Scandinavian Journal of Pain 10 (2016) 90–102

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Original experimental

Analgesic properties of intrathecal glucocorticoids in three well established preclinical pain models

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HIGHLIGHTS

- Efficacy of intrathecal glucocorticoids in neuropathic pain patients is debated.
- Intrathecal methylprednisolone on pain-like behaviour is studied in 3 pain models.
- Generalized allodynia is observed after high intrathecal methylprednisolone doses.
- Intrathecal methylprednisolone has no effect upon inflammatory or nerve pain.
- Our results do not support use of intrathecal methylprednisolone in pain treatment.

ARTICLE INFO

Article history:
Received 19 July 2015
Received in revised form 14 October 2015
Accepted 15 October 2015
Available online 20 November 2015

Keywords:
Methylprednisolone
Efficacy
Intrathecal
Neuropathic pain
Rats

ABSTRACT

Background and aims: Glucocorticoids, a group of anti-inflammatory agents, are frequently administered in pain medicine. Of interest is the reported activity after intrathecal delivery in patients with neuropathic pain syndromes such as postherpetic neuralgia, though its efficacy is controversial. After the publication of two randomized clinical trials in postherpetic neuralgia patients treated with similar intrathecal methylprednisolone acetate (MPA) dosing regimes with conflicting results; one showing significant pain reduction (Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, Asai M, Matsuki A: Intrathecal methylprednisolone for intractable postherpetic neuralgia. N Engl J Med 2000;23: 1514–9), the other increased pain sensations (Rijsdijk M, van Wijck AJ, Meulenhoff PC, Kavelaars A, van der Tweel I, Kalkman CJ: No beneficial effect of intrathecal methylprednisolone acetate in postherpetic neuralgia patients. Eur J Pain 2013;38: 175–200), we decided additional research was warranted. Present study sought to determine effects of intrathecally delivered methylprednisolone on pain-like behaviour and pain-associated markers in three well established rodent pain models: (1) intraplantar carrageenan, (2) intraplantar formalin, and (3) ligation of L5/L6 spinal nerves (SNL model).
Methods: Male rats with intrathecal catheters were examined for (1) tactile allodynia after unilateral hindpaw intraplantar carrageenan injection (2%), (2) flinching and subsequent long term tactile allodynia after unilateral hindpaw intraplantar formalin injection (2.5%) or (3) tactile allodynia after unilateral ligation of the L5 and L6 spinal nerves. Rats were treated with the maximum tolerable intrathecal dose of the soluble methylprednisolone sodium succinate (MP) or the particulate methylprednisolone acetate (MPA). Dorsal root ganglia and spinal cords were harvested for immunohistochemistry to assess markers of neuronal damage (ATF3) and glial activation (GFAP, Iba1).
Results: During dose finding, severe generalized allodynia was observed with high intrathecal doses of both MPA and MP in naive rats. MPA had no effect upon tactile allodynia after carrageenan. MP and MPA did not reverse tactile allodynia in the SNL model, and did not reduce flinching in the formalin model. MP and MPA prevented the delayed (7-day) tactile allodynia otherwise observed in the formalin-injected paw. Systemic MP or perineural MP or MPA did not reduce pain-like behaviour in the SNL model. No reduction of neuronal injury (ATF3) in the dorsal root ganglion or astrocyte activation (GFAP) in the spinal dorsal horn with intrathecal MP or MPA was observed. There was a decrease in microglial activation (Iba1) in the spinal dorsal horn with MPA after SNL.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2015.10.007.
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http://dx.doi.org/10.1016/j.sjpain.2015.10.006

Conclusion: Severe generalized allodynia was observed after high intrathecal doses of MP and MPA in naive rats. No acute analgesic effects with intrathecal glucocorticoids were observed in three well established pain models. Only a late antiallodynic effect was present in the formalin model, 7 days after formalin injection and drug treatment.
Implications: Our results do not support use of intrathecal methylprednisolone in the treatment of pain.

1. Introduction

Glucocorticoids, a group of anti-inflammatory agents, are frequently administered in pain medicine. Of interest is the reported activity after neuraxial (epidural and intrathecal) delivery in patients with low back pain and in patients with neuropathic pain syndromes such as postherpetic neuralgia and complex regional pain syndrome [1–4], though their efficacy is controversial [5–8]. This controversy is surprising, given that glucocorticoids act upon a variety of crucial biological links in the neuraxial pathways after inflammation and nerve injury leading to hyperpathic states [9]. Glucocorticoids can act through transrepression of pro-inflammatory genes (interacting with activator protein-1 and nuclear factor kappa B (NFκB)), transactivation of anti-inflammatory genes (lipocortin I, p11/calpactin-binding protein) and nongenomic effects (interacting with G-protein coupled receptors, mitogen-activated protein (MAP) kinases, phosholipases and protein kinases (SRC)), to down regulate inflammatory processes [10], leading to a reduced production and secretion of inflammatory products such as cyclooxygenase-2, interleukin (IL)-1β, IL-2, IL-6, IL-8, tumour necrosis factor (TNF), interferon-gamma, and inducible nitric oxide synthase [11,12]. These effector products are considered to be important components in neuropathic pain signalling. If these neuroinflammatory products are indeed reduced, it is not clear why the analgesic effects of glucocorticoids are varying and often disappointing.

