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Nonclinical Evaluation of Antibacterial Oxazolidinones Contezolid and Contezolid Acefosamil with Low Serotonergic Neurotoxicity

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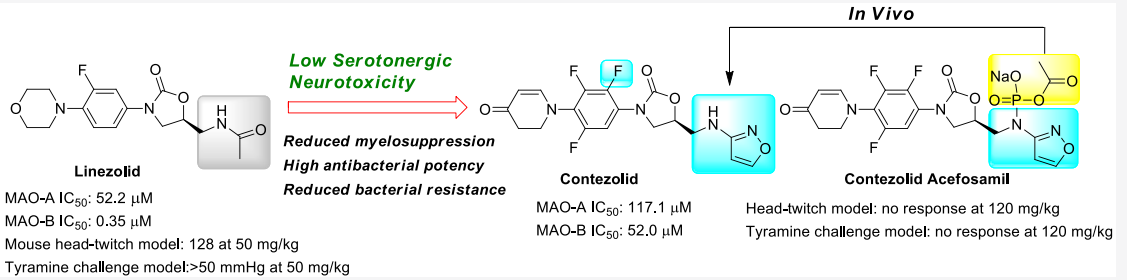

ABSTRACT: Linezolid, the principal oxazolidinone antibiotic for therapy of Gram-positive infections, is limited by its myelosuppression and monoamine oxidase (MAO) inhibition, with the latter manifested as serotonergic neurotoxicity. The oral oxazolidinone contezolid and its injectable prodrug contezolid acefosamil are developed to overcome the above limitations. Serotonergic profiles for contezolid *in vitro* and for orally administered contezolid acefosamil in rodents are reported. Contezolid exhibited 2- and 148-fold reduction over linezolid reversible inhibition of MAO-A and MAO-B human enzyme isoforms. In the mouse head-twitch model, contezolid acefosamil was devoid of neurotoxicity at supratherapeutic oral doses of 40, 80, and 120 mg/kg. In the rat tyramine challenge model, no significant increase in arterial blood pressure was observed for contezolid acefosamil up to 120 mg/kg oral dosing. In these tests, the comparator linezolid has elicited serotonergic responses. Thus, contezolid and contezolid acefosamil exhibited an attenuated propensity to induce MAO-related serotonergic neurotoxicity. The data support a continued clinical evaluation of these agents, with potential to expand oxazolidinone therapies to patient populations on concurrent selective serotonin reuptake inhibitor medications or where MAO inhibitors are contraindicated.

1. INTRODUCTION

Antibacterial oxazolidinones[1] comprise an essential class of pharmaceuticals with a critical role in the therapy of multidrug-resistant (MDR) Gram-positive infections. These protein synthesis inhibitors have attained prominence since the introduction of linezolid (Zyvox) in 2000.[1c] The class has a unique mode of action targeting a distinct region of the 23S rRNA adjacent to the peptidyl transferase center of the 50S ribosomal subunit.[1a] This key feature confers low rates of bacterial resistance to linezolid, with no significant incidence per global surveillance data.[2] Another oxazolidinone, tedizolid,[3] was approved in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Linezolid remains the standard-of-care of this antibiotic class due to its multiple therapeutic indications.[4]

Despite the medical success of linezolid, this drug suffers from certain safety limitations.[5] Myelosuppression and serotonergic monoamine oxidase (MAO) inhibition comprise two independent phenomena responsible for most adverse effects in its therapy. Myelosuppression is often viewed as the chief therapy-limiting effect of linezolid.[4,5] It is associated with its mode of antimicrobial action inhibiting protein synthesis both in prokaryotes and mammals.[6] Resulting adverse effects typically manifest after more than 10 days of therapy.[5]

In contrast, the adverse effects due to MAO inhibition[7] may independently manifest at onset of the treatment,[5] necessitating precautions on the potential drug−drug and food−drug adverse effects noted in the prescribing information for linezolid.[4] This phenomenon is rooted in the intrinsic ability of its aryl oxazolidinone structure to bind and thus inhibit both A and B isoforms of MAO enzymes present in human.[8] The enzymes are essential for metabolic inactivation of the neurotransmitters serotonin, epinephrine, norepinephrine (adrenaline), and dopamine.

