CHEMICAL AGENTS AS ANTIMICROBIAL FACTORS

CARMEN TATU[1,2], GABRIELA TĂNASIE[1,2], CRISTINA GAȘPAR[3], MARIUS GEORGESCU[1], FLORINA BOJIN[2,4], DANIELA PUȘCAȘIU[5], CARMEN PANAITESCU[1,2]

[1]Department of Functional Sciences, Physiology, Center of Immuno-Physiology and Biotechnologies (CIFBIOTEH), "Victor Babeș" University of Medicine and Pharmacy Timișoara, Romania, Eftimie Murgu Sq. no. 2, 300041 Timișoara

[2]OncoGen Research Center, Timisoara County Emergency Clinical Hospital, Liviu Rebreanu Boulevard, no. 156, 300723, Timișoara

[3]Banat's University of Agricultural Science and Veterinary Medicine "King Michael the Ist of Romania" from Timisoara, Aradului str no. 119, 300645, Timișoara, Romania

[4]Department of Functional Sciences, Immunology, Center of Immuno-Physiology and Biotechnologies (CIFBIOTEH), "Victor Babeș" University of Medicine and Pharmacy Timișoara, Romania, Eftimie Murgu Sq. no. 2, 300041 Timișoara

[5]Department of Microscopic Morphology, Cellular and Molecular Biology, "Victor Babeș" University of Medicine and Pharmacy Timișoara, Romania, Eftimie Murgu Sq. no. 2, 300041 Timișoara

ABSTRACT

A wide variety of chemicals can be used as antibacterial agents to prevent contamination. Antiseptics and disinfectants are widely used in hospitals and are an essential element in combating and preventing nosocomial infections. A wide variety of active chemicals or biocides are present in these products. Disinfectants and antiseptics affect bacteria in many ways. The widespread use of antiseptics and disinfectants has contributed to the development of microbial resistance, in particular cross-resistance to antibiotics. In medical practice, antimicrobial agents must be selected taking into account the specific microorganisms, pH, solubility, toxicity, organic material present and last but not least the cost. No ideal antimicrobial chemical exists, however the correct choice and proper use of current substances will result in an adequate level of disinfection. This paper aims to review the main antimicrobial chemical agents, the mechanisms by which they act and their importance in clinical practice.

Key words: antimicrobial chemicals, alcohols, halogens, aldehydes, quaternary ammonium compounds, silver.

INTRODUCTION

During life we are constantly exposed to a wide variety of germs. Last year, the public health emergency surrounding the COVID-19 pandemic highlighted the importance of good biosecurity measures and practices. To prevent the spread of infection, disinfection and hygiene habits are crucial, especially when the microorganism can persist and survive on surfaces. Contaminated surfaces have been called fomites and sometimes microorganisms can survive here even for months [1]. As a result, fomites serve as an important reservoir of pathogens and facilitate the transfer between hosts. To prevent contamination, a wide variety of chemicals can be used as antibacterial agents. At present there are various classifications of them but the vast majority take into account the mechanism of action by which these substances exert their bactericidal effect. Antiseptics and disinfectants are widely used in hospitals and are an essential element in combating and preventing nosocomial infections [2]. A wide variety of active chemicals or biocides are present in these products. Disinfectants and antiseptics affect bacteria in many ways. Those that lead to bacterial death are called bactericidal agents. Those that cause temporary growth inhibition are bacteriostatic agents. There is no single antimicrobial agent that is most effective in all situations. That is why different situations may require different agents. The increase in the potential for microbial contamination and the risk of infection has led to an increase in the use of antiseptics and disinfectants by the general public [3]. Despite this, knowledge about the mode of action of these agents is still limited. It is, however, well known that their spectrum of activity is wider than that of antibiotics. While antibiotics tend to have specific intracellular targets, antibacterial chemicals may have multiple targets. A number of techniques such as: lysis of intracellular constituents, examination by studying the disruption of cellular homeostasis, study of enzyme inhibition, electron transport and oxidative phosphorylation, interaction with macromolecules, examination biocides are used to study the mechanisms of action of antiseptics and disinfectants on microorganisms[4, 5]. The widespread use of antiseptics and disinfectants has contributed to the development of microbial resistance, in particular cross-resistance to antibiotics [2]. A number of factors affect the selection of the best agent for any given situation. Antimicrobial agents should be selected for specific micro-organisms and environmental conditions. Additional variables to consider when selecting an antimicrobial agent include: pH, solubility, toxicity, organic material present and last but not least cost. The present paper aims to review some of the antimicrobial chemical agents, the mechanisms by which they act and their importance in clinical practice.

