gram-positive bacteria, such as *S. pneumoniae*. Disturbance of zinc efflux in the case of this bacterium makes ampicillin-resistant invasive strains sensitive to the action of ampicillin [18].

Ceftriaxone-ZnO nanoparticle complexes activated with ultraviolet radiation have an increased activity against *E.coli*. This antibacterial activity is greater compared to the action of pure ceftriaxone [19]. Zinc also increases the action of this antibiotic against *H. pylori.*

Subinhibitory concentrations of ZnO(zinc oxide) nanoparticles potentiated the antibacterial effect of ceftazidime against resistant *A. baumannii*, increased the uptake of this antibiotic by the pathogenic bacteria and determined some changes in the bacterial body [20].

Tetracyclines

Magnesium is important for the action of tetracycline. This antibiotic binds complexed with two Mg^{2+} ions to the Tet-1(Ten-eleven translocation protein) site. Tet-1 site is a high-occupancy tetracycline-binding site and is located at the level of the 30S subunit of the bacterial ribosome. Tetracyclines form metal complexes with magnesium and can act as chelators of this cation. The formation of complexes between tetracycline and zinc is also important for the action of this antibiotic on the cells of the human body [21].

The administration of PBT2(5, 7-dichloro-2-[(dimethylamino)methyl]-8-hydroxyquinoline) $+Zn^{2+}$ in combination with antibiotics such as tetracycline or doxycycline, demonstrated the existence of an antibacterial activity against multidrug-resistant *A. baumannii*, one of the bacteria that cause great problems, especially due to the high mortality in the case of ventilator-associated pneumonia. The increase in the intracellular concentration of zinc has an influence on the increase in antibiotic sensitivity of resistant *A. baumani* strains [22].

Aminoglycosides

The presence in the culture medium of an ionophore for zinc such as pyrithione (ZnPT) determines the reduction of the growth of some resistant strains of *A.baumani* and *K.pneumoniae*. An ionophore more water soluble than ZnPT such as compound 5002 which forms complexes with zinc added in the incubation medium in association with amikacin completely inhibits the growth of these two resistant bacteria [23].

Against the action of the ionophore zinc pyrithione (ZnPT), some bacteria such as *P. aeruginosa* develop resistance. An important part of the resistance of bacteria to aminoglycosides is

given by the activity of efflux pumps, but another mechanism of resistance of some Gram-negative bacteria to amikacin is produced by the action of 6'-N-acetyltransferase type Ib, an enzyme which catalyzes the transfer of an acetyl group to the 6' position of the amikacin molecule. Increasing the concentration of zinc in the environment reduces or blocks the activity of this enzyme.

Glycopeptides

There are data showing that one of the mechanisms of antibacterial action of vancomycin involves the interaction of this antibiotic with zinc ions. Vancomycin can bind Zn^{2+} ions. In this way, this antibiotic determines a zur-dependent zinc starvation response in bacterial cells [24]. The polymerization of vancomycin dimers increases the antibacterial activity of this antibiotic, including the bactericidal action on resistant bacteria. This polymerization is dependent on the presence of Zn^{2+}.

Zinc increasing vancomycin polymerization followed by increasing the binding affinity of this antibiotic to D-Ala-D-Lac precursors for peptidoglycan biosynthesis. Thus, the synthesis of the bacterial wall is severely affected.

Glycylcyclines

Tigecycline, an antibiotic from the group of Glycylcyclines, forms complexes with magnesium and other bivalent cations. The influence of the formation of these complexes on the antibacterial action of tigecycline is not known, but it seems that it is important for the antibacterial action of this antibiotic [25].

Antituberculosis antibiotics

Zinc oxide (ZnO) nanoparticles reduce the membrane stability of *M. tuberculosis* and make it more vulnerable to the action of antituberculosis drugs [26]. Zinc oxide nanoparticles also reduced hemolysin toxin producing *S. aureus* and disrupted biofilm generation by bacteries [27].

CorA Mg^{2+}/Ca^{2+} transporter is important for maintaining magnesium homeostasis in the cell of *Mycobacterium tuberculosis*. Disturbance of this homeostasis affects the bacterium and for this reason it is considered that CorA Mg^{2+}/Ca^{2+} transporter could be a target for future antituberculosis drugs [28].