Compared to therapeutics intended as MAO inhibitors, linezolid exhibits modest levels of inhibition, with K_i values of

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ca. 56 and 0.7 μM for MAO-A and MAO-B isoforms, respectively. For example, a structurally related antidepressant toloxatone inhibits MAO-A with K_i of 1.8 μM.[9] Linezolid itself was reported to induce mild antidepressant-like effects in certain mouse models.[10]

Neurotransmitters can be neurotoxic,[11,12] and inadequate metabolic deregulation thereof due to MAO inhibition may result in neurologic adverse effects, such as serotonin toxicity.[5,7,8] Serotonin has been implicated in the neurodegeneration associated with depression.[13] An excess serotonin may induce a copper[14,15] and iron-mediated[16,17] neurodegeneration. Serotonin metabolite, tryptamine-4,5-dione, was reported to act as a mitochondrial toxin implicated in neurodegenerative brain disorders.[17]

In linezolid use, MAO inhibition manifests mainly as serotonin syndrome.[5,7] This occurs through a stimulation of serotonin receptors and excessive levels of norepinephrine in the central nervous system (CNS).[18] Principally, it is observed when patients on linezolid are co-administered with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, or other MAO inhibitors.[19] Such neurotoxicity can manifest in a spectrum of adverse effects, including hypertension, hyperthermia, or involuntary muscular activity.[5,20] While the serotonin syndrome is generally reversible and can resolve within days upon discontinuation of cotherapy with a SSRI, the risk of a rapid fatality has been noted.[5] The MAO inhibition by linezolid may also exacerbate anticholinergic effects of antihistamines, including common cold remedies.[21]

Likewise associated with MAO-related effects of linezolid is a dietary precaution on tyramine-rich food consumption.[4] Tyramine is metabolized, in part, into dopamine, a precursor for norepinephrine and epinephrine,[22] effectively acting as a sympathomimetic agent interfering with neurotransmitters.[23] Its accumulation can trigger adverse effects, and a consumption of tyramine-rich foods (such as cheese) while on linezolid may induce hypertension.[24]

Therefore, MAO inhibition is an important safety consideration in the linezolid use, especially when a co-administration of a neurotropic medications is required. Apart from MAO-related drug−drug and food−drug interactions, linezolid therapy is limited in patients with uncontrolled hypertension or endogenous hyperadrenergic and hyperserotonergic states.[5]

Contezolid (initially introduced as MRX-I)[25] is a novel oxazolidinone rationally designed to address the class limitations associated with both myelosuppression and MAO inhibition of linezolid. The agent was originated at MicuRx Pharmaceuticals, Inc. To date, the Phase 2 ABSSSI trial for contezolid has been successfully completed in the United States (US), and its Phase 3 cSSSI study was completed and the New Drug Application (NDA) submitted in China. To facilitate intravenous administration of contezolid, its water-soluble *O*-acyl phosphoramidate prodrug, contezolid acefosamil, was introduced by our team[26] (Figure 1).

The prodrug form of contezolid has no appreciable antimicrobial activity of its own. *In vivo*, the double prodrug structure undergoes a two-step metabolic degradation comprising O-deacetylation followed by N-dephosphorylation with the release of the active drug, contezolid. Details of biochemical mechanisms of the drug release remain to be elucidated. Based on near-instantaneous *in vivo* O-deacetylation of contezolid acefosamil to form N-phosphate intermediate, it is likely that the rapid initial O-deacetylation is an

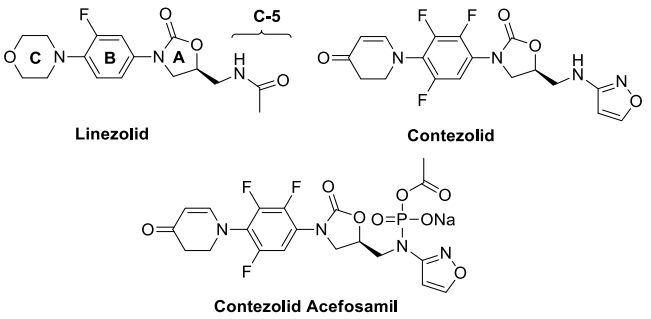

Figure 1. Linezolid, the novel antibiotic contezolid, and its prodrug, contezolid acefosamil.

