Peripheral opioid receptor antagonists: Pain relief without side effects

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ABSTRACT
Methylnaltrexone (MNTX) (by Progenics Pharmaceuticals)* was developed to antagonise the peripheral adverse effects of opiates while preserving centrally mediated analgesia. MNTX is currently being evaluated to prevent or treat opiate-induced inhibition of GI motility in advanced illness (AI), chronic pain, and postoperatively (postoperative ileus (POI)). MNTX is the quaternary derivative of the opioid antagonist naltrexone.1

In a preliminary randomised, double-blind, placebo-controlled study in human volunteers, the administration of small doses of morphine (3–5 mg) slowed GI transit, as measured by oral-cecal transit time, by 50%. These changes were reversed with MNTX (0.4 mg/kg IV) without influencing morphine-induced analgesia. In a subsequent human volunteer study, single oral doses of MNTX (ranging from 0.64 to 19.2 mg/kg) acted quite similarly.

Although the acute effects of opiates on GI motility proved to be completely reversible by MNTX, the efficacy of MNTX as a therapy in opiate-tolerant individuals represented a more complex problem of dose titration. To resolve this problem, a double-blind, placebo-controlled, randomised clinical trial was performed on 22 subjects undergoing chronic methadone maintenance therapy for addiction. Laxation occurred within one minute of injection of IV MNTX in all subjects without withdrawal.2 The GI motility of methadone maintenance patients was exquisitely sensitive to MNTX (five times more sensitive in the chronic opiate users than in naïve subjects). Similar effects were noted with oral MNTX in 12 methadone maintenance subjects but over five hours.3 After subcutaneous (sc) administration, changes in oral cecal transit time occurred over a period of about 15 minutes.4

While MNTX clearly worked in the setting of addiction, an important issue is whether response could be achieved in the setting of AI where co-morbidity is significant, and doses of opiates may be very high. A multi-institutional Phase 2b study of sc MNTX in 33 palliative care patients with opiate-induced constipation revealed dose-related laxation. More than 60% of the treated patients laxated, most within one hour, without significant side effects or any evidence of withdrawal.5 This was confirmed in a randomised double-blind placebo-controlled trial, in which 154 patients with AI received either a single sc dose of MNTX (0.15 or 0.3 mg/kg) or placebo with four weeks of open-label therapy.6 Sixty-two per cent laxated within four hours of their first drug injection vs 13% with placebo (p < 0.0001). Importantly, most patients responded within an hour of treatment, allowing a measure of predictability in these medically complex patients. In a second recently reported Phase 3 study of 133 AI patients, sc administration of MNTX induced laxation within four hours in 51.2% of severely constipated AI patients, more than three times the rate of placebo (15.5%), over a two-week period. For patients who responded to MNTX (0.15 mg/kg), median time to laxation was 30 minutes.

References
1. Yuan C-S. J Support Oncol 2004;2:111–22.
2. Yuan CS, Foss JF, O’Connor M, et al. JAMA 2000;283:367–72.
3. Yuan CS, Foss JF. JAMA 2000;284:1363–4.
4. Yuan CS, Wei G, Foss JF, et al. J Pharmacol Exp Ther 2002;300:118–23.
5. Thomas J, Potenoy R, Moelt M, et al. Proceedings of ASCO, 39th Annual Meeting, 2003.
6. Thomas J, Lipman AG, Slatkin N, et al. Proceedings of ASCO, 41st Annual Meeting, 2005.
7. Ho W-Z, Guo C-J, Yuan C-S, et al. J Pharmacol Exp Ther 2003;307:1158–62.
8. Singleton PA, Lingen MW, Fehste M, et al. Microvasc Res 2006;73:3–11.

*The author has patent interests in methylnaltrexone and serves as a consultant to Progenics Pharmaceuticals, which has acquired the license for its development.