The Relationship between Antibiotics and Disulfiram-like Reaction

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Abstract

Drinking without antibiotics has become the consensus of more and more people. On this phenomenon this paper will introduce the principle of this. The article will briefly introduce the structure of the medication principle and partial historical development. Partial historical development of two different kinds of mainstream antibiotics, cephalosporin and metronidazole. Understand these two mainstream antibiotics from scratch, and understand the principle of the reason why we cannot have them with alcohol fundamentally. Furthermore, the article will briefly analyze the principle and phenomenon of the same side reaction produced by two antibiotics with different structures, namely, a disulfiram-like reaction, to explain and show what will happen if people have these two kinds of antibiotics after drinking the alcohol. In this way, this work will popularize the hazards and precautions of drug use after drinking to more nonprofessionals.

Keywords: Antibiotics; Disulfiram-like Reaction; cephalosporin; metronidazole

1. Introduction

There are many television plays that show suicide by drinking alcohol with anti-cold drug. What will it be like to operate like this in reality? If you want to know this, then it is necessary to introduce this kind of reaction that is very likely to kill people-which called disulfiram-like reaction [1]. After using cephalosporins and metronidazole drugs to drink alcohol, there will be weakness, dizziness, lethargy, hallucination, body flushing, headache, nausea, vomiting, blood pressure drop, even shock and other reactions. And why do we have this kind of reaction?

For cephalosporins and metronidazole drugs, the main reason for disulfiram-like reactions is the existence of the methotriazole side chain and Methylthiotriazine side chain, which inhibits the activity of aldehyde dehydrogenase (ALDH)2 enzyme. This leads to inhibition of ethanol metabolism in the body, which prevents further oxidative metabolism after acetaldehyde production, leading to the accumulation of acetaldehyde in the body, increasing the concentration of acetaldehyde in the body, so that drinking a small amount of ethanol can also cause acetaldehyde poisoning reaction called disulfiram-like reaction. Herein, this review first introduces the two mainstream antibiotics cephalosporin and metronidazole in their chemical structure, therapeutic effects, and side effects. Then we mainly review the potential mechanism of two mainstream antibiotics on the disulfiram reaction.

2. Brief introduction of cephalosporin and metronidazole

Antibiotics refer to a class of secondary metabolites produced by microorganisms (including bacteria, fungi, actinomycetes) or higher animals and plants in the course of life, which have anti pathogen or other activities and can interfere with the development of other living cells. Antibiotics commonly used in clinic include extracts from microbial cultures and chemical or semi synthetic compounds [2].

Nowadays, due to the abuse of antibiotics, the percentage of common community acquired pathogens resistant to antibiotics and the number of drug resistant drugs have been increasing. Data from several studies strongly support the relationship between antibiotic use and drug resistance [1]. The countries with the highest per capita consumption of antibiotics had the highest drug resistance. This shows that antibiotics are double-sided. Although they have strong antibacterial and bactericidal effects, incorrect use and abuse will lead to more serious results. The following part of the article will describe two different kinds of antibiotics, cephalosporin and metronidazole.

1.1. *Cephalosporin*

When it comes to antibiotics, we have to talk about the most mainstream antibiotic, cephalosporin, any of a group of β-lactam antibiotics that inhibit the synthesis of a structural component of the bacterial cell wall. Cephalosporins are divided into five generations of antibiotics according to their coverage spectrum of gram-positive and gram-negative bacteria and their time discovery [3]. As shown in Figure 1, the core of cephalosporin is 7-aminocephalosporin acid (7-ACA), which is derived from cephalosporin C. At the same time, the side chain of 7-ACA is modified to obtain some other very useful cephalosporin antibiotics. And nowadays large number of derivatives have been synthesized by modifying the 7-amino-cephalosporinic-acid (7 ACA) [3].

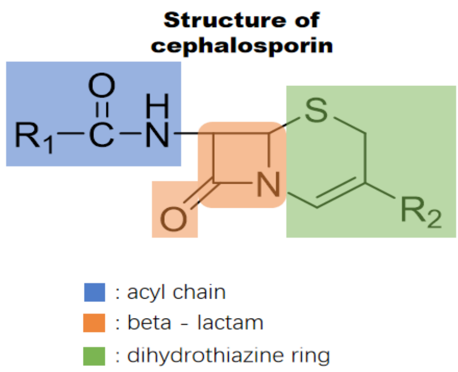

Figure 1. The chemical structure of cephalosporin. R1 and R2 groups can be changed according to the functionality.

