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Review Article

Once again about Acute Erosive and Ulcerative Lesions (OEI) of The Mucous Membrane of The Gastrointestinal Tract - A Review Article

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Abstract

The article discusses the features of nucleotide preparations (oligonucleotides based on natural DNA): the effect on the exchange of nucleic acids, metabolism, the effectiveness of use in erosive and ulcerative lesions of the gastrointestinal tract. The features of interaction with the immune system are considered. New data on the interaction with the system of nucleotide regulation of functions and, in this regard, possible mechanisms of effectiveness in the GI mucosal OEI are discussed in particular detail.

Keywords: Ulcerative lesions; gastrointestinal tract; nucleotide

Introduction

Famotidine itself, like the entire H2-Ras group, is a very worthy drug that has played a role in the pharmacotherapy of acute ulcers and bleeding. It is no coincidence that J. Black was awarded the Nobel Prize in 1988 for the identification of H2 receptors and the development of drugs that block them. This group of drugs dominated in the 1990s and, partly, in the first half of the 2000s. Probably, even now, objectively, they can be used and are widely used in gastroenterology in general. But not in the practice of intensive therapy, for example, with stress ulcers, in the presence of a new generation of highly effective drugs of "high precision" action. Drugs with multiple mechanisms of therapeutic activity may also have the right to exist. At least as an alternative to means with a local mechanism of action. The older generation of doctors probably remembers the outstanding representative of the Soviet school of therapy, Academician E.M. Tareev, who, on a similar occasion, said: "therapy is not shooting at targets, it is shooting at squares. "Deoxyribonucleic acid (DNA) is a macromolecule that provides storage, transmission from generation to generation and implementation of a genetic program for the development and functioning of living organisms. From a chemical point of view, DNA is a long polymer molecule consisting of repeating blocks of nucleotides: "adenine, guanine, thymine and cytosine".

We are talking about a substance (and a preparation made from it) consisting of fragments (nucleotide sequences) obtained from a whole deoxyribonucleic acid. I.e., sodium deoxyribonucleate consists of a short chain of nucleotides (so-called oligonucleotides). Sodium deoxyribonucleate is a fairly well-known substance in pharmaceuticals (at least in Russia), which is widely used in medicine and has been produced under various brand names by several Russian pharmaceutical manufacturers over the past 10-15 years. I use Derinat in my work insofar as it is the most widespread and mass-produced drug in this group in accordance with modern GMP standards. This is a rather rigidly limited number of nucleotides, which is obtained as a result of pre-purification of native natural DNA with subsequent fragmentation of the macromolecule by ultrasound. As a result, the output is yes, a "spiralized chain" of so-

called exogenous oligonucleotides, but within 200-300 base pairs with a minimum weight of 270-500 kD (a molecule that is not at all identical to giant DNA in the polynucleotide chain of which can contain from many thousands to several million nucleotides). This DNA fragment does not carry any significant information for the body in the genetic sense and, being a biologically active substance and a natural metabolite, when introduced into the body, it is included in a wide range of metabolic reactions.

In general, today there are many drugs with the presence of nucleotides / nucleosides in the structure of the molecule, with a different mechanism of action, which with a sufficient degree of conditionality can be attributed to a large heterogeneous group of so-called "nucleotide drugs". Abroad, preference is given to the chemical synthesis of oligonucleotides with a given sequence of bases. For example, antisense oligonucleotides are used in oncology to suppress the synthesis of tumor proteins, or to treat myodystrophy. Antisense oligonucleotides are widely used in the treatment of viral infections, etc. Oligonucleotide conjugates with peptides and a number of other ligands are also becoming increasingly common, which are used in various fields of diagnostics and are considered as promising therapeutic drugs in oncology and other fields of medicine.

In Russia, another approach is quite widespread – the use of natural oligonucleotides from some biological material. This method allows you to obtain medicines with very wide therapeutic possibilities. It would be possible to continue the enumeration of drugs with the presence of some DNA fragments (or nucleotides / nucleosides) in the molecule, the above is enough to understand that this is by no means a whole DNA molecule.