Macrolides

Azithromycin can fix 34-38nm zinc oxide nanoparticles on the surface of the molecule. This complex between the antibiotic and the zinc oxide nanoparticles has an increased antibacterial activity in skin infections in rosacea compared to azithromycin administered alone. Skin bacterial clearance and epidermal regeneration are increased [29]. The gel with azithromycin -ZnONP proved to be very effective against *E. coli* and *S. aureus* resistant to antibiotics (MRSA). The MIC to azithromycin is reduced for both bacteria. The mechanism of potentiation of the antibacterial action of the antibiotic by zinc oxide nanoparticles is the direct action on the pathogenic bacteria and the facilitation of penetration the bacterial membrane by reactive oxygen species. As a result, a severe dysfunction occurs at the level of the bacteria (including sometimes their death). In this way, the antibacterial action of the antibiotic is greatly facilitated [30].

Clarithromycin forms complexes with zinc and magnesium (but also with other bivalent metals). These complexes have reduced MIC against several pathogenic bacteria (*K. pneumoniae S.aureus, S.typhii, E. coli, P. vulgaris*) compared to clarithromycin alone.

Lipopeptides

Daptomycin is a cyclic anionic lipopeptide antibiotic. Its structure makes it possible to bind calcium, but also magnesium. Calcium is considered to be essential for the activity of this antibiotic. The role of magnesium is less known. It could be that the ratio between calcium and magnesium concentrations is important for the antibacterial action of daptomycin [31].

Polypeptide antibiotics

When *P. aeruginosa* is cultivated and grows in an environment with a low concentration of Mg^{2+}, this bacterium produces an increased amount of H1 protein (which is a component of the outer membrane). The H1 protein is involved in increasing the resistance of this bacteria to polymyxins. The lack of magnesium in the environment also causes structural changes in the bacterial wall, which also contribute to the resistance of this bacteria to polymyxins.

Bacitracin inhibits dephosphorylation of C(55)-isoprenyl pyrophosphate. Through this inhibition, the synthesis of peptidoglycans by bacteria is affected. Chelating agents of bivalent metals (Zn^{2+}, Mg^{2+}) suppress this inhibitory action of bacitracin and implicitly its antibacterial action. Bacitracin zinc salts are used in topical applications for the treatment of some skin infections. Bacitracin action of inhibiting some metalloproteases is also dependent on the presence of zinc ions [32].

Lincosamides

In the case of *Hidradenitis suppurativa*, the association of liposomal magnesium with clindamycin 1% gel applied topically had a significantly increased antibacterial activity compared to clindamicin administrated alone

Antibiofilm action

One of the big problems of current antibiotic therapy is overcoming the resistance of bacteria protected by biofilm and creating substances with antibiofilm action that can be used in medical practice.

One of the substances with significant antibiofilm action is zinc oxide nanoparticles (ZnO-NPs). These nanoparticles themselves have an action on *S. aureus* isolates resistant to vancomycin, linezolid and methicillin (MIC 128-2048 µg/ml). In concentrations below the MIC, ZnO-NPs significantly reduced biofilm formation by *S. aureus*. Zinc oxide nanoparticles (ZnO-NPs) have a high antibiofilm activity against biofilm producing by *Staphylococcus aureus* (MRSA and LRSA), *P. aeruginosa* and association of these nanoparticles to linezolid decreased bacterial resistance to this antibiotic [33].

Magnesium-doped zinc oxide nanoparticles (ZnO:MgO NPs) also have a strong antibiofilm action. This was shown against the biofilm produced by *P.mirabilis* [34].

Unlike of (ZnO:MgO NPs), a higher concentration of free Mg^{2+} is involved in the stabilization of the biofilm produced by these bacteria and the increase in exopolysaccharide synthesis. In the case of some bacteria such as *L. monocytogenes*, magnesium significantly increases biofilm synthesis [35]. The involvement of magnesium in antibiotics actions is presented in the Figure 1.