1. Alcohols

The mechanism of action of alcohols is nonspecific, the bacteriostatic effect is explained by their ability to distort proteins. They are also solvents for lipids and as a result, can damage lipid complexes in the cell membrane. Cells will be lysed and cellular metabolism will be disrupted [2, 6]. This is supported since the

Received 4th of July 2021. Accepted 11th of August 2021. Address for correspondence: Carmen Tatu, Department of Functional Sciences, Physiology, Center of Immuno-Physiology and Biotechnologies (CIFBIOTEH), "Victor Babeș" University of Medicine and Pharmacy Timișoara, Romania, Eftimie Murgu Sq. no. 2, 300041 Timișoara e-mail: carmen.tatu@umft.ro

1950s by specific studies that have shown the denaturation of the dehydrogenases of the bacterium Escherichia coli and the delayed growth of Enterobacter aerogenes, actions explained by inhibiting rapid cell division [7]. In addition to these mechanisms, alcohols are also known as dehydrating agents. Under certain conditions, the elimination of water from the cells caused by the action of alcohol has a bacteriostatic effect. This may explain the relative inefficiency of absolute alcohol on “dry” cells. In addition to these mechanisms, part of the effectiveness of alcohol in disinfecting surfaces can be attributed to its cleaning or detergent action which results in the mechanical removal of microorganisms. It has been observed that the general antimicrobial activity of alcohols increases with the length of the carbon chain, the maximum being reached at six carbon atoms [8]. As a result, the most effective are: ethanol, isopropanol and n-propanol. Alcohols have broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses and fungi, but have no sporicidal effect. However, it is known to inhibit the sporulation and germination of spores, an effect that is reversible [9]. Due to the lack of sporicidal activity, alcohols are not recommended for sterilization, but are widely used for disinfecting hard surfaces and skin antisepsis. Lower concentrations can also be used to potentiate the activity of other biocides. Among the mentioned alcohols, isopropyl alcohol is considered more effective against bacteria, while ethyl alcohol is more powerful against viruses [2]. However, this is dependent on both the concentrations of the active agent and the microorganism tested. Against S. aureus, E. faecium or P. aeruginosa, the bactericidal activity of ethyl alcohol appears to be 80% stronger than 95% [10].

Ethanol is also effective against various mycobacteria. Since 1947 it has been shown that ethanol at a concentration of 95% kills M. tuberculosis in sputum within 15 seconds, while a concentration of 70% required a contact time of 30 seconds and at 50% 60 seconds [11]. The same very effective bactericidal activity was observed with 70% ethanol against M. bovis [12]. In addition, ethanol has a wide bactericidal activity against most fungi, including yeasts and dermatophytes [12, 13, 14]. As for the activity of ethanol against viruses, it largely depends on the concentration of ethanol. As expected, higher concentrations of ethanol (95%) generally have better antiviral activity than low concentrations (60 to 80%), especially against non-encapsulated viruses [15]. Most non-encapsulated viruses such as poliovirus, astroviruses, feline calicivirus, rotaviruses and ecoviruses are also inactivated by ethanol [13, 16, 17, 18]. The hepatitis A virus is perhaps the only virus that is not completely inactivated in the presence of ethanol. Regarding encapsulated viruses, ethanol is active against vaccinia virus, influenza A virus, togaviruses, Newcastle disease virus, HIV, HBV and herpes simplex viruses [19, 20].