It is advisable to focus only on aspects related to the various problems of pharmacotherapy of acute erosive and ulcerative lesions (OEI) of the gastrointestinal mucosa, including stress ulcers, discussed here.

a) Since sodium deoxyribonucleate (derinate) has properties to activate immunity and reparative processes (from the manufacturer's instructions), it must be assumed that these features of the drug's action are associated with the presence of DNA fragments in its molecular structure. When injected into the body, it accumulates mainly in actively proliferating tissues, which include not only the organs of immunogenesis, but also the epithelium of the gastrointestinal tract, where cells are updated very often (approximately every three days) and, accordingly, the need for nutrients such as nucleic acids and their precursors is very high. The features of deoxyribonucleate also include the ability to "penetrate into cells in a relatively polymeric form, to be incorporated into the cell nucleus and subcellular structures" (the average retention time in tissues is 72 hours according to radioisotope studies). These pharmacokinetic parameters were studied in preclinical animal studies using the radioisotope method [1].

In pathology, under conditions of a catabolic shift in metabolism, it is obvious that this tendency of "selective accumulation" of the substance will only increase. "The absorption of exogenous biopolymers occurs better in those cells of tissues and organs that fall into extreme stressful conditions that cause violations of tissue homeostasis" [2]. Regarding the gastrointestinal mucosa: there are studies on the effectiveness of deoxyribonucleate (derinate) in various ulcerative lesions of the mucosa. In an experimental study of the effect of derinate and solcoseryl on the healing of ulcers, it was proved that against the background of the use of derinate, the defects of the mucous membrane close twice as fast, and the residual scar after its use becomes less pronounced, without deformation of the surrounding tissues, and often completely invisible [3]. In another work, the content of nucleic acids in the gastric mucosa in patients with acute stage of pancreatic cancer was investigated, which established that in biopsies from the edges of the ulcer, compared with the normal mucosa, there is an almost 3-fold decrease in RNA and 2-fold – DNA [4].

Later, in clinical studies in patients with gastric ulcer and duodenal ulcer, it was shown that the drug is not only a universal metabolic protector, but also a powerful stimulator of cellular regeneration [5]. Thus, sodium deoxyribonucleate (derinate) has the property of correcting disorders of nucleic acid metabolism detected in various pathological conditions. In addition, the drug has a pronounced antioxidant activity, affects energy metabolism (the participation of exogenous nucleotides in the synthesis of ATP), protein and carbohydrate metabolism (moderately reduces blood sugar by improving the penetration of glucose into cells), etc. All the above effects of deoxyribonucleate have been well studied, which makes it possible to attribute it also to drugs of metabolic action and makes it possible to use it in a number of acute conditions occurring with a violation of homeostasis. These identified and well-studied mechanisms were actually the initial prerequisite for its use in acute conditions and, in particular, in the pathology discussed here.

b) However, in recent years, new approaches have been noted in the interpretation of the effects of the drug, associated with the establishment and beginning of the study of a number of receptors for sodium deoxyribonucleate as a kind of biologically active substance. This information seems to help to better understand the effects of deoxyribonucleate (derinat) in acute erosive and ulcerative lesions of the gastrointestinal mucosa.

Some "Mechanisms of its Action" and "at the Cellular and Molecular Level

To date, researchers largely associate the therapeutic activity of sodium deoxyribonucleate (derinate) with the presence of two groups of receptors for it in the body:

a) Innate immunity receptors are a superfamily of Toll– like receptors (so-called "image-recognizing receptors" located intracellularly and reacting to certain (conservative) molecular structures on the surface of a large group of microorganisms at once, but absent in the host body (PAMP fragments, or

pathogen-associated molecular images), and

b) Adenosine (P1) and purine (P2) receptors are located on the cell surface.