enzymatic process, possibly mediated by esterases. The cleavage of resulted N-phosphate (detectable in blood phosphoramidate) may hypothetically proceed through a phosphoramidase and phosphatase-mediated dephosphorylation, analogously to the metabolism of ceftaroline fosamil[27] [featuring a similar to 3-(*N*-phosphonoamino)-isoxazole heteroaromatic azole group 5-(*N*-phosphonoamino)-1,2,4-thiadiazole structure]. Based on the reported nonenzymatic hydrolytic degradation of ceftaroline fosamil[28] and earlier studies on the chemical hydrolysis of other phosphoramidates,[29] a pH-dependent hydrolysis is also possible. The prodrug serves an effective equivalent for contezolid, which is released from intravenously (IV) or orally (PO) administered contezolid acefosamil *in vivo*. The equivalence of orally and intravenously administered forms of contezolid acefosamil was evaluated in rat and dog preclinical pharmacokinetic (PK) models[30] conducted during the IND enabling evaluation for this agent as well as in human Phase 1 and Phase 2 trials completed in the US (details to be reported elsewhere).

In the rat PK model,[30] the systemic exposure (assessed per area-under-the-curve, AUC) to contezolid administered as contezolid acefosamil was essentially identical for PO and IV prodrug regimens: AUC values 41.4 and 44.0 μg·h/mL for PO and IV contezolid acefosamil dosed at 40 mg/kg, and 121.0 and 145.0 for its PO and IV dosing of 120 mg/kg, respectively. Thus, the prodrug form could be used for either PO or IV delivery of contezolid. Alternatively, contezolid acefosamil may be deployed as a soluble IV agent in a hospital, followed by step-down oral therapy in the outpatient setting. In our study, the prodrug was administered to rodents in oral solution form.

Notably, the neurotoxicity evaluation for the oral form of contezolid acefosamil is of special relevance for potential long-term community use of the oxazolidinone agent.[25] This may be required, for example, in therapy of persistent diabetic foot infections. In this context, MAO-related adverse effects are more likely to manifest in self-administration of the oral form used in an outpatient setting, as compared to IV regimen deployed in a controlled hospital environment (including a risk of potential drug−drug interactions, as well as diet-induced complications).

Contezolid maintains the high antibacterial potency and therapeutic efficacy characteristic of linezolid, while exhibiting a markedly attenuated myelosuppression.[25] In addition, the new agent exhibits a reduced propensity toward developing bacterial resistance[31] as well as an improved potency against some Gram-positive isolates.[25,32]

Herein, we describe initial preclinical characterization of the MAO-related safety profile for contezolid and its prodrug form contezolid acefosamil, including *in vitro* testing for the active

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drug form, contezolid, as well as *in vivo* evaluation of serotonergic neurotoxicity and tyramine potentiation profile for contezolid acefosamil in animal models (additional safety data for contezolid were previously reported).[25]

2. EXPERIMENTAL SECTION

2.1. Animals and Test Agents. All animal studies have been conducted in accordance with the Guidance for the Care and Use of Laboratory Animals and approved by the Charles River Laboratories Institutional Animal Care and Use Committee (USA, Ashland, OH). The rodents used in animal studies have been provided by the same institution (USA, Raleigh, NC).

Contezolid and contezolid acefosamil have been prepared according to methods described in refs 25 and 26, respectively. Human recombinant MAO-A and MAO-B enzymes were purchased from Sigma-Aldrich. Linezolid and auxiliary test reagents have been acquired from the common commercial sources.

2.2. *In Vitro* MAO Inhibition Testing. The inhibitory activity of contezolid against the human recombinant MAO-A and MAO-B isoforms was evaluated at BioAssay Systems. The assay is based on the fluorometric detection of hydrogen peroxide generated during the oxidative deamination of the tyramine substrate in a horseradish peroxidase-coupled enzymatic reaction.[33] The known irreversible MAO inhibitors clorgyline and pargyline were used as positive controls. The degree (%) of the enzymatic inhibition at eight concentrations was established relative to the uninhibited control, and the IC_{50} (μM) values were thus calculated for both contezolid and the comparator linezolid.