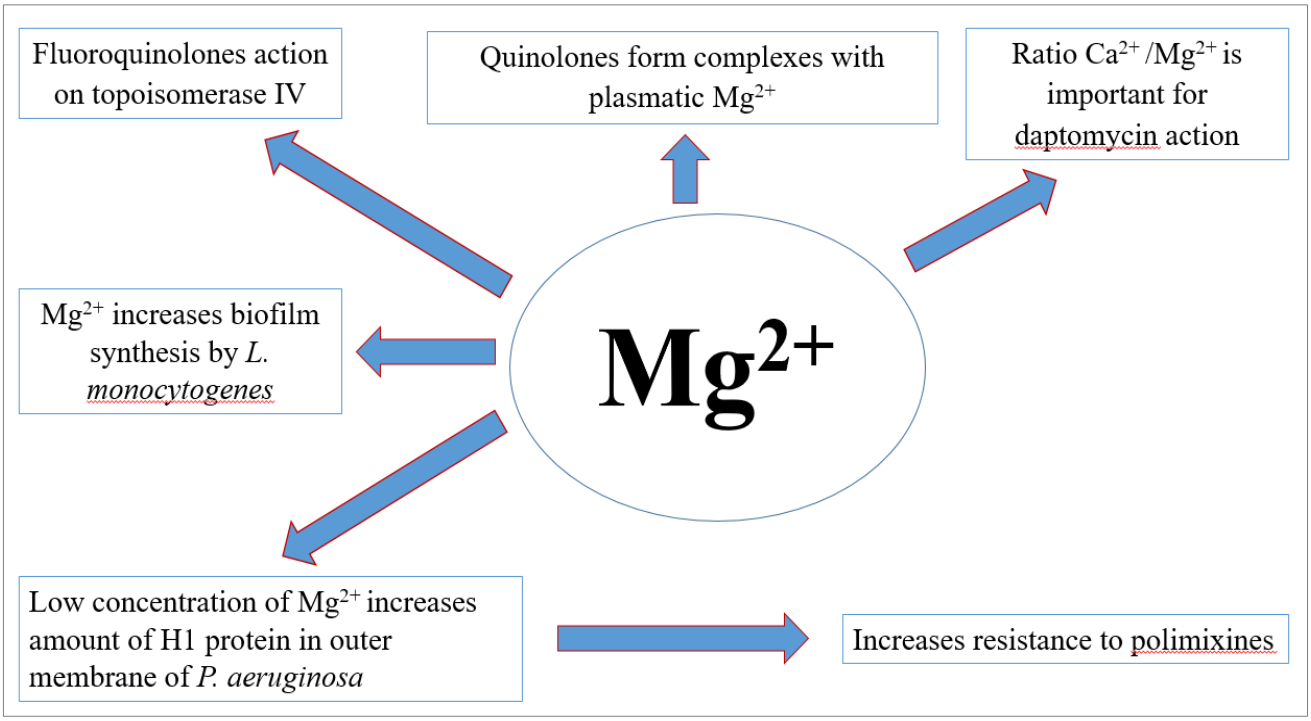

Figure 1. Influences of magnesium on some antibiotics actions.

Other zinc and magnesium actions regarding the antibacterial activity

For the activity and development of bacteria, the intracellular concentration of zinc must be maintained within certain limits. Both excess and lack of zinc are deeply damaging to bacterial activity. Zinc is required for the growth and virulence of *A. baumannii*. The uptake of zinc by this bacteria is dependent on the activity of the zinc uptake regulator Zur. This is a protein with a regulatory role. It controls the expression of genes involved in zinc metabolism and in the regulation of its intracellular concentration [36].

Experimental inactivation of Zur increased the susceptibility of *A. baumannii* to antibiotics such as tigecycline, colistin and rifampicin. In the Δ Zur mutant bacteria, the ability to inactivate reactive oxygen species is reduced and its susceptibility to antibiotics increased [37].

The uptake of zinc by *S. pneumoniae* occurs through the action of some transporters (AdcA and AdcAII). Deletion of these two transporters greatly reduces the uptake of zinc by the cell of some bacteria such as *S. pneumoniae*. In the absence of these two transporters, the growth of these bacteria is severely disrupted and their virulence decreases.

