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GENERAL

NON–ANTIBIOTICS – DRUGS WITH ADDITIONAL ANTIMICROBIAL ACTIVITY

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Abstract: Antimicrobial activity of antibiotics and chemotherapeutics has been investigated for several years. However, a great variety of pharmaceutical preparations, which are applied in the management of non–infectious diseases have shown also some *in vitro* antimicrobial activity. These drugs are called „non–antibiotics". Detected antimicrobial action of non–antibiotics (and non–chemotherapeutics), emphasises a necessity to neutralise this activity during microbial purity examination in the pharmaceutical industry. It is possible that some of these compounds can enhance the activity of certain antibiotics against bacteria or fungi.

Keywords: non–antibiotics, antimicrobial activity, pharmaceuticals

Antimicrobial treatment was developed a few centuries ago. At the beginning, some traditional preparations were used only for topical application as antiseptics in skin diseases. There were few examples of antibacterial agents of proven efficacy in systemic diseases which had been widely used by doctors during treatment since the sixteenth century: chaulmoogra oil was used with some success in leprosy and cinchona tree in malaria treatment. Ipecacuanha root was used for curing diarrhoeas and dysenteries while heavy metals e.g. mercury in the syphilis treatment (1).

Paul Ehrlich „father of chemotherapy" started in 1879 to use dyes (e.g. methylene blue – one of the phenothiazines compounds) as antiprotozoan and antimicrobial agents. He firstly observed selective toxicity of dyes (parasites and host tissues could be stained differentially; as he thought, due to different receptors for the dyes). Later, Ehrlich used arsenic compounds in limiting protozoan and bacterial diseases. These first chemotherapeutics were characterised by great toxicity, but finally arsphenamine (salvarsan) and neoarsphenamine showed a strong antibacterial activity with acceptable toxicity. The use of salvarsan and its derivatives not only reduced the danger of syphilis but also provided stimulation to the pharmaceutical industry.

At the end of nineteenth century, the first report of successful usage of Urotropin (hexamine; methenamine) in cystitis was published. In the next years, hexamine and mandelic acid proved to be therapeutically useful chemicals for urinary tract infections.

Early in the twentieth century a number of inhibitory agents produced by bacteria were shown to inhibit the growth of other bacteria *in vitro*, but attempts to obtain potent preparations of these bacteriocins, that could be safely administered to patients, failed.

The breakthrough in discovery of antimicrobial agents was done by Alexander Fleming in 1929, when he described the antibacterial activity of a substance produced by a *Penicillium* mold (named by him – penicillin), however its potential value was not explored because of penicillin liability.

In the thirties, dynamic investigations of sulphonamides have been developed. Started from Gerhardt Domagk's discovery in 1932, a dye made by diazotization of sulphanilamide – Prontozil, which acts effectively against streptococcal infections. When it was proved that sulphanilamide part of the dye is accounted for the antibacterial activity, in a relatively short time, due to chemical modification of sulphanilamide, several thousands of derivative compounds were synthesised, from which only few dozen possessed antimicrobial activity. Rapid and mass exploitation of sulphonamides (especially in military camps during World War II) was limited starting from 1942, when outbreaks of sulphonamide–resistant *Streptococcus sp.* infections were reported.

During the last seventy years, several hundreds of naturally produced compounds of antimicrobial activity and limited toxicity for host – antibiotics – were discovered. Progress in chemical and pharmaceutical sciences and modern technologies contributed to the invention of new antimicrobial preparations. The knowledge concerning the chemical structure and mechanisms of antimicrobial drugs action, made it possible altering the

structure of the parent compound or its active nucleus and making large numbers of derivatives, where some of which displayed greater activity, wider ranges of antimicrobial action, diminished toxicity. Nowadays, quinolones belong to the largest group of synthetic antibacterial agents.