Isopropyl alcohol (isopropanol) has higher lipophilic properties than ethyl alcohol and is less active against hydrophilic viruses such as polio. The bactericidal activity of isopropanol starts at a concentration of 30% and increases with increasing concentration, but an interesting aspect is the reduction of bactericidal activity to 90% [8]. The same is true for the bactericidal activity of n-propanol. It appears that the bactericidal activity of isopropanol refers to 13 gram-positive species, 18 gram-negative species. Tuberculocidal activity of isopropanol was also tested and good results were observed at concentrations between 50 and 70% [8]. It has limited activity against non-encapsulated viruses. However, if the exposure time is prolonged, it has an effect against non-encapsulated viruses such as ecovirus (90% isopropanol for 10 minutes), feline calicivirus (50-70% isopropanol for 3 minutes) or adenovirus (50% isopropanol for 10 minutes). 10 minutes) [21]. Isopropanol has no sporicidal activity against B. subtilis and Clostridium novyi spores [8].

N-propanol has been discovered since 1904 and has been described as an alcohol with a very strong bactericidal effect starting from a concentration of 30% [22, 23]. The antimicrobial activity of n-propanol is thought to be similar to that of isopropanol [24]. In general, the antimicrobial activity of alcohols is significantly lower at concentrations below 50% and is optimal in the range of 60-90%. Ethanol has been the first recommended for hand disinfection since 1888 and the antimicrobial activity of isopropanol was first investigated in 1904 [23]. This was followed by many studies that supported the use of the two propanols for hand disinfection [8]. The following classification of bactericidal activity was established: n-propanol is stronger than isopropanol and isopropanol is stronger than ethanol. Also, the bactericidal activity is higher at a temperature between 30 and 40 degrees Celsius compared to the range of 20-30 [25].

2. Halogens

A halogen is any of the five elements (fluorine, chlorine, bromine, iodine and astatin) in group VII A of the periodic table. They exist as free diatomic molecules and form salt as compounds with sodium and most other metals. Chlorine or iodine are important halogens used as potent antimicrobial agents either in their free form or in the form of their compounds.

Chlorine and its compounds

Chlorine is most commonly used in gaseous form or as its compounds. Chlorine in gaseous form is difficult to handle unless special equipment is available for its distribution. Therefore, chlorine gas is used in large-scale operations. Many chlorine compounds are now available, which can be used more conveniently than free chlorine and which, under proper conditions of use, are as effective as free chlorine. Calcium and sodium chloride compounds in the form of calcium hypochlorite - Ca (OCl) 2 and sodium hypochlorite - NaOCl are used in small-scale operations. In addition to hypochlorites, there are other chlorine compounds in the chloramine group. Chloramines are more stable than hypochlorites in terms of prolonged chlorine release and are often used as disinfectants, sanitizers or antiseptics. Examples of chloramines are monochloramine (NH2Cl), chloramine-T and azochloramide. As a mechanism of action, it is known that chlorine acts on microbial cells through hypochlorous acid formed as a result of the reaction between free chlorine and water. However, hypochlorites and chloramines undergo hydrolysis, resulting in the formation of hypochlorous acid. The fate of the hypochlorous acid formed in each case is the same, it undergoes decomposition resulting in HCl and oxygen. Oxygen released during the decomposition of hypochlorous acid is a strong oxidizing agent. It acts on the cellular constituents of microorganisms and leads to their death. The destruction of microbial cells by chlorine and its compounds is achieved by direct effects on cell membranes and enzymes.

Iodine and its compounds

Iodine in its crystalline form is black-bluish with a metallic luster. It is poorly soluble in water, but slightly soluble in alcohol and aqueous solutions of potassium or sodium iodide. Although less reactive than chlorine, iodine is bactericidal, fungicidal, tuberculocidal, virucidal and sporicidal, being an extremely effective bacterial agent, unique in that it is effective against all types of bacteria [26]. Iodine solutions are already used 150 years ago as antiseptics, being considered one of the oldest and most effective antimicrobial agents, traditionally used as "iodine tincture". Aqueous solutions are generally unstable, at least seven species of iodine are present in the solution. Of these, molecular iodine is primarily responsible for antimicrobial efficacy [26]. More recently, iodine has been combined with an organic compound to form iodophore. Iodophores are the so-called "iodine carriers" or "iodine-releasing agents". The most used are povidone-iodine and poloxamer-iodine both in antiseptics and as disinfectants. They are considered less active against certain fungi and spores [27]. The mode of action of iodine and its compounds is not clearly understood. Iodine, being an oxidizing agent, is considered to have the property of irreversibly oxidizing and thus inactivating essential metabolic compounds, such as proteins with sulfhydryl groups.

