TD-1211, a potent and peripherally-selective μ-opioid receptor antagonist

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Introduction

Opioid analgesics play a critical role in malignant and non-malignant pain control, but despite their effectiveness, opioid-induced constipation (OIC) is a common problem that can be extremely debilitating (De Luca & Coupar, 1996; Pappagallo, 2001; Walsh, 1990). OIC results from an interaction of the opioid agonist with receptors on enteric neurons in the myenteric and submucosal plexuses, and smooth muscle of the gastrointestinal (GI) tract to reduce coordinated rhythmic contractions associated with transit and secretion.

The ability of the opioid receptor antagonists, naltrexone and naloxone, to attenuate OIC has been demonstrated clinically. These agents readily cross the blood brain barrier, however, and can attenuate opioid-induced analgesia and provoke a behavioral withdrawal syndrome (Pappagallo, 2001). Clinical data indicate that the peripherally-selective μ-opioid receptor antagonists, alvimopan and methylnaltrexone, attenuate OIC without impairing opioid analgesia. Alvimopan (Entereg®) is available in the United States, but only as an oral therapy for post-operative ileus, a condition in which there is stasis of the GI tract after abdominal surgery, while methylnaltrexone (Relistor®) is marketed as a subcutaneous treatment for OIC in patients with advanced illness who are receiving palliative care. There remains an urgent need for an oral, peripherally-selective, opioid receptor antagonist to treat OIC in patients with malignant and non-malignant pain. Here we describe the in vitro and in vivo pharmacological properties of TD-1211, a novel opioid receptor antagonist currently in Phase 2 human clinical development, in comparison to those of naltrexone, alvimopan and methylnaltrexone. The profile of ADL 08-0011, the primary, active, human metabolite of alvimopan, was also examined in the study.

Methods

- The opioid receptor affinity (expressed as a pK_i value) of test agents was determined using radioligand binding assays with [^{3}H]diprenorphine and membranes prepared from Chinese hamster ovary cells stably-transfected with human μ- and δ-, or guinea pig κ-opioid receptor cDNA.
- Off-target activity of TD-1211 (1 μM) was examined by receptor, ion channel, enzyme and transporter binding or functional assays using cell lines or animal tissue. The percent inhibition of specific radioligand binding or functional activity was measured.
- Opioid receptor antagonist potency (expressed as a pA_2 or pK_B value) was evaluated using electrically stimulated guinea-pig ileum and hamster vas deferens preparations mounted in tissue baths. Concentration-response curves to selective μ-, κ- or δ-opioid agonists (i.e., endomorphin-1, U69593 or [D-Pen^{2,5}] enkephalin, respectively) were constructed in the absence and presence of antagonists.
- The in vivo potency of test agents to inhibit loperamide-induced delays in gastric emptying of a charcoal meal, and attenuation of castor oil-induced diarrhea in rats was determined. The influence of TD-1211 on non-productive GI contractility evoked by loperamide was also evaluated in dogs chronically implanted with strain gauges.
- Inhibition of morphine-induced anti-nociceptive activity was evaluated using a hot-plate test in rats and dogs to provide a measure of the CNS activity of test compounds
- The effects of test agents on morphine-induced sedation (scored by blinded visual assessment) was recorded in dogs, providing another measure of their CNS activity.
- Mice dosed for 4 days with morphine (45 mg/kg/day s.c. via an osmotic minipump) were challenged with TD-1211 and comparator compounds to assess if a CNS opioid withdrawal response occurred. Jumping behavior was recorded by a blinded observer.

Results

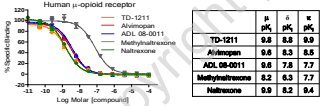
(1) TD-1211 had high affinity for human μ- and δ-, and guinea-pig κ-opioid receptors (pK_i = 9.8, 8.8 and 9.9, respectively). The μ-opioid receptor binding affinity of TD-1211 was similar to that of alvimopan, ADL 08-0011 and naltrexone, and higher than that of methylnaltrexone. TD-1211 was a potent μ-opioid receptor antagonist in the guinea pig isolated ileum (rank order of potency: TD-1211 ≥ alvimopan = ADL 08-0011 > methylnaltrexone). TD-1211 had 50- and 20-fold functional selectivity for guinea pig μ-opioid receptors over hamster δ- and guinea pig κ-opioid receptors, respectively. TD-1211 had >6,000-fold selectivity for the μ opioid receptor over non-opioid receptors (n=56), ligand-gated ion channels (n=8), enzymes (n=6), ion channels (n=10; including hERG) and transporters (n=3).

(2) TD-1211 inhibited loperamide-induced reduction in gastric emptying and attenuation of castor oil-induced diarrhea following acute oral dosing to conscious rats. In dogs, loperamide (0.1 mg/kg i.v.)-induced non-productive contractile activity of the GI tract was reduced following TD-1211 (3 mg/kg) oral pretreatment.

