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A Novel Antibiotic Adjuvant Entity Against Multi-Drug Resistance

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Abstract

In critical care units, multidrug-resistant gram-positive bacteria are the cause of a number of diseases that range in severity from serious to deadly (ICUs). It has been reported that Staphylococcus aureus and its numerous multidrug-resistant forms, such as heterogeneous glycopeptide-intermediate S. aureus (hGISA) and Methicillin-resistant S. aureus (MRSA), are the most virulent pathogens in humans, and there are few or no treatment options available for them. We evaluated the in vitro interaction of ceftriaxone plus sulbactam with disodium edetate, a Non Antibiotic Adjuvant (NAA), against a selection of clinical isolates, and we also did in vitro susceptibility investigations. Our findings may be found in this work.

Keywords: Multidrug resistant, Non Antibiotic Adjuvant**,** treatment.

Introduction

Antibiotic resistance is difficult to overcome, and it may even be impossible, due to the fact that it is rooted in the mechanism of action of antibiotics and is subject to the development of bacteria. Despite this, there are methods that may be used to reduce the occurrence of resistant strains and their effects. Antibiotic adjuvants are one example of this kind of strategy. These are substances that have very little or no antimicrobial activity on their own, but which have the ability to inhibit resistance or otherwise improve the efficacy of antibiotics. Antibiotic adjuvants are therefore administered together with antibiotics and may be separated into two categories: Class I agents, which target the pathogen, and Class II agents, which target the host. Adjuvants provide a way to simultaneously reduce the establishment of resistance and restore the action of current medications, providing an orthogonal method that is complementary to the discovery of novel antibiotics[1].

Antibiotic Adjuvants

Compounds that boost the effectiveness of existing medications and can lessen or even directly block resistance are known as antibiotic adjuvants (see Glossary).

Utilizing antibiotic adjuvants is one of the complementary strategies that can be utilized to safeguard our existing drug supply. Because they are administered concurrently with antibiotics, adjuvants are considered to be combination drugs. There is now resistance to every antibiotic that is used in clinical practice. One of the most significant difficulties confronting the medical industry in the 21st century is a crisis that has spread across the entire world[2].

There is a widening gap between the clinical demand for new antibiotics and the research and development of new drugs. Finding new antibiotics and getting them approved for use in humans is becoming an increasingly difficult task.

There is a way to bridge the gap between the demand for new drugs and the shrinking supply pipeline, and that way is to make sure that our existing antibiotics are protected. There are a number of approaches that may be taken to achieve this goal, one of which is the creation of antibiotic adjuvants[1].

Antibiotic adjuvants are no antibiotic substances that augment antibiotic action in one of two ways: either by inhibiting the development of antibiotic resistance or by increasing the host's natural defences against infection. Several of these are currently in use in clinical settings, particularly the drugs that block beta-lactamases, which are the enzymes that give resistance to beta-lactam antibiotics[3].

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Mechanisms of Antibiotic Resistance

There are many different molecular mechanisms that can lead to resistance to antibiotics. These mechanisms include decreased drug permeability, active efflux, alteration or bypass of the drug target, production of antibiotic-modifying enzymes, and physiological states like biofilms that are less susceptible to the effects of antibiotics. All of these pathways are able to be inhibited by small compounds, and as a result, they are candidates for being targeted by antibiotic adjuvants.

Literature review

There is a growing global worry over the increased antibiotic resistance of Gram-negative bacteria (GNB), which can be acquired in either a hospital or in the community.

The irrational and increased use of antibiotics, especially cephalosporins, in India has resulted in the emergence of multi-drug resistant (MDR) bacteria, which were previously known to be susceptible. This is according to the report of the Global Antibiotic Resistance Partnership – India Working Group. The Indian government has recognised the gravity of the developing threat, and as a result, it has issued a call for decisive action to combat the growing antimicrobial resistance. National Health Policy 2017 was formulated by the Indian Ministry of Health and Family Welfare in collaboration with the World Health Organization. Within this document is a call for an urgent need for standardisation of antibiotic usage guidelines to minimise the development of antimicrobial resistance. As a result, the two organisations came to the conclusion that addressing the problem should be a top priority for their joint effort in 2018–2019. Carbapenems, third- and fourth-generation cephalosporins, and beta-lactams with beta-lactamase inhibitors are the most prevalent types of antibiotics used in the treatment of GNB infections. This is in spite of the fact that antibiotic resistance is on the rise[4].