3. Aldehydes

Most low molecular weight aldehydes are antimicrobial. Two aldehydes, formaldehyde and glutaraldehyde, are the most effective and are most commonly used to kill spores, therefore they are sporicidal. As a mechanism of action, both commonly used aldehydes, formaldehyde and glutaraldehyde, are highly reactive molecules that combine easily with organic nitrogen compounds, such as nucleic acids and proteins, and inactivate them, probably by crosslinking and alkylating molecules. Inactivation of nucleic acids and proteins disrupts the function of cellular organs and, as a result, cells are killed.

Glutaraldehyde has a broad spectrum of activity against bacteria, spores, fungi and viruses. Studies on its mechanism of action have shown a strong adhesion of glutaraldehyde to the outer layers of microorganisms such as E. coli and Staphylococcus aureus, inhibition of the transport of gram-negative bacteria, inhibition of dehydrogenase and other enzymes, prevention of lysis induced by a number of substances in S. aureus and in E. coli and inhibition of RNA, DNA and protein synthesis [2, 28, 29]. Glutaraldehyde is more active at alkaline pH than acid. Because the external pH at the cell surface changes from acid to alkaline, a faster bactericidal effect is reached. The antiviral capacity of glutaraldehyde has also been demonstrated [30]. It reduces the activity of hepatitis B surface antigen (HBsAg) and interacts with lysine residues on the surface of hepatitis A virus (HAV) [2].

Formaldehyde

It is a monoaldehyde that exists as a free water-soluble gas. It is generally used clinically as a disinfectant and sterilizer with bactericidal, sporicidal and virucidal effect, but it works slower than glutaraldehyde [28, 31]. As a mechanism of action formaldehyde is an extremely reactive chemical that interacts with proteins, DNA and RNA in vitro. It has the ability to penetrate inside bacteria, and to modify HBs Ag and HBcAg of HBV [2].

4. Aromatic alcohols

Aromatic alcohols have effective antimicrobial properties for disinfection, even in the presence of biological fluids.

Phenol (C6H5OH) is an organic compound consisting of a benzene ring bearing a single hydroxy substituent. Phenol exerts antimicrobial activity against Gram-positive and negative bacteria, fungi and viruses, but is not as effective as a sporicide [1]. Although the specific mechanism of action of phenol derivatives is not clearly known, there is consensus that these compounds cause physical damage to the plasma membrane of the microbial cell. As a result, the content of essential cell metabolites drains causing cell damage with cell lysis, while acting as a protoplasmic poison that causes the cytoplasm to coagulate, with the death of microorganisms. The efficacy of triclosan (a phenolic derivative) was investigated in vitro and was found to have bacteriostatic effect at lower concentrations, and bactericidal activity at higher concentrations. The activity of triclosan is higher against gram-positive microorganisms than against gram-negative bacteria, especially P. aeruginosa, and the fungicidal activity is good, including yeasts and dermatophytes [8].

Hexachlorophenol is another bis-phenol whose mode of action has been investigated based on studies with Bacillus megatherium. It has been found to be bactericidal at 0 ° C, despite the fact that it causes minimal leakage through the bacterial membrane at this temperature. Despite the efficacy and broad spectrum of hexachlorophen, concerns about its toxicity, especially in newborns, lead to its limited use in antiseptic products [2].

Chloroxyleneol is another phenol used in antiseptic or disinfectant formulas. Chloroxylene is bactericidal against certain bacteria, while others are very resistant, for example P. aeruginosa. Surprisingly, its mechanism of action has been little studied despite its widespread use over time. Due to its phenolic nature, it would be expected to have an effect on microbial membranes.