The pharmacokinetic profile of the drug is well studied

a) As established, after parenteral administration into the body, exogenous oligonucleotides are distributed throughout the body with a predominant accumulation in organs and tissues with increased metabolic (reparative) needs, after which the molecule internalizes into cells through receptor-mediated pinocytosis.

b) once in the intracellular compartments, deoxynucleotides activate a localized intracellularly Toll-like receptor of the 9th type, with which macrophage activation (MF) is associated. This receptor, TLR–9, specifically reacts to the RAMP (pathogen-associated molecular patterns) associated with the DNA of various pathogens, present, in particular, in both gr + and gr (-) microbes but absent in the host body. The specificity of attachment is believed to be determined by the structure of unmethylated DNA "enriched" with so-called CpG nucleotide motifs [6].

The key question in substantiating the presence of this mechanism in exogenous oligonucleotides is: to what extent does the nucleotide sequence of exogenous oligonucleotides injected with the drug correspond to that in PAMP pathogens? Or more precisely: is there enough CpG repeats in the injected exogenous oligonucleotides to which the macroorganism would react with an "alarm reaction"? Recently completed work [7] showed that there are obviously and to a sufficient extent. Since the blockade by a specific soluble inhibitor of the TLR-9 receptor, led to the cancellation of all effects from the oligonucleotides added to the system on the studied parameters of immunity. Oligonucleotides used for therapeutic purposes are able to directly activate macrophages according to the classical type, stimulate immunity, in particular, to H.Pilori, and this action is mediated by the macrophage receptor TLR-9, and the drug is a ligand to it. In addition, activated macrophages produce a number of factors, such as angioblastic factor, fibroblastic factor, epidermal factor, necessary to start the process of repair of mucosal damage.

However, there are also other mechanisms of pharmacological activity of the drug associated with the presence in the body of a large group of the above-mentioned adenosine (P1) and purine (P2) receptors located on the cell surface. After intracellular penetration, in addition to (or simultaneously with) TLR-9 activation, derinate, as a polynucleotide preparation, undergoes enzymatic cleavage by endonucleases to form a number of its metabolites. Including nucleotides/nucleosides, which are actually ligands for P1 receptors (adenosine) and P2 (purine nucleotides - ATP). In this situation, Derinat no longer acts as a drug directly acting on these receptors, but is a prodrug, since it carries out all the effects associated with the receptors through these metabolites. The situation is quite common in modern drug therapy. After hydrolysis of derinate, there is an increase in the intracellular concentration of these metabolites and their active release into the extracellular environment. Thus, unlike the innate immunity receptor located intracellularly (TLR-9), receptors for sodium deoxyribonucleate (derinate) metabolites are located on the surface of various cell types, including exocrine and endocrine, secretory, endothelial, epithelial, skeletal muscle cells, immunocytes, inflammatory cells and a number of others.

In total, at least 15 nucleotide-activated receptors (purinergic P2 receptors) have been identified on cell surfaces to date. According to their molecular structure, they are grouped into 2 subfamilies: P2X and P2U. Receptors for adenosine (P1R) bind adenosine and can either stimulate or inhibit the enzyme adenylate cyclase. Adenylate cyclase consists of two regulatory and two catalytic units, and produces a powerful secondary messenger from ATP, cyclic AMP (cAMP). In addition to binding to adenylate cyclase, adenosine receptors carry signals to many other effector systems in the cell. In conditions of chronic inflammation and tissue hypoxia, purine metabolism proceeds with the predominant production of adenosine, which has numerous cytoprotective properties. The immunotropic effects of adenosine include modulation of bactericidal function and tissue toxicity of neutrophils; switching of the type of cytokine production in macrophages, which leads to a decrease in the activity of the inflammatory reaction and increased angiogenesis and regeneration; inhibition of lymphocyte proliferation.