The most common and ubiquitous method of resistance chosen by GNB to counteract the action of -lactam antibiotics is the production of -lactamase enzymes[5,6]. Extended-spectrum beta-lactamases, often known as ESBLs, hydrolyze oxyimino group-containing beta-lactam antibiotics. These enzymes are typically plasmid-mediated beta-lactamases. Metallo -lactamases, commonly known as MBLs, are a family of enzymes that have a broad substrate spectrum and can hydrolyze the majority of -lactam antibiotics (with the exception of monobactams)[7]. Drug efflux systems, changes in outer membrane proteins, antibiotic-modifying enzymes, and antibiotic-target modification are some of the additional mechanisms that contribute to antibiotic resistance[8]. Because of their resistance to hydrolysis by ESBLs and their broad-spectrum action, carbapenems are utilised in the treatment of infections caused by organisms that produce ESBLs[9]. Increases in carbapenem resistance have been reported among the members of enterobacteriaceae and non-fermenter GNB, such as the Acinetobacter and Pseudomonas group of pathogens[10]. This is due to the appearance of carbapenem-hydrolyzing enzymes, the overexpression of efflux pumps, and changes in outer membrane proteins[11,12].

There is a wide range of variation in the prevalence of ESBL and MBL producers among Gram-negative organisms in India, with each ranging from 7.5% to 71% to 28.0% to 84.0%, respectively[13,14]. There is a growing resistance to the antibiotics that are currently available, and there is also a lack of development of new antibiotics against GNB. This could soon lead to the world experiencing the difficult conditions that prevailed in the era before antibiotics, with an increase in the number of cases of infections that cannot be treated. The utilisation of antibiotic adjuvants is a method that is

more recent and is used to improve the effectiveness of already available antimicrobials. Ceftriaxone, sulbactam, and adjuvant disodium edetate (also known as CSE) are the components of a new antibiotic adjuvant entity that is being utilised in Indian hospitals to treat MDR infections[15,16]. The antibiotic adjuvant entity is a combination of ceftriaxone + sulbactam with disodium edetate, and it has been put through Phase III clinical trials in India under the auspices of the Central Drugs Standard Control Organization[17].

An Adjuvant Strategy for Combating Antibiotic Resistance

Antibiotic resistance in pathogenic bacteria, in particular the six bacterial species called the ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa and Enterobacter species), is one of the greatest threats to human health that the world is facing in the present day. The World Health Organization (WHO) claims that the issue at hand is "so serious that it undermines the achievements of modern medicine" in its study titled "Antimicrobial Resistance: Global Report on Surveillance," which was published in 2014. A post-antibiotic future, which is a very possible prospect for the 21st century, is one in which ordinary diseases and mild injuries have the potential to be fatal. In point of fact, the first example in the United States of a patient with an illness that was resistant to every antimicrobial medicine that was available was reported in August of 2016.

In addition to harbouring the New Delhi metallo—lactamase (NDM-1) gene, the K. pneumoniae isolate that caused the infection and ultimately led to the patient's death was resistant to all aminoglycosides and polymyxins that were put to the test. The infection was ultimately the cause of the patient's passing. It is only because of the availability of efficient antibiotic treatment that many of the life-saving medical procedures that we take for granted in today's society, such as surgery, the treatment of premature infants, chemotherapy for cancer, and transplantation medicine, are even possible. According to projections, if antibiotic resistance continues to rise at the same rate as it is currently rising, drug-resistant infections will be responsible for more than 10 million deaths annually by the year 2050, and the estimated global economic cost will reach $100 trillion United States dollars.

Without a shadow of a doubt, action needs to be taken. The maintenance of effective antibiotic therapy in the face of the declining efficacy of the antibacterial drugs currently in our arsenal will require, in addition to significant improvements in antibiotic stewardship, either the discovery of new antibiotics or the development of antibiotic-resistant bacteria.

(1) A continuous supply of new medications to replace ones that are losing their relevance or
(2) A strategy for extending the effectiveness of already available antibiotics
The former is not likely to occur without major government investment and subsidies as a result of pharmaceutical

corporations withdrawing from the research and development of new antibiotic drugs. The economic and scientific challenges that have been encountered are the root causes of this disengagement. Primarily due to the fact that antibiotic treatment plans are typically much shorter in duration and are frequently curative, new antibiotics have a poor projected return on investment when compared to drugs targeted at chronic diseases such as heart disease and high blood pressure. This is the primary reason why new antibiotics have a poor projected return on investment. In addition, in an effort to minimize the development of antibiotic resistance, new antibiotics are increasingly being held in reserve for situations in which none of the more traditional antibiotics are effective, which further decreases profitability. Since the so-called "golden age" of antibiotic discovery came to an end in the 1970s, only two new antibiotic classes have been brought into clinical practice. This is just one of the many scientific obstacles that must be overcome in order to find new antibiotics. The great majority of antibiotics that have been given the go-ahead since then, as well as those that are in the process of being developed, are derivatives of antibiotics that have already been given the go-ahead and are resistant mechanisms that many bacteria already possess. Additionally, the creation of such derivatives is slowing down as a consequence of the low-hanging fruit being picked and the discouragement of their development by regulators. This is because of the combination of the two factors[11,13].