In conclusion, commonly used phenolic compounds have antimicrobial efficacy against bacteria, fungi, viruses, including HIV. However, literature also reports that some phenolic disinfectants have a limited effect on Coxsackie B4, Enterovirus 11 and Polyovirus [32].

5. Quaternary ammonium compounds

Quaternary ammonium compounds are the most popular cationic detergents. They are characterized by a positively charged nitrogen and a long hydrophobic aliphatic chain. Quaternary ammonium compounds have a structure similar to ammonium chloride, but with some changes. The demand for these disinfectants has increased over the decades, in addition, their use is not limited only as a germicidal agent, but they have been widely used in a variety of industrial, agricultural, clinical and consumer applications [33]. As mechanism of action, it has been shown that microbicidal activity is due to their adhesion to acidic proteins or phospholipids in the membrane, which leads to the formation of so-called hydrophilic voids. Denaturation of essential cellular proteins will increase the permeability of the membrane and ultimately cause the destruction of the microbial cell. In addition, it seems that they are also involved in inactivating energy production and can be linked to DNA [34]. As a result, they are used as solid bactericidal agents, especially against

Gram-positive bacteria and against encapsulated viruses (eg herpes simplex, adenovirus, vaccinia), not being sporicidal, tuberculocidal or with an effect on hydrophilic viruses. Basically, they are commonly used in sanitizing non-critical surfaces, such as floors, furniture and walls. The scientific literature reports the effectiveness of some quaternary ammonium compounds in removing and / or inactivating S. aureus and P. aeruginosa from the computer keyboard. Moreover, a recent paper by Brown et al. [35] demonstrated that the microbial reduction activity following their application on glass, continues for a long time and in humid conditions. A number of advantages of quaternary ammonium compounds can be listed, such as: high stability, low color, no odor and relatively low toxicity, as opposed to phenols and chlorine-based bleaches.

6. Chlorhexidine

Chlorhexidine is a cationic biguanide and its quality as an antimicrobial agent was established in 1954 [8]. It exists as acetate (diacetate), gluconate and hydrochloride salts and is a biocide commonly used in antiseptic products, especially for hand washing and oral products, but also as a disinfectant and preservative. It has a wide spectrum of action and is well tolerated by the skin, rarely causing irritation. A large number of studies have been dedicated to elucidating the antimicrobial mechanism of action of this important substance [2]. Thus, it was noted that chlorhexidine gluconate is rapidly absorbed by bacteria such as E. coli and S. aureus and that this depended on its concentration and pH. The outer layer of the microbial cell deteriorates, though insufficiently to induce lysis or cell death, but then the agent crosses the cell wall - probably by passive diffusion - and subsequently attacks the cytoplasmic bacterial membrane, followed by leakage of intracellular constituents and microbial death. High concentrations of chlorhexidine cause coagulation of intracellular constituents. The antimicrobial activity of chlorhexidine depends on its concentration. Thus, at lower concentrations, chlorhexidine has a bacteriostatic effect against most gram-positive bacteria, on many gram-negative bacteria and bacterial spores. At very high concentrations, a bactericidal effect can be expected, as well as activity against yeasts [8]. In liquid soap, chlorhexidine usually has a concentration of 4% and has a bactericidal activity against Gram-negative and Gram-positive bacteria [36]. In a number of comparative studies, chlorhexidine suspension (4%) was less effective against MRSA than against methicillin-resistant S. aureus [8]. Chlorhexidine does not inactivate non-encapsulated viruses such as rotavirus, hepatitis A virus or poliovirus, this is explained by its activity limited to nucleic acid or the outer shell. It seems that the latter is a more important target [2]. And compared to dermatophytes, such as Trichophyton mentagrophytes, chlorhexidine (1.5%) has no activity. Chlorhexidine testing in clinical practice demonstrated in a study of 52 volunteers who washed their hands with a 4% chlorhexidine liquid soap 24 times a day for 5 days, a significant decrease in the number of resident bacteria of skin compared to a batch that was washed with classic soap [8]. Another study in which hands were artificially contaminated with MRSA liquid chlorhexidine soap proved to be as effective as plain soap. A similar result has been reported after contamination of the hands with S. aureus [37]. In conclusion, chlorhexidine (2-4%) has a good activity against most vegetative bacteria, yeasts and encapsulated viruses but limited activity against mycobacteria, dermatophytes and non-encapsulated viruses. Washing your hands with a chlorhexidine soap can reduce the number of bacteria.