The nucleotides themselves (ATP) are ubiquitous extracellular regulatory molecules (extracellular messengers). Currently, various physiological and pathophysiological effects of nucleotides and nucleosides are known, both short-term (neurotransmission, mechanosensory, induction of secretion and vasodilation) and long-term (induction of proliferation, cell differentiation, activation-associated apoptosis, and regeneration). The object of nucleotide regulation, as it turned out, are also immune system cells that respond to nucleotide stimuli by proliferation, differentiation, chemotaxis, cytokine secretion, release of lysosomal components and generation of reactive oxygen radicals or nitric oxide. Nucleotides act as powerful early growth factors on hematopoietic progenitor cells, which makes their use in bone marrow transplants and as stimulators/regulators of hematopoiesis promising. Detailed reviews can be read here [8,9]. A schematic drawing clearly showing the chain of successive transformations of sodium deoxyribonucleotide (derinate) from an inactive prodrug into active metabolites (in modification) is taken from the first work.

Considerable attention to nucleotide regulation in recent years has been determined by the fact that the regulatory role of nucleotides in such processes as inflammation, ischemia, wound healing, response to stress, reduction of drug toxicity, modulation of pain sensitivity, tumor transformation and progression has been proven. Thus, derinat should also be attributed to drugs that affect the metabolism of nucleotides. And, consequently, its mechanism of action cannot be properly understood without taking into account the system of nucleotide regulation of functions

discussed above. We are talking about the work published on the website "Acute erosive and ulcerative lesions (OEI) of the mucous membrane of the gastrointestinal tract. A look at the problem from an anesthesiologist-resuscitator (some aspects of the treatment of acute stress ulcers) on August 31, 2012, in which the effects of the drug at the level of morpho-histological substrates of the target organ (stomach, duodenum 12) and correlates of some functional parameters were studied.

It was found:

a) Inhibitory effect on the activity of parietal cells producing HCL.

b) Protective, activating effect on the pool of mucus producing cells (goblet cells), which is a water-insoluble gel consisting of glyco-protein polymers closely adjacent to the surface of epithelial cells.

c) Very pronounced effect on microvessels in the gastrointestinal mucosa (increased microcirculation).

d) Effect on gastrointestinal peristalsis (strengthening).

According to such integral morphometric criteria as the severity of the lesion, the ulcer index and the average number of erosions, deoxyribonucleate (derinate) exceeds the effect of the recent "reference" drug in the prevention of stress ulcers. It is impossible to reduce all these effects to any one mechanism associated with the impact on the system of purinergic regulation of functions. As noted in a recent review: "exogenous DNA oligomers (Derinat) can be an alternative to the use of selective agonists and antagonists of purinergic receptors," the search for which is actively underway all over the world. One of the probable biochemical mechanisms of regulation of cellular functions by sodium deoxyribonucleate (derinate) may be the effect on protein kinases, in particular on protein kinase, tyrosine kinase and a number of others. As is known, kinases carry out phosphorylation of proteins, after which the function of the substrate is changed or modified, including the enzymatic activity, the position of the protein in the cell, or interaction with other proteins may change. It is believed that 30% of all proteins in the cell can be modified by protein kinases. In particular, they regulate metabolic pathways, as well as signal transduction and signal transmission pathways within the cell.

Another intracellular mechanism that can respond to changes in the concentration of nucleotides associated with the introduction of derinate is the functioning of cyclases: cAMP, c-GMF. The pronounced effect of derinate on the microcirculatory bed of ischemic tissues is obviously also due to multiple pharmacological effects. Both ATP and adenosine are primarily involved in the functioning of mechanisms that exercise local control of vascular tone [10,11]. And first of all, this concerns the nucleotide control of vascular tone precisely in acute situations, which also occurs with stress ulcers. The key element of such control is the activation of P1(A2) receptors in the smooth muscles of the vessels of the stomach wall, leading to vasodilation. The signaling messenger of this process is ATP released from endothelial cells during stress and hypoxia. Another important effector link of vasodilation may be the effect of ATP on P2U1, P2Y2 and partly on P2Y4 purinoreceptors, leading to the production of NO and subsequent vasodilation.