2.3. Animal Studies: The Head-Twitch Model in Mice. Serotonergic toxicity was evaluated as follows.[34] Adult male mice were pretreated with an intraperitoneal (IP) 10 mg/kg dose of the decarboxylase inhibitor, carbidopa, administered to animals randomized into 5 groups (10 animals per group). After about 15 min, each animal received a single oral treatment of contezolid acefosamil formulated in water at 0, 40, 80, and 120 mg/kg. In a single test cohort, linezolid was dosed orally as a positive control at 50 mg/kg. Approximately 15 min thereafter, the animals were administered (IP) serotonin precursor 5-hydroxytryptophan (5-HTP) dosed at 50 mg/kg, to elicit a characteristic head-twitch response. After about 15−35 min, animals were observed for a manifestation of the head-twitch response. The latter is defined as a short burst of rapid left−right head shaking that is distinct from a grooming behavior. Observed instances of head twitches within this time period were quantitatively recorded.

2.4. Animal Studies: The Tyramine Challenge Model in Rats. The tyramine challenge assay was designed based on ICH Harmonized Tripartite Guideline S7A (Safety Pharmacology Studies for Human Pharmaceuticals). Specifically, the blood pressor response for contezolid acefosamil and the control linezolid was assessed in radiotelemetry-instrumented conscious Sprague−Dawley male rats (randomized into groups of 6). A single dose of contezolid acefosamil formulated in water at 40, 80, and 120 mg/kg was administered by oral gavage. Linezolid at 50 mg/kg was dosed orally as a positive control to one test cohort. Two h after the test agent administration, each animal received a single 15 mg/kg dose of tyramine hydrochloride by oral gavage. Thereafter, the following parameters and end points were evaluated: overall clinical signs, heart rate, arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, and body temperature.

3. RESULTS AND DISCUSSION

3.1. Characterization of Contezolid Inhibition of Human MAO-A and MAO-B Enzyme Isoforms *In Vitro*. The test results for the enzymatic MAO inhibition of contezolid and the comparator linezolid *in vitro* are presented in Table 1. As clear from these data, contezolid exhibited a notably attenuated vs linezolid inhibition.

The attenuated inhibition of the B-isoform may be of clinical significance, since the latter has been implicated in the neuropathic adverse effects of linezolid.[5] Indeed, a low platelet MAO-B activity was associated with the incidence of neuropathic pain,[36] with a potential role of this MAO isoform in the perception of pain.[37] Therefore, it may be considered whether the MAO-B inhibition is a contributing factor to the neuropathic adverse effects of linezolid, generally ascribed to the independent from MAO inhibition myelosuppression by this drug (and tracked to a protein synthesis inhibition in the human mitochondria).[5]

Table 1. *In Vitro* MAO Inhibition and Antibacterial Activity against MRSA for Contezolid, Compared to Linezolid

test agent	MAO-A IC_{50}, μM	MAO-B IC_{50}, μM	MRSA[a] MIC_{90}, μg/mL
linezolid	52.2	0.35	2.0[b]
contezolid	117.1	52.0	0.5[c]

[a]Minimum inhibitory concentration for 90% strains tested. [b]Data from ref 35. [c]Data from ref 25.

In line with early finding of Barbachyn et. al[38,39] for a set of fluorinated linezolid analogs, the minimized MAO inhibition observed for contezolid may be rationalized in context of the unique subclass of antibacterial *N*-aryl oxazolidinones featuring an *ortho*-fluorophenyl group. This structural modification at the aromatic ring fragment can force a dihedral angle between the phenyl B-ring and the oxazolidinone A-ring[39] (for substructure designations,[1c] see Figure 1). In contrast to the nearly planar linezolid A/B structure,[39] the resulting nonplanar A/B constructs may exhibit a poor fit with the relatively tight binding tunnel in MAO enzymes.[40]

Notably, this structural modification is not tolerated by the structure−activity relationships for the class, and such ortho-fluorinated oxazolidinone variants generally exhibit a poor antibacterial activity.[25] Contezolid is a sole oxazolidinone antibiotic of this unorthodox structural type that has advanced into clinical development.