Most of the first generation cephalosporins begin with "ceph -" in English, especially in North America, Australia and other countries. Europe began with "cef -", which is the beginning of the new first generation cephalosporins and their successors. Cephalosporins are classified according to their antibacterial properties. The initial cephalosporins were named as the first generation (cefadroxil, cefalexin, cefazolin, cefazedone), and the subsequent cephalosporins were divided into the second generation. Take an example of the second generation cephalosporins. Cefonidici is [7-D-mandelidine-3 -(1-sulfomethyltetrazolium thiomethyl) - 3-cephem-4-carboxylic acid disodium salt] [4]. Cefuroxime is structurally related to cefmandorl, but the difference is that there is an acidic substitute at position 1 of the dihydrothiazide ring. The chemical substitution of the third position of the dihydrothiazide ring is the main reason for the improvement of the drug properties of cefonix and its aftermath. Compared with the previous generation, each new series has significant antibacterial activity against gram-negative bacteria which are escherichia coli, klebsiella, salmonella, etc. [4]. However, in some varieties, like the generation fourth, its antibacterial activity against gram-positive bacteria, such as streptococcus pneumonia and haemophilus influenza, etc., is reduced [4]. The fourth generation cephalosporins have extensive appliance, such as cefepime and cefquinome. These two fourth generation cephalosporins are more effective in enhancing the antibacterial activity. extended spectrum beta-lactamases (ESBLs) are more stable than those of the previous generation. At the same time, they are more active against gram-positive cocci [5].

According to the chemical structure in Figure 1, the β-Lactam is the principle functional group related to the drug effectiveness. Although the side chains, especially the R_1 and R_2 groups can be changed according to the demands, such as increased permeability, and stability, it would not significantly influence the role of β-Lactam in potential side effects and therapeutic effectiveness.

The presence of β-Lactam functional group contributes to the antibacterials properties of cephalosporins. β-Lactam antibiotics can destroy the synthesis of peptidoglycan layer that forms bacterial cell wall. The peptidoglycan layer is important for the structural integrity of the cell wall. Penicillin binding protein (PBP) promotes the final peptide transfer step in peptidoglycan synthesis. PBPs bind D-Ala-D-Ala at the end of the cell peptide (precursor of peptidoglycan) to cross link peptidoglycan. β-Lactam antibiotics mimic D-Ala-D-Ala sites, thereby irreversibly inhibiting PBP crosslinking of peptidoglycans, achieving the effect of sterilization [5].

According to abovementioned principle, this antibiotic is supposed to be used to treat bacterial infections, such as skin or soft tissue infections, urinary tract infections (UTIs), streptococcal laryngitis, meningitis, gonorrhea, etc. At the same time, cephalosporins in the later stage are also used in the later stage of animal husbandry to gain weight for the animals [5].

Even such commonly used antibiotics have many side effects, they have low toxicity and are generally safe. The most common adverse reactions of cephalosporins are nausea, vomiting, anorexia and abdominal pain, even this it will still have some serious side effect, such as hypersensitivity reaction, drug-induce immune haemolyticanemia (DIIHA), disulfiram-like reaction, vitamin K deficiency, pseudomembranous colitis, increased nephrotoxicity of aminoglycosides, etc.

1.2. *Metronidazole*

Also, the disulfiram-like reaction will affect while you use metronidazole. Metronidazole belongs to nitroimidazole group. It inhibits nucleic acid synthesis by forming nitroso free radicals, which can damage deoxyribonucleic acid (DNA) of microbial cells. The chemical structure of metronidazole is 1 - (2-hydroxyethyl) - 2-methyl-5-nitroimidazole, as shown in the Figure 2. This effect only occurs when metronidazole is partially reduced, and because this reduction usually occurs only in anaerobic bacteria and protozoa, it has relatively little impact on human cells or aerobic bacteria. Its use has been associated with toxicity; However, the potential mechanism is still unclear [6].

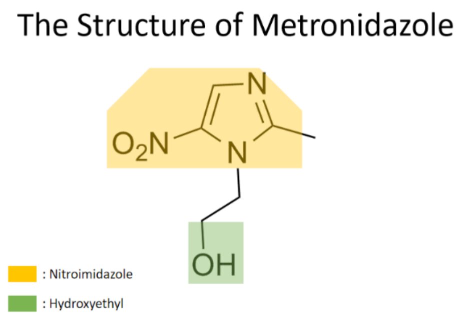

Figure 2. The chemical structure of metronidazole.