In the case of some anaerobic bacteria, it was found that the Zn ionophore PBT2 has significant antibacterial activity and that its action is synergistic with that of some antibiotics frequently used in infections with anaerobic bacteria, such as metronidazole. This zinc ionophore inhibits the growth of anaerobic bacteria and can reduce the MIC for the antibiotics used even when the bacteria are protected by biofilm [38].

There is also the possibility that some of these nanoparticles are carriers for some antibiotics, facilitating their entry into the bacterial cell. ZnONPs have a bactericidal action not only due to their very small size but also due to a higher surface energy [39]. In bacteria such as *E. coli* and *K. pneumoniae*, ZnONPs cause membrane deformations, leakage of cellular contents and elongation of the bacterial body [40].

Part of the antibacterial action of ZnONPs is due to the increase in ROS starvation. Under the action of these nanoparticles, bacterial growth stops and the bacterial wall presents deformations. This fact facilitates the action of antibiotics on these pathogenic bacteria. ZnONPs cause an increased release of zinc at the level of the bacterial cell and thus toxic levels of zinc are reached for the bacteria. These high levels of zinc associated with the increase in ROS (reactive oxygen species) production cause the death of the bacterial cell and the increase in the elimination of DNA from it [41].

Zinc and beta-lactamases inhibitors

Overcoming the antibiotic resistance given by these beta-lactamases depends on finding new beta-lactamase inhibitors. Experimentally, it has been proven that some compounds such as aspergillomarasmine A inhibit MBLs by chelating and removing the active site zinc ions.

Some bismuth compounds used for a long time in anti-*Helicobacter pylori* therapy (such as colloidal bismuth subcitrate) have been shown to inhibit MBLs by displacing the two zinc atoms in the structure of these enzymes.

Another group of beta-lactamase inhibitors that have been tested experimentally are the NMD-1(New Delhi metallo-β-lactamase-1) inhibitors with the benzimidazole and benzoxazole structure. They are ionophores for zinc and in some cases they restored the sensitivity of resistant strains of *E.coli* to meropenem [42].

Since MBLs (metal binding betalactamases) pose major problems in practice and greatly reduce the effectiveness of many antibiotics, new inhibitors of these enzymes are being sought. A group of zinc-selective spiro-indoline-thiadiazole analogues have been synthesized that potentiates the in vitro action of beta-lactam antibiotics. These substances are zinc chelators [43]. The involvements of zinc in the action of some antibiotics are shown in figure 2.