An adverse effect potential for a new agent is often assessed alongside its intended activity. To illustrate the reduced *in vitro* MAO-related toxicity potential for contezolid in context of its antibacterial activity, *in vitro* data for its potency and the comparator linezolid against a representative Gram-positive pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA), are included in Table 1. The attenuated MAO inhibition of contezolid may be underscored by its improved activity against certain MRSA isolates, apparent from the reduced MIC_{90} value (minimum inhibitory concentration for 90% strains tested), as compared to that for linezolid.[25]

In vivo, the administration of contezolid (as an oral active drug, or as its prodrug contezolid acefosamil) results in exposure levels similar to that for linezolid.[25] Therefore, the *in vitro* data for contezolid suggest that both agents may exhibit diminished MAO-related adverse effects in mammals.

The prodrug was not directly evaluated for MAO inhibition *in vitro* due to its instability under the assay conditions. Furthermore, a minimal or no MAO inhibition for the prodrug featuring a nonlinear and polar *N*-[(*O*-acetyl)phosphoryl] group incorporated into [(isoxazole-3-yl)amino]methyl C-5 fragment of contezolid (Figure 1) is anticipated per structure−toxicity relationships (STR) for the antibacterial oxazolidinones. Reck et al.[40] has reported about an 8-fold reduction in the MAO-A inhibition for 5-[*4-methyl*-(triazole-1-yl)methyl]-oxazolidinone derivative, as compared to its (triazole-1-yl)methyl analog lacking the *4-methyl* substituent. Based on

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the active site docking studies, these authors have concluded that the MAO-A binding tunnel may not accommodate nonlinear C-5 structures. These STR observations are also in line with an elevated *in vitro* inhibition for tedizolid featuring a compact 5-hydroxymethyl C-5 group, as compared to linezolid with 5-acetamidomethyl fragment.[25] In any event, the level of MAO inhibition for contezolid acefosamil structure appears unlikely to exceed that for the parent drug, contezolid. In addition, the metabolically labile character of the prodrug precludes its accumulation *in vivo*.

The reversibility of MAO-A and MAO-B inhibition by contezolid was assessed through dialysis, using the comparator linezolid as well as irreversible MAO inhibitors clorgyline and pargyline incorporated as positive controls. As expected for oxazolidinones,[5,7] both contezolid and linezolid inhibited MAO-A and MAO-B in a reversible manner (data not shown).

3.2. Serotonergicity of Contezolid Acefosamil in the Mouse Head-Twitch Model. The potential serotonergic activity of contezolid acefosamil was assessed in a validated mouse model[34] with quantitative observations of a characteristic head-twitch response induced by the decarboxylase inhibitor, carbidopa, and the serotonin precursor, 5-HTP.

The effect of contezolid acefosamil on the elicited head-twitch response was assessed against that for the comparator linezolid and the vehicle control. In contezolid test cohorts, the average response for 40, 80, and 120 mg/kg contezolid acefosamil was recorded as 18, 31, and 24 twitches, respectively (see Figure 2). Notably, this effect was similar to

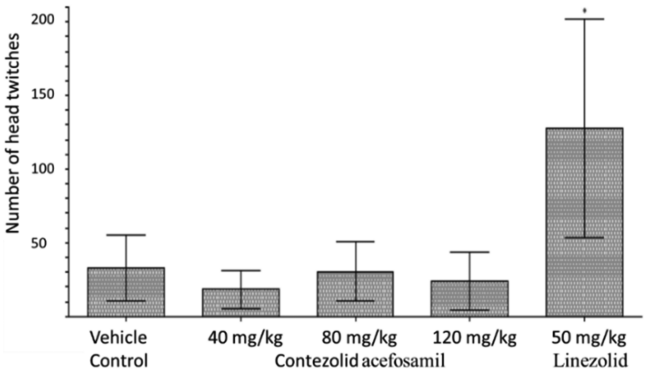

Figure 2. Head-twitch responses in the mouse model for contezolid acefosamil (40, 80, and 120 mg/kg oral dosing; 10 mice per group) and linezolid (oral 50 mg/kg; 10 animals); bar graphs include standard deviations within each of the data sets.

that in the vehicle control group, where 33 head twitch responses were detected. The results indicate that contezolid acefosamil is essentially devoid of serotonergic neurotoxicity at all doses tested.