In the 1950s, scientists found metronidazole from Streptomyces. It is a synthetic derivative of azopenicillin and a class of drugs with nitroimidazole ring structure. Unlike cephalosporin, this antibiotic is mainly used to kill protozoa and parasites rather than bacteria, and it does not have other effects like livestock fattening. On the contrary, it has certain cancer risk.

In 1959, this special compound was used to treat trichomoniasis, an infection caused by Trichomonas vaginalis, a protozoa. In addition, metronidazole also has a great therapeutic effect on dysentery and liver abscess caused by intestinal protozoan parasites, histolytic entamoeba, and Giardia lamblia. Generally speaking, there are several indications, such as amoebiasis, giardiasis, trichomoniasis, bacterial vaginosis, helicobacter pylori, clostridium difficile, anaerobic infections, Crohn's disease, surgical prophylaxis, and rosacea.

All drugs have side effects, including metronidazole. Its side effects include such as nausea, abdominal pain, and diarrhea. Serious neurotoxicity, optic neuropathy, peripheral neuropathy, and encephalopathy have been also reported in rare cases. The neurotoxicity of metronidazole is not clear. However, when the dose is higher than 42g, the risk of peripheral neuropathy increases. When drug treatment is stopped, the effect can be reversed [6].

Although metronidazole and cephalosporin have different chemical structure as shown in Figure 1 and 2, these two antibodies can induce the same side effects called disulfiram-like reaction. Then we will explore the potential mechanisms behind the disulfiram-like reaction caused by these two antibodies.

3. Principle of disulfiram-like reaction

In clinical, the disulfiram-like reaction seems as being drunk. Therefore, this reaction will be very similar to excessive drinking and alcoholism. The mechanism of this reaction involves disulfiram or drugs that inhibit aldehyde dehydrogenase (ALDH), an enzyme responsible for converting ethanol metabolite acetaldehyde into acetate. As a result, the acetaldehyde intake by drinking in the body is increased and cannot be metabolized. The severity of the simultaneous effect is different, which is proportional to the exposure to alcohol and drugs [7].

Therefore, about cephalosporin, especially cephalosporin antibiotics with methylthiotetrazole substituents are widely known to cause this reaction. The reason is that the substituent of methylthiotetrazole (thiomethyltetrazole), which is similar to the disulfiram molecule, on position 3 of the parent nucleus 7-aminocephalosporanic acid (7-ACA) ring in the drug, prevents acetaldehyde from continuing to oxidize, resulting in the accumulation of acetaldehyde. According to the reaction mechanism, we can easily conclude that the disguised form of these drugs leads to the reduction of the human body's ability to decompose acetaldehyde, which leads to excessive accumulation of acetaldehyde in the body and poisoning.

Although metronidazole has the different chemical structure with the cephalosporin, some researcher also reported that metronidazole can induce the disulfiram-like reaction. However, the potential mechanism is still unclear. There are articles that report cases of death caused by drinking after taking medicine [8].

With the development of medical technology, people began to question whether metronidazole would really cause such a reaction. Some people believe that early medical conditions are prone to misdiagnosis, and there is no conclusive evidence to prove the existence of this reaction [9]. Even if some people raised doubts, all the drug instructions of metronidazole indicated that alcohol should not be drunk during drug use.

4. Conclusion

Cephalosporins and metronidazole are first-line antibacterial drugs, which have been used clinically since they were discovered. Because of its maturity, so far, there is conclusive evidence that most cephalosporins contain structures that can lead to disulfiram-like reaction to inhibit the production of alcohol lyase. Most of these special structures exist in their functional groups, which also leads to a small part of cephalosporin antibiotics will not produce such side affection. However, metronidazole is also a mainstream antibiotic that has been put into use for a long time, and it was also recognized as having such side effects in the early stage. However, recent studies have rejected some of the causes, even though the disulfiram-like reaction occurred at the same time when taking metronidazole, which led to the uncertainty of the performance and principle of metronidazole for these side effects. At the same time, recent studies have denied that metronidazole has disulfiram-like reaction, which also confirms that the formation reason of this reaction will be known more accurately in the near future.

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