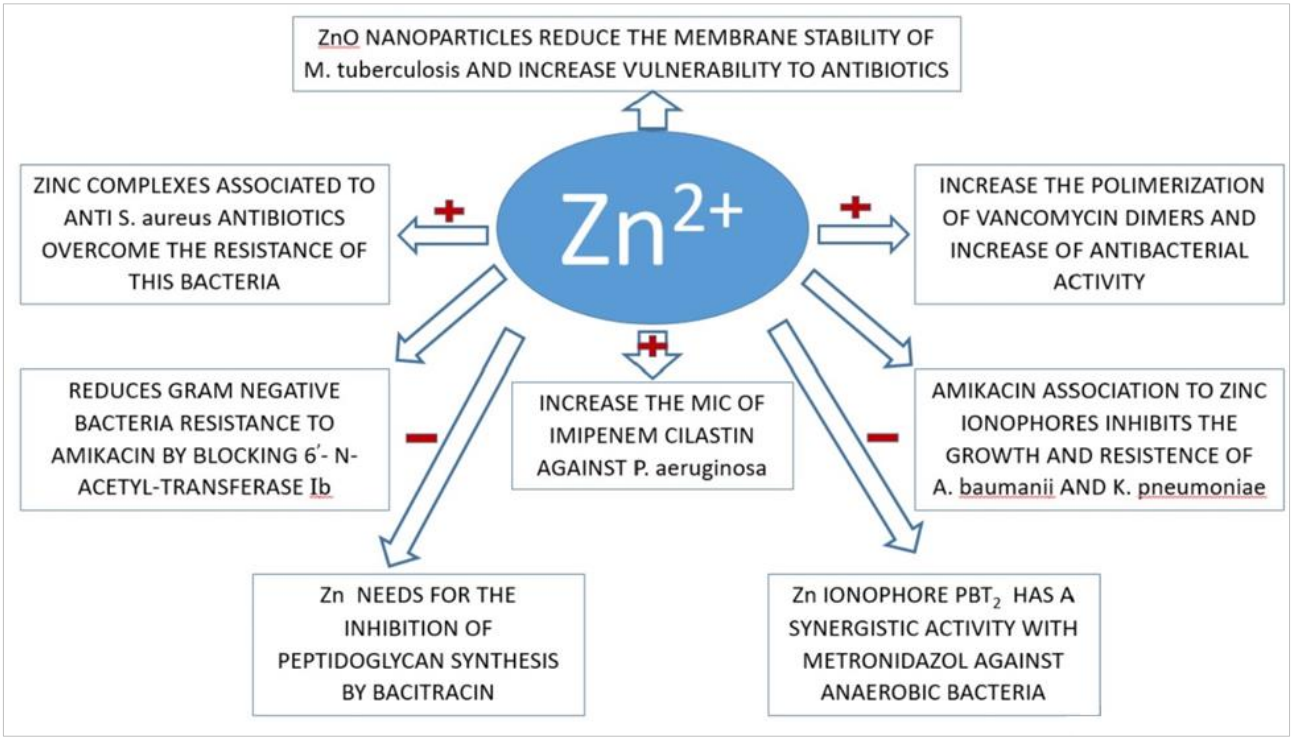

Figure 2: Involvement of zinc in the action of some antibiotics.

c. Zinc and magnesium influence on antibiotics pharmacokinetics

The absorption of many antibiotics is reduced by the presence of magnesium or zinc salts in the digestive tract. The reduction of bioavailability after oral administration of quinolones is produced by the formation of compounds through the reaction of the functional groups of the quinolones with these metals. These complexes are more difficult to absorb.

Administration of dietary supplements containing zinc simultaneously with cephalexin causes a reduction in the digestive absorption of this antibiotic [44]. The quinolones must be administered at least 2-3 hours before antacids containing magnesium or zinc. Pefloxacin *per os* treatment at the same time with magnesium hydroxide determines important changes in the pharmacokinetics of this antibiotic. Cmax decreases significantly and Tmax were prolonged. AUC also decreases significantly and the bioavailability of pefloxacin is only 44+/-23% of the bioavailability of pefloxacin administered alone. These results absolutely contraindicate the administration of pefloxacin (and other quinolones) with magnesium-containing antacids. Digestive absorption of moxifloxacin is also significantly reduced by magnesium-containing antacids [45].

Aluminum magnesium hydroxide significantly reduced the intestinal absorption of doxycycline and its bioavailability.

Magnesium-containing antacids also decrease the digestive absorption of ethambutol. The changes in pharmacokinetics of this drug are important and must be taken into consideration in the case of tuberculosis therapy with ethambutol. Unlike ethambutol and isoniazid, the pharmacokinetics of pyrazinamide is not significantly influenced by the presence of food or antacids in the stomach.

In addition to changes in gastric pH, magnesium trisilicate and magnesium oxide also have a high adsorption capacity for antibiotics such as doxycycline, chloramphenicol, cloxacillin and others. Tetracyclines are the most strongly adsorbed by these two magnesium compounds. Although the adsorption of different antibiotics is very unequal, oral administration of antibiotics in combination with magnesium trisilicate and magnesium oxide should be avoided. Magnesium trisilicate reduces the digestive absorption of trimethoprim and AUC by about 50%.

Zinc reduces the intestinal absorption of some beta-lactam antibiotics. This reduction is not due to pH changes, but to zinc's inhibition of intestinal peptide transporters (PEPT1 and basolateral peptide transporter). Administration of linezolid together with magnesium containing antacids does not changes the absorption or other pharmacokinetics parameters of this antibiotic [46].

But there are also positive, therapeutically useful influences of magnesium and zinc on the pharmacokinetics of some antibiotics.

Zinc/clindamycin gel which is used in the treatment of acne has a lower skin absorption than clindamycin lotion applied for the same therapeutic purpose. Cmax, and AUC0-12 of clidamycin after applying Zinc/clindamycin gel are 30-50% lower than in the case of applying the lotion with clindamycin alone. This fact can be favorable in medical practice because it reduces the risk of adverse effects that may occur after an increased absorption of clindamycin.