In contrast to a lack of apparent neurotoxicity potentiation in animals administered with contezolid acefosamil, a markedly increased signal (128 head-twitches) was observed in the group of animals dosed with the linezolid comparator at 50 mg/kg. The potentiation effect for linezolid was in agreement with that reported by Flanagan et. al,[41] for identical dose of the drug.

The reduced serotonergic effect of contezolid acefosamil is further underscored by the lack of the head-twitch response at the top dose tested, 120 mg/kg. Relevant in this context, an average value for the antibacterial efficacy (ED_{50}, the dose for survival of 50% tested animals) of contezolid acefosamil in five systemic infection murine models of MRSA and methicillin-sensitive *S. aureus* (MSSA) infections is about 9.5 mg/kg.[42] The highest tested dose of contezolid acefosamil (120 mg/kg) with no neurologic response potentiation is suggestive of a safety margin of more than 12-fold. This is well over of the about 5-fold safety margin that may be assessed based on the average ED_{50} value of linezolid (9.6 mg/kg) and its pronounced serotonergic response induced by its dosing of 50 mg/kg.

Furthermore, the oral administration of both linezolid and of contezolid acefosamil results in a similar exposure to the active drug (linezolid and contezolid, respectively) in mouse PK models.[42] At significantly higher dosing for contezolid (administered as 120 mg/kg contezolid acefosamil) relative to linezolid (50 mg/kg), the new agent elicited no apparent neurotoxic effect. These results suggest a markedly improved safety of both contezolid and its prodrug acefosamil with respect to the MAO-related serotonergic overstimulation in the mouse head-twitch model.

3.3. Serotonergic Profile of Contezolid Acefosamil in the Rat Tyramine Challenge Model. The tyramine challenge animal model is commonly used to characterize antibacterial oxazolidinines.[7,41,43] The pressor response of contezolid acefosamil was evaluated in conscious male rats prepared for radiotelemetry observations. The agent was dosed orally at 40, 80, and 120 mg/kg. About 2 h postadministration of contezolid acefosamil or the comparator linezolid (single linezolid cohort dosed at 50 mg/kg), animals were given an oral dose of tyramine. The pressor response induced by tyramine in ambulatory rats was then recorded and expressed as the maximal increase in mean arterial pressure within 30 min of the tyramine administration.

Contezolid acefosamil was well tolerated in all dose groups, and no clinical observations were noted in any rat cohort. No significant pressor response (defined as ≥30 mmHg increase in the mean arterial pressure) was noted in any of the contezolid acefosamil groups, up to 120 mg/kg dose tested (see Figure 3 below). In contrast, an appreciable pressor response (above 50 mmHg) was noted in the linezolid comparator group dosed at 50 mg/kg, as compared to the pretreatment baseline pressure. Mild variations in the pulse pressure were noted following

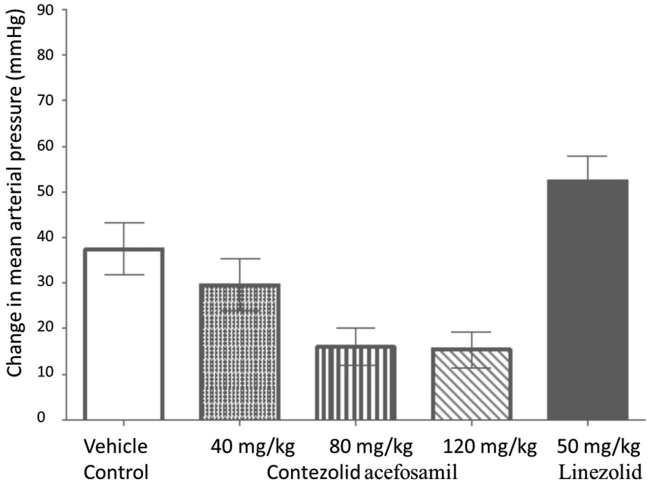

Figure 3. Mean arterial pressure in the tyramine challenge rat model for contezolid acefosamil (40, 80, and 120 mg/kg oral dosing; 6 rats per group) and linezolid (oral dose 50 mg/kg; 6 animals).

