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Expert Opinion

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Evaluating the feasibility of lantibiotics as an alternative therapy against bacterial infections in humans

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Since the commercialization and ubiquitous use of antibiotics in the 20th century, there has been a steady increase in the number of reports on resistant bacteria. In recent years, this situation has become even more dramatic. The relatively slow development of new drugs, especially those with novel modes of action on target bacteria, is not paired with the rapid rate of resistance appearance. Lantibiotics form a group of antimicrobial peptides of bacterial origin with a dual mechanism of action not shared by other therapeutic compounds in use. They have a high potency to inhibit diverse (multidrug resistant) bacteria, combined with a low tendency to generate resistance. These properties make lantibiotics attractive candidates for clinical applications. This paper discusses some of the most recent results obtained in lantibiotic clinical application, paying special attention to the pharmacokinetic and pharmacodynamic properties they display. The objective of this paper is to give insight into the actual clinical applicability of lantibiotics and to point to the unexplored aspects that should be addressed in future research. The authors feel that lantibiotics could increase the number of second line antibiotics for systemic use in the future; however, further research is still needed before this is possible.

Keywords: lantibiotics, medical application, multidrug resistance, novel antibiotics, pharmacodynamics, pharmacokinetics

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1. Introduction

The occurrence of multidrug-resistant microorganisms in the clinical environment is continuously increasing over time. This problem has got worse with the appearance of community acquired multidrug-resistant bacteria. Alarmingly, the discovery of new antimicrobial agents is outpaced by the occurrence of new resistance mechanisms, underpinning the need for new antimicrobial compounds, especially those with new modes of actions [1]. Lantibiotics are ribosomally synthesized antimicrobial compounds of bacterial origin containing modified amino acids, most notably dehydrated amino acids and lanthionines and methyl-lanthionines from which their name originates [2,3]. They are promising candidates to increase the number of available substances for treatment of bacterial infections. Lantibiotics interfere with cell wall synthesis by interacting with lipid II, sequestering it from its location, that is, the sites of cell wall synthesis. Moreover, some lantibiotics are able to insert into the bacterial membrane after the interaction and create pores [4].

In this paper we will give an overview of the publicly available pharmacokinetic and pharmacodynamic data on lantibiotics. While there are still important gaps in the current knowledge that should be addressed (as discussed later), the feasibility of applying lantibiotics as antibiotics is discussed in the expert opinion section.

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2. Lantibiotics versus antibiotics

Nisin, the first lantibiotic described and the most extensively used around the world, was identified, as was penicillin, in 1928. Due to its peptide nature it initially did not draw a lot of attention from the scientific community. With the development of molecular biology techniques and the discovery of its ribosomal synthesis (which enables peptide engineering) and peptide modification techniques, lantibiotics attracted renewed interest. Peptide engineering studies report the creation of improved lantibiotics in terms of physicochemical properties and activity [5-8]. Lantibiotics have high heat and protease resistance but their low stability at neutral or high pH can be a problem for specific applications. Nisin, for instance, is inactivated at neutral and basic pH values and only a few lantibiotics (e.g., haloduracin) are stable at pH > 7. Lantibiotics (1800 ~ 4600 g/mol) have a significantly higher molecular mass than antibiotics (138 – 1908 g/mol) (Figure 1).

Lantibiotics and antibiotics display activity against bacteria at similar concentration ranges (Table 1). The activity range of lantibiotics against Gram negative bacteria is modest compared to antibiotics with the exception of glycopeptide antibiotics. However, certain Gram negative species of *Neisseria* and *Moraxella* are very sensitive to lantibiotics such as microbisporicin [9]. Since antibiotics are in clinical use the prevalence of resistance against them is rising. Although it is difficult to compare this feature with lantibiotics, nisin has been used in food for the last 40 years and up to now no significantly resistant bacteria have been observed [10]. Resistance has been achieved in laboratory conditions using sublethal concentrations of lantibiotics and has been accounted to physiological changes rather than genetic alterations although some authors have also referred a stable threefold increase in MIC to some lantibiotics [11]. Innate resistance in *Listeria monocytogenes* to nisin or gallidermin has been studied and is related mainly with the presence of diverse transporters, penicillin-binding proteins and an increase in the number of positive charges present in teichoic acid and phospholipids. This is a general response when coping with membrane-active antimicrobials not specific for lantibiotics [12].

Like the antibiotic vancomycin many lantibiotics target lipid II, which is essential for bacterial cell wall synthesis. Stable vancomycin resistant strains occur but they are still susceptible to lantibiotics, which interact with a different part of lipid II, that is, the pyrophosphate moiety.

The ranges of applications for medical purposes that are under study are quite similar to those of antibiotics with the exception of CNS infections (Table 2) for which no reports exist to our knowledge. Lantibiotics are specially promising for treating skin and mucosal infections. Nisin has been tested in mastitis in humans with high success and moreover due to its peptide nature and low toxicity it does not require stopping lactation [13].

Discovery of new naturally occurring lantibiotics can be greatly facilitated by (automated) screening genetic databases due to the fact that lantibiotics are ribosomally synthesized, which is more difficult for antibiotics as they are not directly genetically encoded [14,15].

