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 inhibition 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, naloxone and nalbuphine, to alleviate OIC has been demonstrated clinically. These agents readily cross the blood-brain barrier and can attenuate opioid-induced analgesia and provide a bowel-stimulant withdrawal syndrome (Pappagallo, 1997). Clinical data indicate that the peripherally-selective opioid receptor antagonists, alvimopan, ADL 08-0011 and naltrexone, attenuate OIC without impairing opioid analgesic effects (De Luca). Neither is suitable for the United States, but both are on clinical trials to assess their potential for OIC. Alvimopan (Relistor®) is marketed as a subcutaneous treatment for OIC in patients with advanced diseases who are receiving palliative care. Thirty minutes after oral ingestion of TD-1211, a novel opioid receptor antagonist currently in Phase 2 human clinical development in comparison to those of naloxone, alvimopan and methylnaltrexone. The profile of Alvimopan 0.01 mg/kg, primary, human, metabolite, (TD-1211) was also examined in the study.

Methods

The opioid receptor affinity (expressed as a pIC50 value) of test agents was determined using radioligand binding assays with [3H]diprenorphine and morphine prepared from Chinese hamster ovary cells stably transfected with human μ-opioid receptors (Opiate) or α2-adrenoceptors (AVP). Opiate receptor antagonist potency (expressed as a pIC50 value) was evaluated using electrically stimulated guinea pig ileum and transected rat ileum assays. Preparations were mounted in Lucite tissue baths. Concentration-response curves were obtained using a computerized data acquisition system (Medical System). The pIC50 values were corrected for the presence of non-specific binding, and the percentage of specific binding was calculated. In vivo evaluation of TD-1211 was performed in rats and dogs. The efficacy, tolerability and pharmacokinetics of TD-1211 are currently being investigated in a Phase 2 study in OIC patients.

Results

TD-1211 (3 mg/kg) was a potent, orally active, peripherally-selective μ-opioid receptor antagonist. 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 inhibitor of loperamide-induced reduction in gastric emptying and attenuation of castor oil-induced diarrhea. TD-1211 was less potent than naltrexone and ADL 08-0011 at inhibiting morphine-induced anti-nociception, but it was effective in reducing the morphine-induced CNS responses (anti-nociception, behavioral withdrawal or sedation) with low oral doses producing jumping >10 mg/kg, >10 mg/kg, 1 mg/kg 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 i.v.) produced a marked inhibition of the morphine-induced responses. 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, 1997). Clinical data indicate that the peripherally-selective opioid receptor antagonists, alvimopan, ADL 08-0011 and naltrexone, attenuate OIC without impairing opioid analgesic effects (De Luca). Neither is suitable for the United States, but both are on clinical trials to assess their potential for OIC. Alvimopan (Relistor®) is marketed as a subcutaneous treatment for OIC in patients with advanced diseases who are receiving palliative care. Thirty minutes after oral ingestion of TD-1211, a novel opioid receptor antagonist currently in Phase 2 human clinical development in comparison to those of naloxone, alvimopan and methylnaltrexone. The profile of Alvimopan 0.01 mg/kg, primary, human, metabolite, (TD-1211) was also examined in the study.

References