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administration of the vehicle control as well as contezolid and linezolid cohorts, with the pulse pressure in all groups returned to the baseline values by the end of the data collection period.

Thus, in the tyramine challenge assay, contezolid acefosamil did not produce any pressor response (as defined above) at its highest dose of 120 mg/kg, while the increase in the arterial blood pressure was detected in the linezolid group, at nearly 2-fold lower dosing of 50 mg/kg.

Tyramine is metabolized by both MAO-A and MAO-B human enzymes, with both isoforms present in the intestines.[44] The apparent difference between the pressor response to linezolid following the tyramine ingestion and the lack of the response to contezolid acefosamil may be rationalized by a stronger MAO inhibitory effect of linezolid, as compared to contezolid (see Table 1 and discussion therein). Based on the significantly elevated inhibition levels of the MAO-B isoform by linezolid as compared to that for MAO-A isoform (MAO-B IC_{50} 0.35 μM, vs MAO-A IC_{50} 52.2 μM; Table 1), it may be rationalized that the pressor effect triggered by ingested tyramine could be mainly due to the MAO-B isoform inhibition. In contrast, contezolid inhibition of both MAO-A and MAO-B is characterized by relatively closer inhibition levels: IC_{50} values 117 and 52 μM, respectively.

The about 148-fold attenuated (vs linezolid) MAO-B inhibition of contezolid likely accounts for the marked difference in the pressor effect, with the lack thereof for contezolid, observed in the tyramine challenge study. The data from the tyramine challenge model further validate the improved MAO-related safety profile for contezolid (tested as its prodrug, contezolid acefosamil), with projected minimized risk of drug-food interactions, as compared to linezolid.

Taking into account a reported association of serotonin metabolism with myelosuppression,[16,17] further research into a potential contribution of MAO inhibition to adverse effects of linezolid largely ascribed to the mitochondrial protein synthesis inhibition[5] (such as peripheral and optical neuropathy) would be of interest.

Notably, the apparent potential for enhanced safety of oral contezolid and contezolid acefosamil is further underscored by the high potency of contezolid against Gram-positive bacteria and its diminished over linezolid propensity for development of the bacterial resistance[31] as well as the attenuated myelosuppression potential.[25]

4. CONCLUSION

An emerging oxazolidinone agent contezolid has a molecular structure designed to minimize MAO-related adverse effects typical for the standard-of-care oxazolidinone antibiotic linezolid.[4] *In vitro* testing of contezolid indicates a 2-fold reduced propensity to inhibit MAO-A isoform and a nearly 150-fold reduction in MAO-B isoform inhibition, as compared to linezolid.

Studies of serotonergic neurotoxicity potential and MAO-related blood pressure effects in the mouse head-twitch model and in the rat tyramine challenge model revealed no responses for contezolid dosed as oral contezolid acefosamil, the prodrug form of contezolid suitable for both intravenous and oral administration. In contrast to the comparator linezolid, no apparent neurotoxicity was observed at elevated dosing, at over 12-fold of its efficacy dose (ED_{50}) in rodent infection models.

Thus, contezolid and oral contezolid acefosamil exhibit a significantly attenuated propensity to induce MAO-related neurologic and blood pressor adverse effects. The nonclinical data support further evaluations of these agents as potential next-generation antibiotics. Subject to clinical development, these agents bear potential to extend the use of the oxazolidinone class beyond the current linezolid therapy, including the patient populations on concurrent SSRI medications, or where MAO inhibitors are likewise contraindicated (such as some CNS patients and patients with inadequate control of blood pressure).

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ABBREVIATIONS

ABSSSI, acute bacterial skin and skin structure infections; ED_{50}, effective dose for 50% survival of animals tested; 5-HTP, 5-hydroxytryptophan; IV, intravenous; MAO, monoamine oxidase; MAO-A, monoamine oxidase isoform A; MAO-B, monoamine oxidase isoform B; MDR, multidrug resistant; MIC_{90}, minimum inhibitory concentration for 90% strains tested; MRSA, methicillin-resistant *Staphylococcus aureus*; NDA, new drug application; PO, oral; SAR, structure−activity relationships; SSRI, selective serotonin reuptake inhibitor; cSSSI, complicated skin and skin structure infection; STR, structure−toxicity relationships

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