However, the great progress in antibacterial, antifungal, and antiviral treatment efficacy was inhibited by the appearance and then rapid evolution and spreading of different mechanisms of microbial resistance. The ongoing struggle between the bacteria and drugs developed by the pharmaceutical industry to combat them, become more and more rapid and severe. Some people even predict the „end of antibiotic era" in the nearest future. However, several new preparations indicating a strong antimicrobial activity, resistant to existing microorganisms defence mechanisms, are under scientists' attention, passing the last clinical trials before registration and releasing for the market. Recently, preparations: Synercid (injectable streptogramins) and Zyvox (linezolid – first oxazolidinone) have been registered in Poland and introduced into treatment of severe infections caused by glikopeptide (vancomycin) resistant Gram–positive coccal strains (staphylococci, streptococci and enterococci). First, new, ketolide antibiotic – telithromycin (Ketek) for curing bacterial respiratory tract infections, was also registered by Aventis in Poland last year. Parallely, there are ongoing investigations of new preparations from known antibiotic groups; ß–lactams, macrolides and fluoroquinolones as well as preparations from new groups of chemical compounds, e.g. benzoxazines and oxazolidinones.

Diversity of microorganisms resistance mechanisms and their rapid adaptation to new antibiotics and chemotherapeutics, force scientists to seek different solutions allowing efficient microbial elimination and infectious disease treatment.

Scientific investigation and clinical practice showed that some compounds (mostly of heterocyclic structure), which are used in the management of pathological symptoms of a non–infectious aetiology possess a broad–spectrum antimicrobial activity. The knowledge of these synthetic chemical compounds is not popular world–wide. Scientists attended 1st International Conference on the Antimicrobial Action of Non–Antibiotics and Non–Chemotherapeutics, which was held in Statens Serum Institute, Copenhagen, Denmark in 1990, collectively but informally decided to use the name „non–antibiotic" for the mentioned above agents. Actually, three main groups of scientists working in India, Denmark, and Hungary and some other particularly outstanding investigators are performing research on this interesting subject. Some investigations of non–antibiotics antimicrobial activity have been also performed in Drug Institute, Warsaw, Poland (2,3). Over two hundred different pharmaceutical preparations were analysed and some interesting observations were achieved.

In 1990, International Society for Antimicrobial Action of Non–Antibiotics (ISAAN) was established and then the name changed into International Society of Non–Antibiotics (ISN). Recently, during 5th Congress of European Association for Clinical Pharmacology and Therapeutics, which was held in Odense, Denmark in September 2001, a satellite meeting concerning antimicrobial activity of non–antibiotics was organised. Also, during 4th European Congress of Chemotherapy and Infection (Paris, May 2002), a separate scientific session was dedicated to non–antibiotic effects on efflux pumps in bacterial and cancer cells.

Many actual information concerning non–antibiotics were combined in a book „Non Antibiotics a new class of unrecognised antimicrobics" (1), what should arise a broad interest and new non–standard, but effective infection treatment.

It was shown that several non–antibiotics, compounds possessing different chemical structure, belonging to groups: general and local anaesthetics, antihypertensive agents, diuretics, anti–inflammatory drugs, mucolytic agents, Na^+, K^+–ATPase modulators, proton pump inhibitors, calcium antagonists, antihistamines, and psychotherapeutic compounds, might be active against different pathogens (1). However, since the activity of majority non–antibiotics is probably manifested at the level of the bacterial plasma membrane, as is the case for the sensitive eukaryotic cells, it would be reasonable to expect that the action of the non–antibiotics would influence the permeability of the cell (1,4). Different mechanisms might be present, involving, among others: disturbing of effective efflux pumping mechanism, cross–membrane ions transport, cell energy transport, activity of membrane–bound enzymes (responsible, for instance, for cell wall biosynthesis) (1).