Pathophysiology and Therapeutic Potential of Purinergic Signaling. Such modulation of the NO-synthase system may be one of the pathogenetically significant targets for sodium deoxyribonucleate. The mechanisms of regulation of microvascular tone of the mucosa and other layers of the stomach wall discussed here suggest their relationship with the introduction of sodium deoxyribonucleate, by changing extracellular concentrations of ATP and adenosine. It is obvious that such regulation is carried out through the influence of deoxynucleotide metabolites on various subtypes of purine receptors, exerting a bimodal effect on them, depending on the situation. As an example, we will analyze possible ways to reduce the functional activity of parietal cells producing HCL, which was noted in the study (a significant decrease in the volume of the nucleus and cytoplasm of these cells under the influence of derinate). As one of the probable mechanisms mediating the effect of derinate on the parietal cell, there may be an effect on protein kinase through the regulation of Ca++ influx into the cell by nucleotides (pathway 1).

A decrease in the intake of Ca++ through the regulation of ion channels by ionotropic P2X receptors may reduce the activity of the gastrin receptor and, accordingly, the activity of protein kinase, as a consequence of which there may be a decrease in HCL production. Another mechanism for reducing the metabolism of parietal cells is the possible effect on P2Y – purinergic receptors (pathway 2). They belong to the metabotropic family, which includes a subfamily of transmembrane receptors associated with the Gi protein. They also regulate ion channels, but also inhibit adenylate cyclase. It is adenylate cyclase that synthesizes cAMP from ATP, which, in turn, activates protein kinase again, as a universal mechanism of the proton pump. A similar mechanism is characteristic of adenosine P1-receptors, which, like P2Y-receptors, are associated with G-proteins. Extracellular adenosine receptors bind adenosine with both high (P1A - P1A2a) and low affinity (P1A2b and P1A3) and can either stimulate or inhibit the enzyme adenylate cyclase. Signals from P1 receptors change the concentrations of intracellular cAMP (pathway 3a), as well as Ca2+ ions (pathway 3b). Thus, even a preliminary analysis of the mechanisms of action of sodium deoxyribonucleate (derinate) "at the molecular level" shows their complexity and fundamental irreducibility to anyone (Figure 1).

