Approval of oliceridine (TRV130) for intravenous use in moderate to severe pain in adults

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Editor—Opioids used for the treatment of moderate to severe pain in an appropriate setting with appropriate management (stewardship) have good efficacy. However, when these are used long term their efficacy is questionable. Tolerance develops leading to escalating doses and a vicious circle of side-effects.[1] These side-effects include respiratory depression and immune suppression; both are relevant in the coronavirus disease 2019 (COVID-19) pandemic.[2] Design and evaluation of analgesics with reduced side-effect profiles is an important goal; where these side-effects include addiction, this approach can also address the opioid crisis.[3]

Opioid receptors signal via a number of pathways[4] including G-protein and β-arrestin pathways. Seminal animal work indicates that β-arrestin gene (and hence protein) knock out facilitates opioid analgesia devoid of side-effects.[5,6] Ligand bias or functional selectivity is the principle that allows a drug to activate one pathway over another selectively, or to produce bias. Therefore, opioids that bias towards G-protein and away from β-arrestin signalling should produce analgesia with reduced side-effects.[4] That said, partial agonists (drugs with reduced efficacy) have the potential to produce similar effects where G-protein-driven transduction represents an amplified signal and β-arrestin recruitment does not. Consider the partial agonist buprenorphine as an example[7]; efficacy for inhibition of G-protein-driven cyclic adenosine monophosphate (a second messenger) formation is seen but there is no/reduced recruitment of β-arrestin.[8] This profile is seen as beneficial in reducing its side-effect profile.

There has been much pharmacological development in the design of biased ligands for the μ-opioid peptide (MOP) receptor, the main clinical target for opioid analgesics. The ligand with most advanced development is TRV130 (also named oliceridine),[9] but there are others at various stages, such as SR17018[10] and PZM21.[11] There has been growing interest in PZM21 as a biased MOP receptor agonist; whilst there are no clinical data, there are non-human primate data showing that laboratory bias does not translate to *in vivo* advantage in this species.[12]

In late 2018, Trevena® was narrowly (eight against: seven for) refused US Food and Drug Administration (FDA) approval for oliceridine (TRV130), but after resubmission the FDA recently approved this new opioid (trade name Olinvyk™) for short-term i.v. use in 'hospitals and other controlled settings'.[13] Restriction from use at home reduces the impact of another opioid on the current opioid crisis. In the prescribing information leaflet,[14] Olinvyk™ is described as 'a full opioid agonist and is relatively selective for the mu-opioid receptor …. there is no ceiling effect to analgesia. The precise mechanism of the analgesic action is unknown'. Clinical description is based largely, but not exclusively, on two Phase 3 clinical studies of oliceridine.

APOLLO-1[15] showed oliceridine analgesia in 389 bunionectomy patients at 0.1, 0.35, and 0.5 mg patient-controlled analgesia (PCA) demand doses (loading dose 1.5 mg). Analgesia was rapid in onset and at the two higher doses non-inferior to 1 mg morphine PCA demand dose (loading dose 4 mg). Respiratory compromise measured as a composite respiratory safety burden was dose-dependent for oliceridine and not significantly different from morphine. This finding is in contrast with an earlier Phase 2 study in acute postoperative pain where ventilatory frequency, respiratory effort, and hypoxaemia were improved compared with morphine.[16] Further analysis of the components of respiratory safety burden in APOLLO-1 showed that 0.1 and 0.35 mg doses were less likely to produce respiratory safety events compared with morphine. Like other opioids, nausea and vomiting were observed, but use of a rescue antiemetic was lower in the oliceridine than in the morphine group. Discontinuation because of side-effects was less frequent with oliceridine than morphine.

APOLLO-2[17] showed that in 401 abdominoplasty patients, also with a loading dose, oliceridine 0.1, 0.35 and 0. 5 mg PCA demand doses were analgesic with the two higher doses equianalgesic to morphine 1 mg. Respiratory safety burden was similarly dose-dependent, but unlike morphine was not significantly different from placebo. Adverse gastrointestinal events were observed with oliceridine and there were fewer oliceridine-treated patients requiring rescue. Overall, oliceridine (Olinvyk™) produces analgesia with a favourable safety and tolerability profile compared with morphine. In a recent paper, Dahan and colleagues[18] proposed a 'utility function' derived from a pharmacokinetic-pharmacodynamic analysis of analgesia and respiratory depression in healthy male volunteers exposed to oliceridine and morphine; a positive value indicated analgesia was more likely than respiratory depression and a negative value indicated the reverse. In a reanalysis of the APOLLO cohorts, oliceridine utility function was positive while that of morphine was negative (both in the clinical concentration range) indicating that analgesia is more likely for oliceridine over respiratory depression.

One feature most of the currently described MOP biased agonists have in common is that they are partial agonists *in vitro*. There is an excellent detailed and systematic analysis of this for oliceridine, SR17018, and PZM21, in which this low intrinsic efficacy is proposed to explain a reduced side-effect profile.[19] Whether Olinvyk™ is a biased or partial agonist

(evidence is strong for the latter) is immaterial if it provides good analgesic efficacy with a favourable side-effect profile in the clinic. Further evaluation of this and similar ligands may clarify this uncertainty. Our view is that bias at the MOP receptor is debatable as a simple pharmacological descriptor as a partial agonist is sufficient in this case.

Declarations of interest

DGL is chair of the board of the *British Journal of Anaesthesia*. GC declares he has no conflicts of interest.

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