3. Pharmacokinetic and pharmacodynamic studies on lantibiotics

3.1 Administration

Due to their peptidic nature systemic application of lantibiotics would require parenteral invasive administration as do glycopeptide antibiotics. Although oral administration is not suitable for systemic applications, it is suitable for local applications. Using specialized tablets Ugurlu *et al.* were able to deliver nisin to specific parts of the gut [16]. Other local administration routes as intravaginal, dermic or inhaled forms can be used to achieve local effect as only very low absorption is detected [17-20].

3.2 Distribution

Lantibiotics strongly bind plasma proteins and can also bind to blood cells. Mutacin 1140, for instance, is bound to blood components to a high degree (92.7% bound) lowering the available active molecule [21]. Therefore, a model describing the pharmacokinetic and pharmacodynamic parameters of mutacin 1140 could only be fitted to the experimental data after the addition of an open second compartment (the plasma proteins) [17]. Next to this, the interaction between this lantibiotic and blood components can change the activity against a specific strain [21]. This implies that special considerations must be taken for dosage studies in order to achieve an effective lantibiotic concentration at the site of infection.

3.3 Metabolism and excretion

Only few reports on the fate of lantibiotics in mammals exist. According to McNulty *et al.* duramycin is not modified prior to excretion [22]. *In vitro* experiments have shown their increased resistance to proteases due to the presence of lanthionines and methyl-lanthionines. The only elimination studies performed *in vivo* refer to duramycin applied as aerosol in the lung or in the nose. In these cases it is mainly excreted in feces due to lung mucus removal and swallowing. Available data of elimination rates between animal and human are quite different, thus requiring a more thorough study [18,19,23]. The renal elimination rate of duramycin depends on its binding to serum [21]. Duramycin administered intravenously to mice and rats accumulates mainly in the liver; it is excreted renally and has a relatively long half-life of ~ 5 days [22].

3.4 Toxicity of lantibiotics

In vitro toxicity studies using diverse epithelial cell lines only show low toxicity after lantibiotic treatment, thus

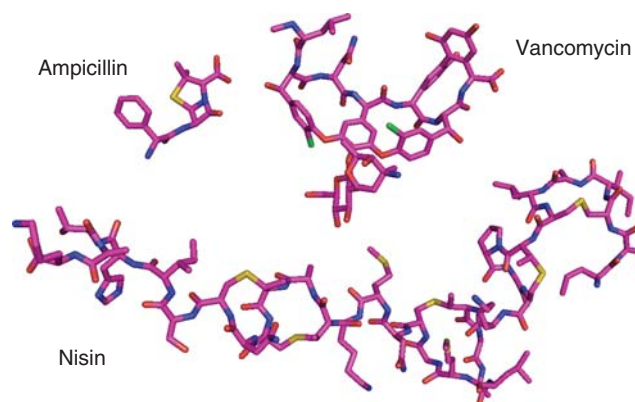


Figure 1. Comparison of the structures of nisin (from pdb ID: 1UZZ; doi:10.2210/pdb1wco/pdb) with ampicillin (from pubchem database CID_6249), a beta-lactam antibiotic, and vancomycin (pdb ID: 1C0R; doi:10.2210/pdb1c0r/pdb), a glycopeptide antibiotic. The image was made using pymol (version 1.3), the hydrogen atoms are not displayed.

Table 1. Mean MIC values for lantibiotics nisin A and mutacin B-Ny266 and antibiotics oxacillin and vancomycin against diverse bacteria.

Strain	MIC ($\mu\text{g/ml}$)			
	Mutacin B-Ny266	Nisin A	Vancomycin	Oxacillin
Gram-positive				
<i>Enterococcus spp.</i>	12.8	16.7	3.9	11.9
<i>Staphylococcus spp.</i>	1.6	4.2	3.8	7.9
<i>Streptococcus spp.</i>	0.4	8.4	0.5	0.1
<i>Clostridium spp.</i>	0.2	1.1	0.5	1.1
<i>Gardnerella vaginalis</i>	0.03	1.1	0.4	0.1
<i>Mycobacterium smegmatis</i>	32	8.4	8.0	95.1
<i>Propionibacterium acnes</i>	1.2	2.1	1.0	0.5
Gram-negative				
<i>Helicobacter pylori</i>	0.07	0.3	1.0	0.5
<i>Neisseria spp.</i>	1.6	8.4	30.1	11.2
<i>Haemophilus influenzae</i>	13	66.9	> 120	63.4
<i>Campylobacter jejuni</i>	0.07	1.1	1.0	0.1
Multidrug resistant organisms				
<i>N. gonorrhoeae</i> O13x (OxaR)	1.6	4.2	30.1	127
<i>N. gonorrhoeae</i> O22 (VanR)	3.2	12	60	32.7
<i>N. gonorrhoeae</i> INF2 (OxaR VanR)	2.3	8.4	60.2	31.7
<i>E. faecalis</i> 2 L.5.07 (OxaR)	6.4	8.4	1.9	31.7
<i>E. faecalis</i> EF-Chul (OxaR VanR)	6.4	8.4	> 120	10.2
<i>S. aureus</i> R678 (OxaR)	3.2	8.4	2.7	15.9
<i>S. aureus</i> R650 (OxaR)	3.2	8.4	3.8	44.8

Multidrug-resistant bacteria are at least resistant to four different antibiotics.