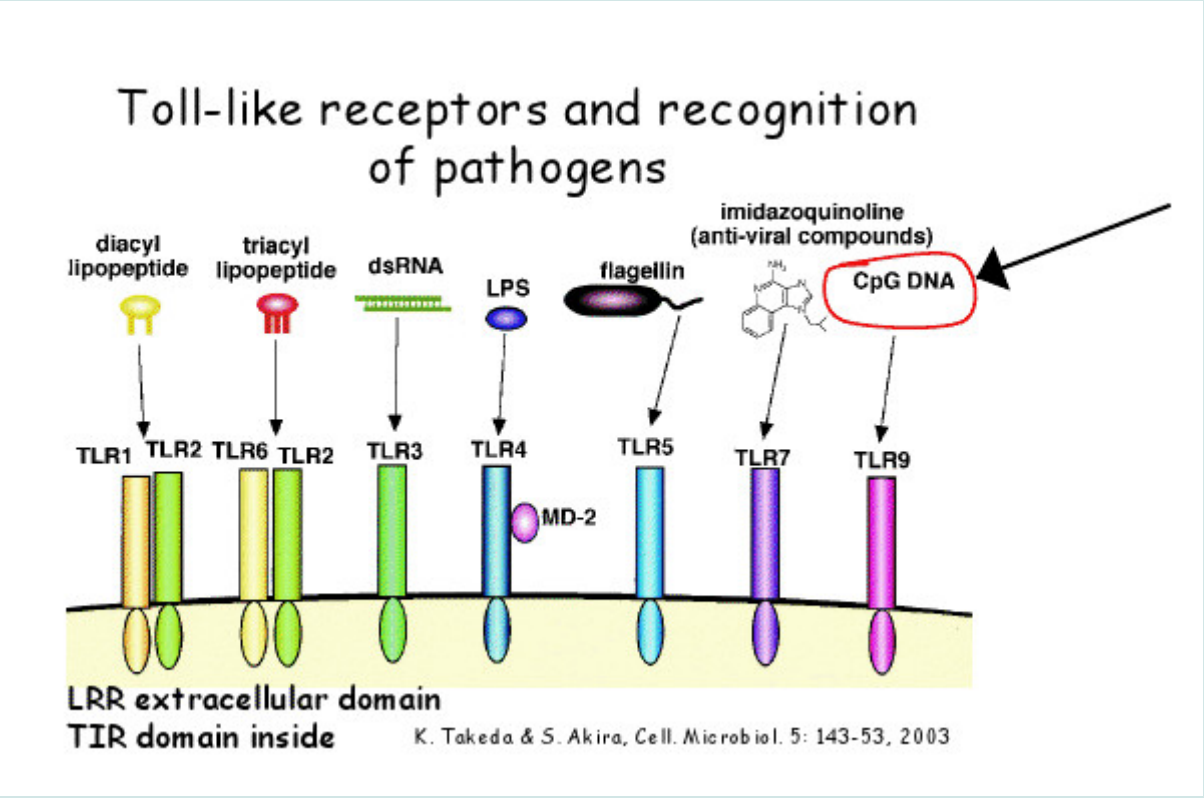

Figure 1: Shows the Toll – like receiver's superfamily. TLR-9 here is a key element in the recognition of "alien" DNA and its activation by a fragment of exogenous DNA (derinate) can obviously be the initial link of the chain at the end of which there is an increase in resistance to helicobacter infection. Plays a very definite role in the frequency and severity of manifestations of AGIB (irregular gastrointestinal bleeding) in OEI of the gastrointestinal mucosa in patients with OAR.

The introduction of derinate, rapidly increasing the endogenous nucleotide pool, modifies a complex system of nucleotide regulation, which, along with nucleotides and their receptors, is also represented by ectonucleotidase enzymes, providing not only the catabolism of nucleotides to nucleosides, but also participating in the processes of intercellular interaction as specific receptors (CD39, CD73), and their expression is inducible and, again also, it depends on the concentration of extracellular nucleotides. Thus, "the cellular response to nucleotides and their metabolites depends on the context (the concentration of nucleotides, the expression of enzymes that determine their metabolism, the presence of various cytokines) and is largely regulated by microenvironment factors". This fundamental concept of the pharmacological activity of sodium deoxyribonucleate (derinate) in GI mucosal OEI is, of course, significantly different from the mechanism of action of, for example, locally acting drugs such as proton pump inhibitors, which irreversibly inhibit H+/K+ - ATRase in parietal cells, H2 receptor blockers or cytoprotectors. It seems that the identified mechanisms of the effectiveness of derinate in stress ulcers, gastrointestinal mucosal OEI with the threat of bleeding can significantly expand the arsenal of the doctor and improve the prognosis in severe cases of diseases.

With regard to the dose, the frequency of administration of the drug per day and the course dose:

a) 75 mg of sodium deoxyribonucleate is the dose of derinate that the manufacturer produces in vials for intravenous administration with a concentration of 15 mg / ml (i.e., 75 mg / 5 ml).

b) The recommended frequency of administration is according to the manufacturer's instructions from 24 to 72 hours (i.e., every day, every other day, two days later), but no later than 72 hours from the previous administration, which is due to the peculiarities of the pharmacokinetics of the drug. According to experience, it can be recommended, in acute severe cases, to administer the drug 1 time a day (this is on average), from 5 to 10 days (but not less than five). However, in particularly severe cases (and the threat of massive bleeding, especially the first 72 hours after the event, certainly refers to those), a regime of double administration per day is allowed, i.e., after 12 hours. In my opinion, such a regime, in addition to the severity of the condition, can be justified by the need for a rapid increase in the endogenous pool of nucleotides (as discussed in detail above), rapid binding of P2 receptors, with subsequent regulation of critically impaired homeostatic parameters. Since the peculiarities of the pharmacodynamics of derinate also

include the dose dependence of effects, which can be justified by the above-mentioned features of the pharmacokinetics (metabolism) of nucleotides.

Conclusion

It should be emphasized that an essential feature of derinate and similar drugs is obviously the substrate-receptor type of regulation of impaired functions, which can give them an important advantage over the use of drugs with a predominance of local effects.

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