The in vitro high-throughput screening of synthetic chemical libraries for the identification of new antibiotics has been a catastrophic failure. This is especially true for the development of antibacterial drugs that are effective against Gram-negative bacteria. The failure to achieve success can be attributed to a number of different factors. The metrics that pharmaceutical companies use to define a hit or lead compound are one factor that contributes; for instance, until relatively recently, many campaigns sought only to identify broad-spectrum agents that exhibit in vitro activity against several isozymes of the target enzyme or protein from both Gram-positive and Gram-negative bacteria. A lack of association between activity in a biochemical test and whole-cell activity is another reason. The nature of the chemicals that make up the majority of small-molecule synthesized libraries is arguably the most important factor, particularly in the case of Gram-negative active drugs. In most cases, the vast majority of the compounds in these libraries were conceived of and created during the age of combinatorial chemistry specifically for the purpose of being screened against mammalian targets. The majority of known antibacterial drugs lie outside of this chemical space, which is occupied by these libraries, which often occupy a constrained space[2,5,13].

Several of these problems have been identified, and solutions are now being developed for them. Since more rapid and sensitive diagnostic tests have been developed, the use of narrow-spectrum antibiotics has become more practical. As a result, the European Medicines Agency (EMA) and the Food and Drug

Administration (FDA) have recently added narrow-spectrum antibacterial compounds to a list of treatments that are eligible for a shorter route to registration. The issue of a lack of translation of activity from biochemical tests can be solved by using whole cell phenotypic screening; however, this sort of screening does need subsequent research on the mechanism of action. In conclusion, screening natural products provides access to an expanded chemical diversity, which is desperately required, but sadly it also frequently results in the discovery of recognized scaffolds. In the fight against drug-resistant bacterial infections, one of the most significant ongoing priorities is the hunt for new stand-alone antibacterial medicines, particularly those with novel mechanisms of action. However, the difficulties that have been outlined above, in conjunction with the nearly certain likelihood that resistance to such medicines will develop, indicates that it is necessary that alternative methods also be investigated.

Adjuvants have the potential to be useful in a variety of contexts, the most evident of which is when bacteria that were previously sensitive to a treatment have developed resistance to that treatment. In addition, adjuvants that inhibit intrinsic resistance have the potential to broaden the activity spectrum of antibiotics. This might, for instance, make it possible to utilize antibiotics that are now selective for Gram-positive bacteria to treat Gram-negative illnesses. Finally, adjuvants such as colistin that increase bacterial susceptibility to antibiotics like those for which there is a concern regarding their toxicity would make it possible for these antibiotics to be effective at lower doses, thereby reducing the likelihood that they will cause adverse effects. It is known that optimally designed combination antibiotic therapies have the potential to slow resistance evolution. On the other hand, the identification of no bactericidal adjuvant compounds holds several advantages over the development of new antibiotics. Perhaps the most significant advantage is that the evolutionary pressure on bacteria to evolve resistance to a compound that does not exert bactericidal or growth inhibitory effects appears to be abated. Given the finite number of essential genes and the extensive exploration that this method has already received, another benefit is that truly novel antibiotic targets are uncommon. This is because of both the fact that the number of essential genes is finite and the fact that this method has already been extensively explored. In contrast, because the adjuvant method is still in its very early stages of development, it is quite conceivable that there are a bigger number of unexplored targets as well as previously recognized chemical scaffolds[11,15,17].