The use of erythromycin in combination with zinc in the treatment of acne potentiated the penetration of the antibiotic through the stratum corneum of the skin and prolonged the time that erythromycin remained on the skin. This fact has favorable effects regarding the treatment of acne.

d. Adverse effects of antibiotics

d.1. Reduction of adverse effects of some antibiotics by magnesium

Experimental studies have shown that arthropathy is one of the most important, if not the most important adverse effect of quinolones in young animals. It occurs at higher concentrations than the therapeutic concentrations of quinolones in the human body. The lack of magnesium aggravates the cartilage damage produced by quinolones [47]. In adult animals, quinolones did not cause cartilage damage either at normal concentrations of this cation or at low levels.

Damage to the articular cartilage after the administration of quinolones has also been observed in children. In clinical practice, most arthropathies after the administration of quinolones were observed after levofloxacin.

Isoniazid, rifampicin, pyrazinamide and ethambutol are drugs classically used as first-line medication in tuberculosis Their association, but also each of these drugs separately, has important adverse effects on the liver. Experimental studies in mice showed that magnesium isoglycyrrhizinate 40mg/kg ip significantly reduced liver injury produced by the association of these antituberculosis drugs. Besides all, this magnesium compound also has anti-inflammatory, anti-apoptotic activity and reduces neutrophil infiltration of the liver [48].

Considering all these actions, we consider that the association of magnesium isoglycyrrhizinate should be done in all cases of treatment with these antituberculosis drugs.

Efflux pumps are an important resistance mechanism to chloramphenicol and other antibiotics.

Magnesium concentration has a modulating role on the functioning of these efflux pumps. Between 26-50% of chloramphenicol efflux from *P. aeruginosa* is dependent on the magnesium concentration in the environment [49].

The administration of intravenous infusion of magnesium sulfate at the same time (but in separate administrations) with these antibiotics reduced nephrotoxicity. A level of 1.9 mg/dl magnesium decreases nephrotoxicity by decreasing the increased oxidative stress that was proven in the mechanism of vancomycin nephrotoxicity [50].

Experimental research has shown that magnesium sulfate reduces the nephrotoxicity of colistin. Mg+colistin rats group had significantly lower creatine, urea and MDA values compared to the group of rats that received the same dose of colistin alone for seven days [51]. The experimental data shown revealed only the effect of magnesium sulfate, but we believe as a hypothesis that other magnesium compounds with a superior capacity to increase the intracellular concentration of magnesium could have a stronger protective effect against the tubular lesions produced by colistin. Magnesium influence on some adverse effects of antibiotics is shown in Figure 3.