7. Heavy metals and their compounds

Most heavy metals and heavy metal compounds or metal salts have some degree of toxicity to microorganisms. For many years, heavy metal ions have been used as germicides, but more recently, they have been replaced by other less toxic and more effective heavy metals and their compounds. The most toxic heavy metals are mercury, silver and copper, and the least toxic are sodium and potassium. Mode of action: heavy metals and metallic compounds combine with proteins, often with their sulfhydryl (SH) groups and inactivate them. The high concentration of metal salts, especially those of mercury, silver and copper, coagulates cellular proteins that lead to damage or death of the microbial cell. Metal salts can also precipitate and in high concentrations can cause the death of a microbial cell. Silver compounds have been used to prevent burn infections and some eye infections. It appears that silver salts and other heavy metals such as copper act by binding to functional groups of fungal enzymes. The mechanism is similar in the case of microbes, silver ions bind to enzymes important for microbial activity, causing their inhibition [2]. In addition to its effects on enzymes, silver ions produce other changes in microorganisms. It has been demonstrated that silver nitrate is able to cause a marked inhibition of Cryptococcus neoformans growth by depositing in the vacuoles of this fungus and in its cell wall in the form of granules [38]. Silver ions inhibit cell division and damage the cell lining and contents of P. aeruginosa. Bacterial cells increase in size and there are structural abnormalities of all cellular components. In addition, the interaction of silver ions with nucleic acids has been noted, preferably with DNA bases rather than phosphate groups, although the significance of this in terms of its lethal action is unclear [39]. Silver sulfadiazine is a combination of two antibacterial agents, silver and sulfadiazine. The question was asked which of the two compounds is due to the antibacterial effect or whether it occurs as a result of the interaction of the two. Silver sulfadiazine has a broad spectrum of action and unlike silver nitrate, it causes damage to the membrane of sensitive bacteria, it binds to cellular components, including DNA. Bacterial inhibition is likely to occur when silver binds to sufficient base pairs in the DNA helix, thereby managing to inhibit transcription. The complete mechanism of action of silver sulfadiazine has not yet been elucidated [40].

In conclusion, the perfect antimicrobial chemical probably does not yet exist, but we have the opportunity to make the right choice and proper use of current chemicals, so as to avoid both the increase in antimicrobial resistance and environmental problems. Thus, a deep knowledge of the antimicrobial agent together with the type of surface on which it is to be applied, would result in an adequate level of disinfection.

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AGENȚII CHIMICI CA FACTORI ANTIMICROBIENI

REZUMAT
O mare varietate de substante chimice pot fi folosite ca agenti antibacterieni in vederea prevenii contaminarii. Antisepticele și dezinfectanții sunt folosiți pe scară largă în spitale si reprezinta un element esențial de combatere si prevenire a infecțiilor nosocomiale. In aceste produse sunt prezenti o mare varietate de agenți chimici activi sau biocide. Dezinfectanții și antisepticele afectează bacteriile în multe feluri. Utilizarea pe scară largă a antisepticelor și a produselor dezinfectante a contribuit la dezvoltarea rezistenței microbiene, în special a rezistenței încrucișate la antibiotice. In practica medicala, agenții antimicrobieni trebuie selectați având în vedere microorganismele specifice, pH-ul, solubilitatea, toxicitatea, materialul organic prezent și nu in ultimul rand costul. Agentul chimic antimicrobian ideal probabil ca nu exista, dar alegerea corectă și utilizarea adecvată a substanțelor actuale, va avea drept rezultat un nivel adecvat de dezinfecție. Aceasta lucrare isi propune o trecere in revista a principalilor agentii chimici antimicrobieni, a mecanismelor prin care ei actioneaza si a importantei lor in practica clinica.

Cuvinte cheie: agenții chimici antimicrobieni, alcooli, halogeni, aldehide, compusi cuaternari de amoniu, argint.

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