EDITORIAL

Spinal Neuropharmacological Agents for the Management of Pain

Rui V. Duarte[1,*], Jon H. Raphael[2] and Sam Eldabe [3]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK; [2]Faculty of Health, Birmingham City University, Birmingham, UK; [3]Department of Pain and Anaesthesia, The James Cook University Hospital, Middlesbrough, UK

Spinal neuropharmacological agents have been widely used for the management of chronic pain since the discovery of opiate receptors in the spinal cord. Within the spinal cord, opiate receptors are localized in an area corresponding to the substantia gelatinosa, which is a first site for the integration of sensory information in the central nervous system [1]. Medications delivered directly into the spinal space, namely the intrathecal space bypass the blood brain barrier and theoretically should provide better analgesic efficacy without the adverse effects that accompany systemic administration of these composites [2]. Spinal opioids act on the substantia gelatinosa of the dorsal horn causing both pre-synaptic and post-synaptic inhibition of primary afferent transmission [3]. The analgesic effect of morphine when administered at the spinal level was first demonstrated in 1976 in animal studies [4]. Prior to this investigation it was believed that narcotic analgesia was mediated by the action of a drug on a supraspinal level. The clinical application of these discoveries was demonstrated when spinally administered opioids were used to manage cancer pain successfully [5].

Subsequent use of adjuvant analgesics: bupivacaine and clonidine appeared to improve clinical efficacy and the development of the novel analgesic ziconotide limited to intrathecal use maintained a need for technological intrathecal delivery. The long term management of chronic non-cancer pain and many cases of cancer pain using spinally administered drugs is conducted *via* implantable intrathecal drug delivery (ITDD) systems. There is evidence supporting the use of ITDD for chronic non-cancer pain [6, 7], cancer pain [8, 9] and spasticity [10, 11]. However, the value of this technology for the management chronic non-cancer pain is not consensual. In the United Kingdom, the British Pain Society working group considered that there is mounting evidence of the effectiveness of ITDD in patients with chronic non-cancer pain [12, 13]. NHS England has recently decommissioned ITDD for severe chronic non-cancer pain as it was considered that there was insufficient evidence to support routine commissioning [14]. The decision was based on clinical and economic studies available. Although there is an obvious need for a good quality randomised controlled trial with a nested economic evaluation of ITDD using opioids for patients with chronic non-cancer pain, purchasers and regulators should recognise and appreciate the considerable clinical, cost and regulatory hurdles of attempting to conduct randomised controlled trials on a drug therapy of last resort in the management of chronic pain. Moreover, for the purposes of adequate decision-making, the best studies currently available should be selected, and their usefulness and limitations correctly interpreted. Currently, in the UK access to patients with non-cancer pain that can potentially benefit from ITDD is denied.

This thematic issue assumes therefore additional importance by focusing on advances in spinal neuropharmacological agents for the management of chronic non-cancer pain.

Moore and McCrory present the first review investigating proteomic changes associated with intrathecal morphine, hydromorphone, fentanyl, bupivicaine, methyprednisolone, baclofen, clonidine, and ziconotide [15]. This review discusses common proteomic pathways associated with the initiation and maintenance of neuropathic pain, and the mechanism of action of intrathecal analgesics.

The review by Pope and colleagues discusses the pharmacology, safety and efficacy of commonly used intrathecal agents for the management of chronic non-cancer pain providing important information to consider for medication selection, taking into account the physiochemical properties of these agents [16].

Brookes *et al*. conducted the first systematic review of randomised controlled trials evaluating the effectiveness of ziconotide monotherapy for the management of chronic neuropathic pain [17]. The pooled effect from the meta-analysis was statistically significant demonstrating that intrathecal ziconotide as a monotherapy was superior to placebo for the management of patients with chronic neuropathic pain.

Yaksh and colleagues present a comprehensive assessment as to the state of the art of spinal agents [18]. This review not only provides information on the mechanism of action, drug molecules, adverse events and future directions of current spinal agents but also gives indications about novel approaches to modify the function of systems that process nociceptive information and future issues of intrathecal delivery.

1875-6190/17 $58.00+.00

We expect this special issue to be of great interest to the clinical and scientific community, opening new directions for the adequate management of chronic non-cancer pain.

REFERENCES

[1] Snyder, S.H. Opiate receptors in the brain. *N. Engl. J. Med.*, **1977**, *296*, 266-271.