Our research team encountered disappointing analgesic effects with glucocorticoids in a randomized controlled clinical trial conducted in patients suffering from postherpetic neuralgia [4]. Four intrathecal injections with methylprednisolone acetate (MPA) with 7 day intervals were administered in patients with intractable neuropathic pain. Patients treated with intrathecal MPA reported increased pain and with statistical evidence of futility, the trial was ended early. Our results were in sharp contrast with results of an earlier trial with a similar drug and dosing regime, showing pain reduction in 92% of patients in the intrathecal MPA treated group [13]. Since we did not understand the differences in results between the two trials, we decided to conduct a preclinical study using a similar MPA formulation. Additional to (i) the MPA formulation, a suspension with depot characteristics and reduced preservative concentrations, we also studied (ii) methylprednisolone sodium succinate (MP), a solution without preservatives, both frequently used in pain medicine.

We argued that since the aetiology of postherpetic neuralgia is not clear and we were interested to see if intrathecally delivered MPA had any effect on pain like behaviour and surrogate markers in a severe pain state, we should study the efficacy of glucocorticoids in multiple models inducing pain like behaviour with; (i) an inflammatory, (ii) a neurotoxic, and (iii) a direct nerve injury stimulus.

Three well established preclinical pain models in rats were selected: (i) intraplantar carrageenan leading to a robust inflammation and tactile allodynia of the injected paw [14]; (ii) intraplantar formalin leading to a biphasic flinching behaviour acutely after injection and an evolving tactile allodynia that develops over the ensuing 7 days [15,16]; (iii) unilateral ligation of the L5/6 spinal nerves (SNL model) yielding a unilateral mononeuropathy characterized by a robust tactile allodynia [17]. We further examined the effects of glucocorticoids on the expression of well characterized markers including activation transcription factor 3 (ATF3) in the dorsal root ganglion (DRG) and induced astrocyte (glial fibrillary acidic protein (GFAP)) and microglia activation (ionized calcium-binding adapter molecule 1 (Iba1)) in the spinal dorsal horn. ATF3 is upregulated in injured DRG neurons after peripheral nerve injury and has a survival function driving neurite outgrowth [18]. Glial cells are activated by cytokines such as IL-1β, IL-6, TNFα and monocyte chemoattractant protein (MCP)-1 produced through MAP kinases (p38 and SRC-family kinases) phosphorylation and NFκB activation. We hypothesized that intrathecal glucocorticoids would reverse the hyperpathic states and the indices of DRG and dorsal horn neuroinflammation.

2. Methods

The protocol of the present study has been approved by the AAALAC accredited (International, Association for Assessment and Accreditation of Laboratory Animal Care) Institutional Animal Care and Use Committee (IACUC) of the University of California, San Diego, USA.

2.1. Animals

Male Harlan Sprague-Dawley rats (200–225 g for the carrageenan and 80–100 g for the SNL model) and male Holtzman rats (200–225 g for the formalin model) (Indianapolis, IN, USA) were maintained 2 per cage in standard cages at room temperature on a 12:12 h light/dark cycle with free access to food and water. After arrival at the housing facility, they were allowed at least 2–3 days of acclimation before use.

2.2. Drug administration

In all three pain models rats received intrathecal drug treatment. Only in the SNL model, additional groups of rats received intraperitoneal or perineural drug treatment;

(A) For intrathecal drug injections, rats were surgically implanted with intrathecal catheters as described previously under general anaesthesia (inhalation of isoflurane 2.4% in a room air/oxygen mixture) [19]. Intrathecal catheters were externalized for injection. Rats were given post-operative subcutaneous fluids including analgesics (lactated Ringers + 5 mg/kg Carprofen) and then housed individually for post-operative recovery. Following implantation, catheters were flushed with saline and rats were monitored daily for viability, allowing at least 5 days of recovery before testing. Animals showing any evidence of motor dysfunction or distress after catheter placement were immediately euthanized in a carbon dioxide chamber.
(B) Intraperitoneal drug injections were performed in awake rats. The injection was given in the lower left abdominal quadrant. Injection of the drug was preceded by careful aspiration to determine correct placement of the needle tip.