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THE IDEAL OPIOID: IS OLICERIDINE THE ANSWER?

There is no ideal opioid available in present clinical practice. Characteristics of an ideal opioid should be rapid onset of action, short acting, minimal respiratory depression, least peripheral side effects like constipation, urinary retention and devoid of dependence or tolerance with chronic use. Morphine is the prototype opioid which is popularly used in acute and chronic pain management through intravenous, subcutaneous, intramuscular, intrathecal, epidural, and oral routes. The problems associated with its use are drowsiness, respiratory depression, constipation, urinary retention, tolerance, and dependence. Fentanyl, remifentanil, alfentanil are short acting opioids effective in the form of intravenous infusion or boluses. All opioids have a side effect profile similar to morphine.

β-arrestin 1 and β-arrestin 2 are adaptor and signal transduction proteins which are responsible for desensitization and internalization of G-protein coupled receptors thereby helping in molecular regulation. They are expressed in the neuronal tissues.

The β-arrestin mediated regulation is responsible for cell growth, apoptosis, chronic injury related deposition of extracellular matrix, activation of inflammatory cascade and development of fibrotic diseases.[1] Opioid receptor agonism results in the recruitment of β-arrestin 2 proteins which is responsible for the side effects frequently observed with morphine and other μ-agonists when used in the perioperative period and during the management of chronic cancer or non-cancer pain.[2] The postoperative side effects like constipation is undesirable and causes a lot of discomfort to patient. Peripherally acting μ-receptor antagonists like alvimopan and methylnaltrexone are available and are approved to reverse these side effects to facilitate bowel function. They do not cross blood-brain barrier and therefore antagonises the systemic effects produced peripherally without affecting the pain relief.[3] However, the peripherally acting opioid antagonists are very costly and also involve a lot of formalities to procure and for regular use. Therefore a μ-agonist which acts only by providing analgesia without having peripheral effects and without recruiting β-arrestins are the opioids which can be considered ideal for postoperative pain management. Recent pharmacological research has revealed a lot of other potential therapeutic benefits conferred due to β-arrestin inhibition in diseases like leukemia, cirrhosis, fibrosis involving cardiovascular system, kidney, intestines, myelofibrosis and multiple sclerosis.[4]

Oliceridine (TRV130) is being developed with the intention to optimise opioid receptor pharmacology so as to have a better analgesic efficacy with lesser adverse effects and can be used in moderate to severe acute post-operative pain. It is a μ-receptor G protein pathway selective modulator (μGPS). The drug was referred to as a breakthrough therapy by the USFDA for its use in moderate to severe postoperative pain when used intravenously.[5] As oliceridine has a better peripheral side effect profile compared to morphine and also has a lesser propensity for tolerance or dependence due to its β-arrestin 2 inhibition, it might be the ideal opioid we were waiting for so long. Once oliceridine gets approved for acute postoperative pain, the routinely encountered side effects due the presently available μ-agonist will take a backseat thereby hastening the recovery of the patient with better quality of analgesia.

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REFERENCES

1. Yang CH, Huang HW, Chen KH, et al.: Antinociceptive potentiation and attenuation of tolerance by intrathecal β-arrestin 2 small interfering RNA in rats. *Br J Anaesth.* 2011; 107(5):774-781.

2. Hales TG: Arresting the development of morphine tolerance and dependence. *Br J Anaesth.* 2011; 107(5): 653-655.

3. Kraft MD: Emerging pharmacologic options for treating postoperative ileus. *Am J Health Syst Pharm.* 2007; 64(20 Suppl 13): S13-S20.

4. Groer CE, Tidgewell K, Moyer RA, et al.: An opioid agonist that does not induce mu-opioid receptor β-arrestin interactions or receptor internalization. *Mol Pharmacol.* 2007; 71(2): 549-557.

5. Trevena Inc.: Trevena reports third quarters 2015 financial results and provides corporate update. Nov 10, 2015. Available at: *www.trevenainc.com/news-details.php?id=126.* Accessed April 8, 2016.