Numerous studies *in vitro* showed that several microorganisms: Gram–positive as well as Gram–negative, aerobic and anaerobic bacterial isolates, some fungal species and viruses were affected by non–antibiotics (5,6,7,8). Besides, activity of these compounds against protozoa and tumour cells (e.g. phenothiazines, nitrosoureas) has been described (9,10). There are only few reports showing *in vivo* activity, first of all phenothiazines (mostly investigated group of non–antibiotics) but also other agents (11,12). Activity of phenothiazine derivatives against various strains of *M. tuber-*

culosis, including isolates that are resistant to one or more conventional antimycobacterial agents, seems to be very interesting (1,13,14).

The curing effect of non–antibiotics, connected with ridding many of the plasmid–mediated resistant genes, restoring susceptibility of antibiotic resistant bacteria has also been reported (1).

Non–antibiotics might themselves be effective or enhance the activity of certain antibiotics, against bacteria or fungi. This positive interaction – synergism, consists of combined effect of the drugs being examined, is significantly greater than expected, if compared with independent effects when drugs are used separately.

Antimicrobial drug combinations are used most frequently to provide broad–spectrum empirical coverage in the treatment of patients with severe infections. Less frequently, combinations of antimicrobials are chosen because an identified pathogen is resistant to inhibition and/or killing by conventional doses of a single antimicrobial, but against it the combination may exert the desired antimicrobial activity. In both instances, the clinical outcome may depend on the effects of antimicrobials combinations against individual microorganisms. Clinically, this synergetic combinations of antimicrobial agents offer certain theoretical advantages whenever one of the elements of the combination has potential toxicity, since it may make possible the use of this drug at lower than usual concentrations. Another theoretical advantage is the use of drug that has no useful antimicrobial activity at the concentration used but where its presence increases the activity of the second antimicrobial agent to which the organism was previously resistant.

A number of investigations showed such synergy between conventional antibiotics (aminoglycosides, β–lactams, tetracyclines, quinolones) and non–antibiotics /neurotropic compounds, antihistamines, calcium antagonists, diuretics/ (1, 15, 16). A strong synergy was observed when, e.g., promazine and tetracycline, diclofenac and streptomycin, trimeprazine and sulfatiazole, chlorcyclizine and ciprofloxacin, chlorpromazine and erythromycin, propranolol and tobramycin were used simultaneously (1,17). Very interesting specific type of synergy – reversion of resistance, has been described (5,18). This mechanism might change antibiotic resistant bacteria into susceptible to previously ineffective drugs. It was observed on β–lactams–resistant microorganism models (e.g. MRSA) treated by a combination of phenothiazines and a β–lactam antibiotic, which changed isolates to β–lactam sensitive. Besides synergy, the antagonism between two or more non–antibiotics and antibiotics or chemotherapeutics might also sometime be present (1). So, deep *in vitro* and *in vivo* investigations should be undertaken before application of joint therapy.

Some of the antimicrobial and antitumour activities of non–antibiotics were discovered by chance, after monitoring side effects caused by these drugs. A similar situation is observed from the other side. Role of various anti–infectious agents in the treatment of non–infectious diseases (e.g. ketoconazol – dermal cancers, sulfasalazine, griseofulvin – rheumatology) has also been described (1,19). There are antibiotics which are used mostly not as antimicrobial agents, but as antitumour drugs (doxorubicin and it's derivatives) or prostatomegaly drug – mepartricin.

Actual emergency clinical problems – severe infections caused by multidrug resistant microorganisms: methicillin resistant staphylococci, vancomycin resistant staphylococci and enterococci, penicillin resistant pneumococci, Gram–negative rods producing extended spectrum β–lactamases, antibiotic resistant mycobacteria, and *B. cepacia* (in cystic fibrosis), may be resolved with the use of non–antibiotics. Also antiviral and antitumour activity of non–antibiotics (alone or in combinations) might help us to successfully treat severe and difficult to cure diseases.

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ERRATA

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„Feasibility of the Ph. Eur. flow–trough cell for dissolution testing of the compounded rectal suppositories containing indomethacin or sodium diclofenac."