(3) TD-1211, like alvimopan, was less potent than naltrexone and ADL 08-0011 at inhibiting morphine-induced anti-nociceptive activity (ID_{50} values of >100, 1.0 and 1.7 mg/kg, respectively), and in evoking a CNS withdrawal response in morphine-dependent mice (lowest oral doses producing jumping: >10, >10, 1 and 10 mg/kg, respectively). In dogs, oral dosing of TD-1211 (3 mg/kg) had no effect on morphine (1 mg/kg i.v.)-induced sedation or anti-nociception, while naltrexone and ADL 08-0011 (3 mg/kg orally) produced a marked inhibition of the morphine-induced responses.

Results (1): TD-1211 is a high affinity and potent opioid receptor antagonist

- Binding affinities for human μ- and δ-,and guinea pig κ-opioid receptors



	μ pK_i	δ pK_i	κ pK_i
TD-1211	9.8	8.8	9.9
Alvimopan	9.6	8.3	8.5
ADL 08-0011	9.6	7.8	7.7
Methylnaltrexone	8.2	6.3	7.7
Naltrexone	9.9	8.2	9.4

- Antagonist potencies at guinea pig ileal μ- and κ-, and hamster vas deferens δ-opioid receptors

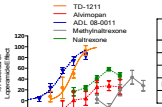
	μ-opioid receptor pA_2	δ-opioid receptor pK_B	κ-opioid receptor pK_B or pA_2	μ/δ ratio	μ/κ ratio
TD-1211	10.1	8.4	8.8	50	20
Alvimopan	9.6	8.9	8.4	5	16
ADL 08-0011	9.4	7.8	7.2	63	158
Methylnaltrexone	7.6	6.4	6.6	16	10
Naltrexone	Not tested				

- Off-target activity of TD-1211 (1 μM)

  No affinity (i.e., <50% inhibition of radioligand binding) at all non-opioid receptors (n=56), ligand-gated ion channels (n=8), enzymes (n=6), ion channels (n=10; including hERG) and transporters

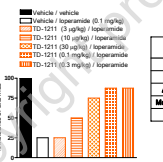
Results (2): TD-1211 is a potent inhibitor of loperamide-induced GI activity in rats and dogs following oral dosing

- Reversal of loperamide-induced delay in gastric emptying in rats



	ID_{50} vs. loperamide-induced delay in gastric emptying
TD-1211	0.35
Alvimopan	>10
ADL 08-0011	0.08
Methylnaltrexone	>300
Naltrexone	15.4

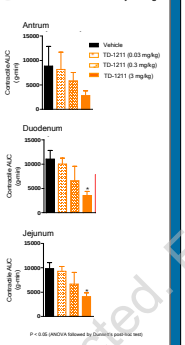
- Attenuation of loperamide-induced inhibition of diarrhea evoked by castor oil in rats



	Lowest oral dose (μg/kg) associated with ≥50% diarrhea
TD-1211	10
Alvimopan	30
ADL 08-0011	30
Methylnaltrexone	300
Naltrexone	IND

IND: Indeterminable due to non dose-related activity

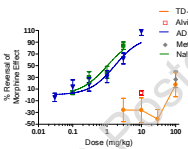
- Inhibition of loperamide-induced non-productive GI contractile activity in dogs



P < 0.05 (ANOVA followed by Dunnett's post-hoc test)

Results (3): TD-1211 inhibits morphine-induced CNS responses (anti-nociception, behavioral withdrawal or sedation) with low potency in rats and dogs following oral dosing

- Inhibition of morphine-induced anti-nociception in the rat hot-plate test

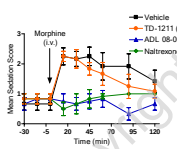


	Rat hot-plate ID_{50} (mg/kg)
TD-1211	>100
Alvimopan	>10
ADL 08-0011	1.7
Methylnaltrexone	>100
Naltrexone	1.0

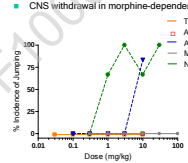
	Peripheral selectivity (rat gastric emptying and hot-plate ID_{50} ratio)
TD-1211	>278
Alvimopan	IND
ADL 08-0011	21
Methylnaltrexone	IND
Naltrexone	0.06

IND: Indeterminable

- Inhibition of morphine-induced sedation in dogs

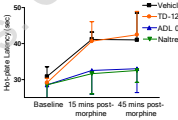


- CNS withdrawal in morphine-dependent mice



	Dose producing jumping behavior (mg/kg)
TD-1211	>10
Alvimopan	>10
ADL 08-0011	10
Methylnaltrexone	>100
Naltrexone	1

- Inhibition of morphine-induced anti-nociception in the dog hot-plate test



Conclusions

- TD-1211 is a potent, orally active, peripherally-selective μ-opioid receptor antagonist.
- TD-1211 has successfully completed Phase 1 single ascending and multiple ascending dose studies in healthy subjects.
- The efficacy, tolerability and pharmacokinetics of TD-1211 are currently being investigated in a Phase 2 study in OIC patients.

References

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Pappagallo, M. (2001). Am. J. Surgery, 182, 11S - 18S.

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