[2] Raphael, J.H.; Grady, K. Intrathecal drug delivery. In: *Clinical Pain Management: Practice and Procedures*, 2nd ed.; Rice, A.S.C., Ed.; Hodder and Arnold: London, **2008**; pp. 370-379.

[3] Cousins, M.J.; Mather, L.E. Intrathecal and epidural administration of opioids. *Anesthesiology*, **1984**, *61*, 276-310.

[4] Yaksh, T.; Rudy, T. Analgesia mediated by a direct spinal action of narcotics. *Science*, **1976**, *192*, 1357-1358.

[5] Wang, J.K.; Nauss, L.A.; Thomas, J.E. Pain relief by intrathecally applied morphine in man. *Anesthesiology*, **1979**, *50*, 149-151.

[6] Duarte, R.V.; Raphael, J.H.; Sparkes, E.; Southall, J.L.; LeMarchand, K.; Ashford, R.L. Long-term intrathecal drug administration for chronic nonmalignant pain. *J. Neurosurg. Anesthesiol.*, **2012**, *24*, 63-70.

[7] Raphael, J.H.; Duarte, R.V.; Southall, J.L.; Nightingale, P.; Kitas, G.D. Randomised, double-blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain. *BMJ Open*, **2013**, *3*, e003061.

[8] Ballantyne, J.C.; Carwood, C.M. Comparative efficacy of epidural, subarachnoid, and intra cerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst. Rev.*, **2005**, (1), CD005178.

[9] Smith, T.J.; Staats, P.S.; Deer, T.; Stearns, L.J.; Rauck, R.L.; Boortz-Marx, R.L.; Buchser, E.; Català, E.; Bryce, D.A.; Coyne, P.J.; Pool, G.E.; Implantable Drug Delivery Systems Study Group. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J. Clin. Oncol.*, **2002**, *20*, 4040-4049.

[10] Coffey, J.R.; Cahill, D.; Steers, W.; Park, T.S.; Ordia, J.; Meythaler, J.; Herman, R.; Shetter, A.G.; Levy, R.; Gill, B. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. *J. Neurosurg.*, **1993**, *78*, 226-232.

[11] Narendran, R.C.; Duarte, R.V.; Valyi, A.; Eldabe, S. The need for and provision of intrathecal baclofen therapy for the management of spasticity in England: an assessment of the Hospital Episode Statistics database. *BMJ Open*, **2015**, *5*, e007517.

[12] Eldabe, S.; Duarte, R.; Raphael, J.; Thomson, S.; Bojanic, S. *Intrathecal Drug Delivery for the Management of Pain and Spasticity in Adults; Recommendations for Best Clinical Practice*. British Pain Society: London, **2015**.

[13] Duarte, R.; Raphael, J.; Eldabe, S. Intrathecal drug delivery for the management of pain and spasticity in adults: an executive summary of the British Pain Society's recommendations for best clinical practice. *Br. J. Pain*, **2016**, *10*, 67-69.

[14] NHS England. Clinical Commissioning Policy: Intrathecal Pumps for Treatment of Severe Cancer Pain [online]. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d08pb-intra-pumps-trtmnt.pdf (Assessed February 1, **2016**).

[15] Moore, D.M.; McCrory, C. The proteomics of intrathecal analgesic agents for chronic pain. *Curr. Neuropharmacol.*, **2017**, *15*, 198-205.

[16] Pope, J.E.; Deer, T.R.; Amirdelfan, K.; McRoberts, W.P.; Azeem, N. The pharmacology of spinal opioids and ziconotide for the treatment of non-cancer pain. *Curr. Neuropharmacol.*, **2017**, *15,* 206-216.

[17] Brookes, M.E.; Eldabe, S.; Batterham, A. Ziconotide monotherapy: a systematic review of randomised controlled trials. *Curr. Neuropharmacol.*, **2017**, *15*, 217-231.

[18] Yaksh, T.L.; Fisher, C.; Hockman, T.; Wiese, A. Current and Future Issues in the development of spinal agents for the management of pain. *Curr. Neuropharmacol.*, **2017**, *15,* 232-259.

Dr. Rui Duarte
(Guest Editor)
Research Fellow
University of Birmingham
Institute of Applied Health Research
Room 124, Learning Centre
Edgbaston, Birmingham
West Midlands
B15 2TT
Tel: +44 (0) 121 414 7784
E-mail: ruivduarte@gmail.com