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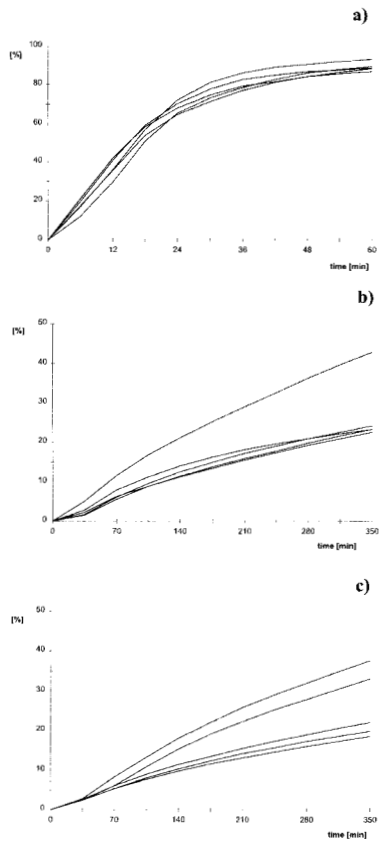

Figure 2. Dissolution profiles of indomethacin from macrogol (a), Witepsol (b) and Adeps solidus (c) suppositories.

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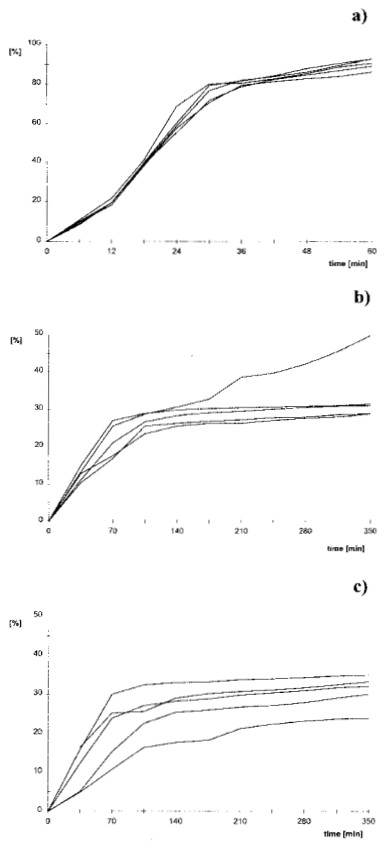

Figure 3. Dissolution profiles of sodium diclofenac from macrogol (a), Witepsol (b) and Adeps solidus (c) suppositories.

An antibiotic is a type of antimicrobial substance active against bacteria. It is the most important type of antibacterial agent for fighting bacterial infections, and antibiotic medications are widely used in the treatment and prevention of such infections. They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity. Antibiotics are not effective against viruses such as the common cold or influenza ; drugs which inhibit viruses are . 2003. Flurbiprofen, a unique non-steroidal anti-inflammatory drug with antimicrobial activity against Trichophyton, Microsporum and Epidermophyton species. Lett Appl Microbiol37:158â€“161. doi:10.1046/j.1472-765X.2003.01370.x. OpenUrl CrossRef PubMed.Â . 2002. Search of antimicrobial activity of selected non-antibiotic drugs. Acta Polon Pharm59:436â€“439. OpenUrl. Regards the synergistic activity between the antibiotics and non-antibiotic drugs, the best synergistic activity was recorded between Ampicillin and each of paracetamol and loperamide HCL against S. aureus, and among Nalidixic acid and each of paracetamol and loperamide Hcl. In addition synergistic activity was observed with Co-trimoxazole and each of paracetamol and loperamide Hcl against E. coli; Amikacin and paracetamol and loperamide Hcl against P. aeruginosa. REFERENCES. Abd Rabou.Â Anti- Mycobacterial Activity of Garlic (Allium sativum) Against Multi-Drug Resistant and Non-Multi-Drug Resistant Mycobacterium tuberculosis. Pakistan Journal of Pharmaceutical Sciences Vol.24, No.1, 81- 85. Hussain. M and Gorsi. M (2004).