Adapted from [38] with permission of the American Society for Microbiology.

OxaR: Oxacillin resistant; VanR: Vancomycin resistant.

encouraging *in vivo* experiments [24,25]. While testing nisin, which was mucosally applied in an animal model, researchers did not detect any immune response, noted no other visible symptoms and found that the cytokine levels were not altered [24]. Feeding rats a diet containing $\leq 5\%$ nisin showed no measurable toxicological effects [26]. Some toxic effects have been shown to be caused by contaminants in the nisin preparation, which disappear when using HPLC purified

nisin [27]. Most lantibiotics are only hemolytic at high concentrations (nisin: 175 mg/l) [25] with the exception of cytolysin, a two-component lantibiotic from *Enterococcus faecalis*, which is highly hemolytic [28]. Also it has been shown that subtle changes in amino acid composition can convert a non-hemolytic lantibiotic into a hemolytic one [29].

The teratogenic potential of nisin was investigated with no effect on the first and second generation of offspring in treated

Table 2. Clinical trials and (pending) patents involving lantibiotics.

Lantibiotic and commercial name(s)	Purpose	Ref.
<i>Clinical trials</i>		
Duramycin/Moli1901/Lancovutide/2622U90	Phase II placebo-controlled, double-blinded, single-center study of the safety of nebulized duramycin for the treatment of cystic fibrosis	[19]
<i>Pending patents</i>		
Microbisporicin/107891/NAI-107		[36]
Actagardine/NVB302		[39]
Streptococcus salivarius K12 salivaricin A	Treatment of halitosis	[40]
BLIS (salivaricins)	Acne treatment	[41]
Mersacidin	Skin and systemic infection	[42]
Nisin	Bovine mastitis	[43]
Nisin	Oral cavity applications	[44]
Mutacin producing <i>S. mutans</i>	Replacement therapy for caries	[45]
Nisin and lantibiotic combinations	Skin infection treatment	[37]

animals [27]. Interestingly nisin has been investigated as a contraceptive agent because of its spermicidal activity [30,31]. This is only observed at high concentrations and is selective for spermatozoa due to their special membrane composition [32]. No differences were observed in the blood parameters and histological samples of animals topically treated with nisin and duramycin compared to an untreated control [19,23,24,27,33]. Humans treated with aerosolized duramycin also showed no differences in their blood parameters after treatment [34].

Furthermore, it has been reported that rapid infusion of mutacin 1140 in rats causes reversible hypersensitivity reactions that can be blocked using diphenhydramine prior to the treatment [17].

In conclusion the toxicological data sets a limit to the therapeutical window that is broad enough to encourage further research. Hemolytic activity of lantibiotics appears to be unpredictable and should, therefore, be individually assessed.

4. Expert opinion

Lantibiotics constitute a family of very stable ribosomally synthesized peptides amenable to molecular engineering with high antimicrobial potency, comparable to that of conventional antibiotics. Their unique mechanism of action and their low propensity to generate resistance are attractive properties of these compounds. Until now research in lantibiotics has focused on bio-engineering to improve activity, to investigate the structure-activity relationship and to understand the modification process. It is now time to focus more on clinical aspects of lantibiotics. Although important knowledge has been acquired, as discussed in this paper, some questions remain unanswered.

Lantibiotics show low absorption rates thus enabling local delivery. This could represent one advantage minimizing their effect on normal microbiota somewhere else in the organism and reducing the dose. Systemic applications would require invasive parenteral administration, but for this some hurdles

have to be taken. First of all, the bio-availability can be a problem especially since some lantibiotics have a high affinity to blood components. Second, most lantibiotics are not very stable at physiological pH. Although we do not anticipate problems arising from the hemolytic activity of lantibiotics, it can only be excluded to form a problem once more data that relate dosage to effectiveness are available [35]. Lantibiotics do not significantly affect organs, tissues or blood parameters in animals. In humans similar results indicate the safety, but so far the number of participants in these studies is low and, therefore, rare adverse effects cannot be discarded.

In our opinion it is necessary to evaluate the *in vivo* concentration of a given lantibiotic and its elimination rate. With this data, dosage regimes that can be compared to concentrations needed for effective therapeutic use can be established. This will allow, in addition, a more precise toxicological study at therapeutic concentrations with time. These data can also be used to define which properties need to be improved on by protein engineering (i.e., stability or solubility). In parallel, pharmaceutical technology can provide the tools to circumvent these problems.

Local applications of lantibiotics look very promising also to potentially fight re-occurring infections. The work conducted on microbisporicin and nisin to treat *Clostridium difficile* and *Staphylococcus aureus* infections, respectively, is especially encouraging [36,37]. Lantibiotics could extend the number of second-line antibiotics for systemic use in the future, provided the open questions mentioned here can be answered.

Declaration of interest

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