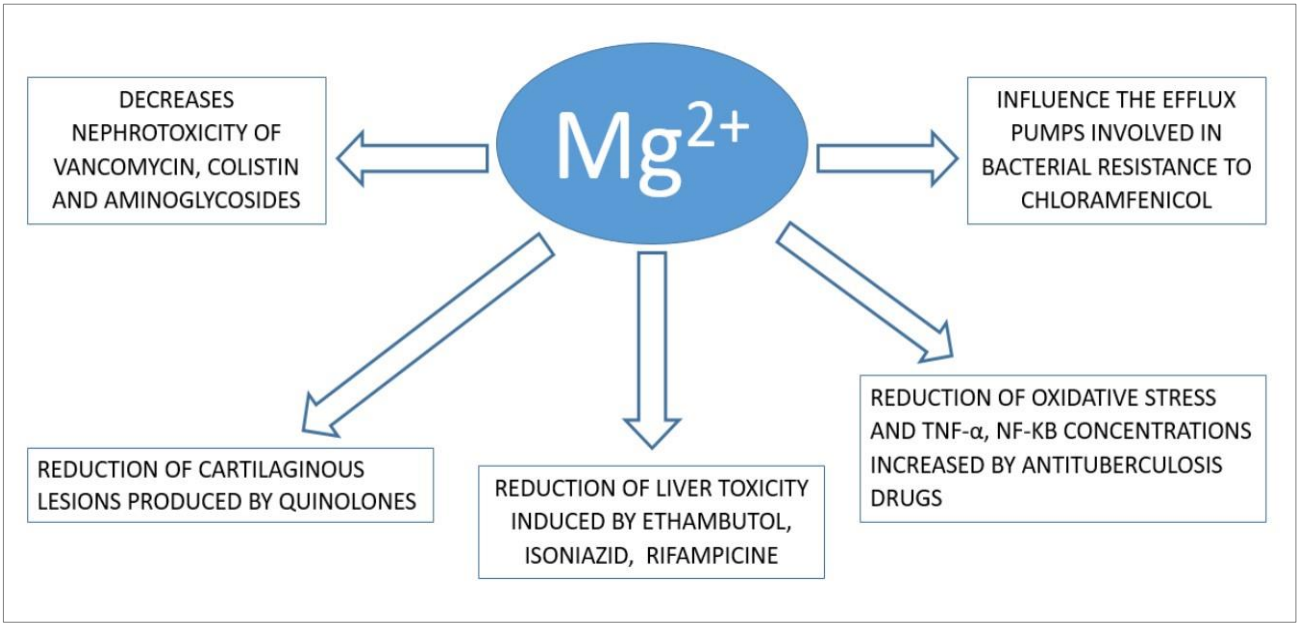

Figure3. Influence of magnesium on some adverse effects of antibiotics

d2. Involvement of zinc in some adverse effects of antibiotics

a) Zinc involvement in beta-lactamases activity

One of the most important problems related to treatment with beta-lactam antibiotics is the action of beta-lactamases from different groups that reduce or completely cancel the antibacterial action of these antibiotics. Metallo-β-lactamases are zinc dependent hydrolases.

Among the groups of beta-lactamases, the group whose activity is dependent on the presence of zinc atoms poses special problems in practice because it inactivates many new beta-lactam antibiotics [52]. In the structure of these beta lactamases there are one or two active centers that contain zinc. The activity of these enzymes is therefore zinc dependent. The role of zinc atoms in the active site of metallo-β-lactamases is essential because they are involved in the polarization of water molecules which is absolutely necessary for the hydrolysis of beta-lactam antibiotic molecules.

One of the most active groups of beta-lactamase class B carbapenemases involved in the degradation of carbapenems and in bacterial resistance to these antibiotics requires zinc at their active site [53]. Zinc chelating substances inhibit the activity of these enzymes.

b) Zinc concentration influence on other adverse effects of antibiotics

Ethambutol can cause injuries to the cells of the human body by accumulating of zinc at the level of lysosomes. This drug induces enlarged lysosomes. By accumulating zinc, the acidic pH of the lysosomes is neutralized, which disturbs the normal functioning of the human cell disrupts and leads to the blocking of autophagy [54].

Zinc-induced metallothionein reduces gentamycin nephrotoxicity.

In some cases, when some antibiotics produce serious DNA damage, error-prone DNA polymerases which induces a higher rate of mutations (a hypermutation) are activated in the bacteria. Zinc reduces the occurrence of hypermutation and a zinc ionophore (zinc pyrithione) was approximately 100-fold more potent than zinc in inhibition of ciprofloxacin-induced hypermutation in *E. cloacae* [55].

Conclusions

Monitoring plasma concentrations of magnesium and zinc during therapy with antibacterial antibiotics is strictly necessary. In all cases where it is necessary, disturbances in cationic concentrations must be corrected.

In some cases, to reduce the adverse effects of antibiotics, the administration of zinc or magnesium is necessary and must be done as soon as possible after the adverse effect is identified.

List of abbreviations

MIC: Minimal inhibitory concentration
ZnONPs: Zinc oxide nanoparticles
ZnO: zinc oxide
Ten-1: Ten-eleven translocation protein
PBT2: 5, 7-dichloro-2-[(dimethylamino)methyl]-8-hydroxyquinoline
ZnPT: Pyrithione Zn
CorA: Family of membrane transport proteins
NPs: Nanoparticles
MRSA: methicillin-resistant Staphylococcus aureus
NMD-1: New Delhi metallo-β-lactamase-1
MBLs: Metallo-β-lactamases
ROS: Reactive oxygen species

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Conflicts of Interest

"The authors declare that there is no conflict of interest regarding the publication of this paper."

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