Cebranopadol: a first in-class example of a nociceptin/orphanin FQ receptor and opioid receptor agonist

D. G. Lambert*, M. F. Bird and D. J. Rowbotham

Department of Cardiovascular Sciences, Division of Anaesthesia, Critical Care and Pain Management, University of Leicester, Leicester Royal Infirmary, Robert Kilpatrick Clinical Sciences Building, Leicester LE2 7LX, UK

* E-mail: dgl3@le.ac.uk

Nociceptin/orphanin FQ (N/OFQ) is the endogenous peptide agonist for the N/OFQ receptor (NOP).1 NOP is classified as a non-classical member of the opioid family as it shares structural and transduction homology and anatomical localization with the classical µ-opioid receptor (MOP), δ-opioid receptor (DOP), and κ-opioid receptor. However, its actions are not sensitive to the universal opioid antagonist naloxone.2 This peptidergic receptor system has been implicated in the physiology and pathophysiology of anxiety/depression, learning/memory, feeding, airway disease, immune dysfunction, gastrointestinal motility, urological disease, and pain.3 Modulation of activity at this receptor produces variable effects on the nociceptive (pain) response in laboratory animals, with N/OFQ and NOP agonists in general producing antinociception when given spinally and pro-nociceptive/anti-opioid actions when administered supraspinally in rodents. Spinal administration of N/OFQ or NOP agonists also produces antinociception in non-human primates.1,3 The link to the clinic, as is often the case, revolves around discovery and evaluation of novel chemical entities: the pharmaceutical pipeline. The N/OFQ–NOP system is no exception in this regard. Indeed, in 2004, one of us (D.G.L.) wrote an editorial ‘Nociceptin/Orphanin FQ peptide receptor system; are we any nearer the clinic?’.4 At that time, there were some limited studies in urology examining intravesical in-}
potent than the gold standard morphine. Pharmacokinetic analysis in the rat shows rapid absorption and widespread distribution, with oral bioavailability of 13–23%. Tolerance to opioids is a particularly troublesome side-effect that leads to dose escalation. Dose escalation per se leads to increased tolerance and a vicious cycle ensues.13 There is good evidence that mixed opioids might be beneficial in this regard, with data showing morphine tolerance is reduced in the rat, tolerance to morphine develops quickly; in contrast, an equi-analgesic dose of cebranopadol (only 0.8 μg kg⁻¹ i.p. daily) was still effective for a further 15 days, or 26 days in total. For the N/OFQ–NOP system, evidence suggests that NOP antagonism reduces tolerance to morphine,18 19 while NOP activation reduces the manifestations of drug dependence.20 21 This is at variance with data for cebranopadol, but it should be remembered that these studies modulated NOP and MOP simultaneously with two discrete ligands. Typical opioid-induced side-effects include loss of motor co-ordination and respiratory depression. In the rotarod test for motor co-ordination, i.v. doses of cebranopadol that were analgesic were ineffective; morphine (i.v.) at analgesic doses profoundly affected motor co-ordination. Using whole-body plethysmography to assess respiratory function, i.v. doses of cebranopadol that were analgesic produced a transient increase in respiratory rate and tidal volume, while morphine (s.c.) produced a profound depression of respiration.

Cebranopadol Clinical development

Cebranopadol is currently being co-developed globally by Grünenthal and Forest Research Institute, Inc. Excluding phase I first in man, publicly available clinical trial databases indicate that there are six completed and one ongoing phase II trials and one ongoing phase III trial in cancer pain (Table 1). All of these studies appear to be based on the preclinical profile already published. The scientific and patient community eagerly await the results of these trials.

To return to our 2004 editorial—are we any nearer the clinic? Ten years on and the answer would seem to be a definite yes with cebranopadol representing a first in class NOP receptor and opioid receptor agonist.

Authors’ contributions

D.G.L., D.J.R., and M.F.B. researched material and wrote the editorial.

Declaration of interest

D.G.L. held a consultancy with Grunenthal GmbH and is a board member and administration director of British Journal of Anaesthesia. D.J.R. is a board member and director of British Journal of Anaesthesia. M.F.B. is a recipient of a PhD studentship funded by British Journal of Anaesthesia and Royal College of Anaesthetists.

References

The third ultrasound dimension in anaesthesia and intensive care

A. Ng1* and J. Swanevelder2

1 Heart and Lung Centre, Royal Wolverhampton Hospital NHS Trust, Wolverhampton, West Midlands WV10 0QP, UK
2 Department of Anaesthesia, Groote Schuur and Red Cross War Memorial Children’s Hospitals, University of Cape Town Medical School, Anzio Road, Observatory 7925 Cape Town, South Africa
* Corresponding author. E-mail: ang@nhs.net

The use of perioperative echocardiography is well established in cardiac and non-cardiac practice. It is indicated for monitoring patients at risk of haemodynamic complications, and also in rescue situations when there may be cardiovascular instability. There have been advances in transoesophageal transducer technology, specifically the matrix array transducer, which has enabled the acquisition of three-dimensional (3D) images in real time. Standardization of the diagnostic use of 3D echocardiography has been recommended by officials on both sides of the Atlantic. Increasingly complex perioperative applications of 3D echocardiography are also becoming established for cardiac surgery and in the catheter laboratory. There is now a growing expectation that anaesthetists should be able to obtain accurate clinical measurements to guide decisions in these situations. This editorial explores the additional 3D data that could be potentially valuable, over and above standard two-dimensional (2D) ultrasound images.

In current practice, we are required to provide measurements of length, area, and volume of a cardiac structure. Using 2D imaging by a standard phased array transducer, it is possible to obtain cross-sectional images so that the length and area of a structure are measurable in the specific planes, obtained at the time of ultrasound scanning. Often, several 2D images are required. Volumetric estimations have to be calculated from geometric assumptions originating from measurements of length and area. Since the development and miniaturization of the matrix array transducer, a pyramidal data set of a cardiac structure may be obtained from the...