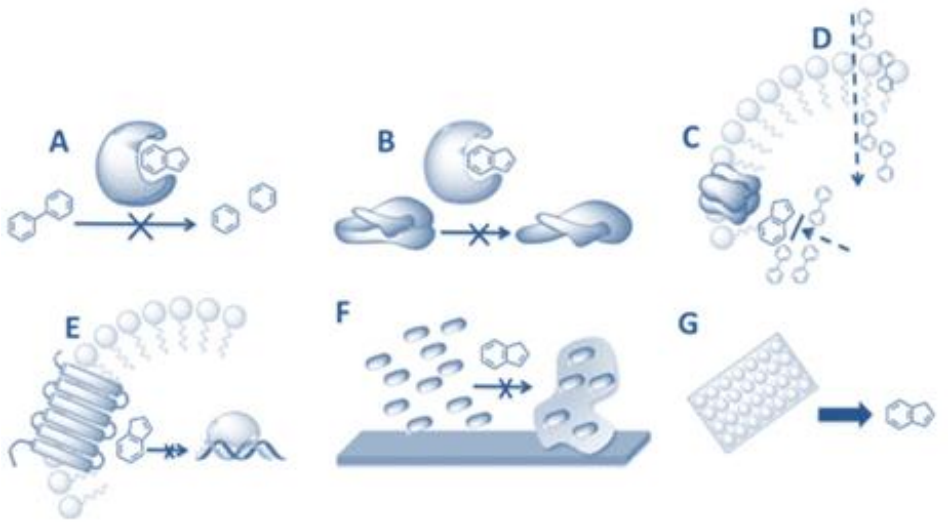

Figure 1 shows the mechanisms of action and the discovery of adjuvants.

The adjuvant strategy is not without its share of difficulties. The process of locating adjuvants presents its own unique set of challenges, many of which are similar to those that are encountered in the discovery of new antibiotics (for example, locating compounds that have the required physicochemical properties to access bacterial targets). In addition, as is the case with any combination therapy, there is the possibility of harmful drug–drug interactions, and it is necessary for the antibiotic and the adjuvant to possess pharmacokinetic and pharmacodynamics properties that are compatible with one another in order to be able to formulate an effective codosing regimen. Although the use of combination therapy in the treatment of bacterial infections has a long history of success (for instance, in the treatment of tuberculosis and certain Gram-negative infections), it is possible that formulating a treatment plan that ensures the optimal temporal and spatial delivery of the antibiotic–adjuvant combination will prove to be a more challenging endeavour. This is in contrast to combination therapies in which the targets are independent of one another.

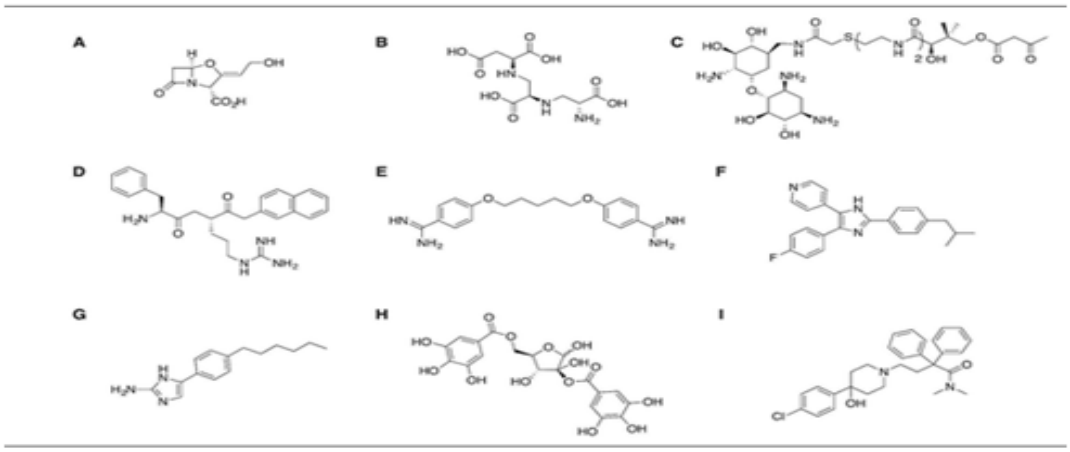

Figure 2 shows some examples of chemicals that can increase the effectiveness of antibiotics.

The beta-lactamase inhibitors are the prototypical example of small-molecule antibiotic adjuvants, and they are also the only type that has received clinical approval. In the treatment of gram-positive and gram-negative infections, beta-lactamase inhibitors, when used in conjunction with beta-lactam antibiotics, have been shown to be effective for more than 30 years and have been the subject of substantial research and analysis. The ongoing development of new beta-lactamase inhibitors to extend the spectrum of activity, for example, to include metallo—lactamase (MBL) enzymes for which there are no currently clinically approved inhibitors, remains an important area of development. On the other hand, there are numerous other resistance mechanisms that represent potential adjuvant targets that have been much less thoroughly explored. There is a possibility that any product, pathway, or phenotype that contributes to reduced antibiotic susceptibility could be a potential adjuvant target. However, the majority of these possibilities have not yet been fully investigated[11,15,17].

Conclusion

The situation with antibiotic resistance is quite serious, and we need to investigate and pursue every possible lead if we want to find a solution to this problem. Although the production of novel antibiotics and advancements in antibiotic stewardship remain of the utmost importance, additional strategies, such as the production of adjuvants that prevent antibiotic resistance, constitute a potent and underutilized tool in the fight against this problem.

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