European Journal of Pharmacology 814 (2017) 302–312

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Gabapentin and its salicylaldehyde derivative alleviate allodynia and hypoalgesia in a cisplatin-induced neuropathic pain model

Nisar Ahmad[a], Fazal Subhan[a,*], Nazar Ul Islam[b], Muhammad Shahid[a,b], Faiz Ur Rahman[c], Robert D.E. Sewell[d]

[a] Department of Pharmacy, University of Peshawar, Peshawar 25120, Khyber Pakhtunkhwa, Pakistan
[b] Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar, Pakistan
[c] Department of Chemistry, Fudan University, Shanghai, China
[d] Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff CF10 3NB, UK

ARTICLE INFO

Chemical compounds studied in this article:
Gabapentin (PubChem CID: 3446)
Salicylaldehyde (PubChem CID: 6998)

Keywords:
Chemotherapy-induced neuropathic pain
Peripheral neuropathic pain
Gabapentsal
Motor incoordination
Rat neuropathic pain model
Thermal hypoalgesia

ABSTRACT

Cisplatin is an effective chemotherapeutic agent indicated in cancer chemotherapy. However, its clinical use is associated with peripheral neuropathy that invariably impairs patient quality of life. Gabapentin (GBP) is an effective analgesic for neuropathic pain conditions but its clinical efficacy in cisplatin-induced neuropathic pain (CINP) is limited, in addition to generating unwanted side-effects. In this study, a gabapentin-salicylaldehyde derivative [gabapentsal (GPS)] was synthesized and evaluated to explore any potential benefit in comparison with GBP in a rat model of CIPN. Administration of cisplatin (3.0 mg/kg/week, i.p.) for five consecutive weeks generated reproducible mechanical-allodynia (decreased paw withdrawal threshold to von Frey filament application; PWT, g) and thermal hypoalgesia (increased nociceptive reaction latency in the hot plate paradigm; s). Treatment with GBP or its derivative on the 37th day of the experimental protocol, dose dependently attenuated cisplatin-induced nocifensive behaviors. Accordingly, doses of GBP (50–100 mg/kg, i.p.) and GPS (25–100 mg/kg, i.p.) suppressed the expression of CINP by normalizing the PWT and hot plate response latency 1 h and 3 h post administration. In the rotarod paradigm, GBP at all doses markedly impaired motor performance, whilst GPS was devoid of motor incoordination except at the highest dose, when a mild impairment occurred. Salicylaldehyde alone had no effect on CINP or rotarod performance and neither was there any synergism when coadministered with GBP. These findings suggest that both GBP and GPS have beneficial effects in the neuropathic pain model though GPS may be potentially more useful in the management of CINP.

1. Introduction

The clinical use of anticancer agents is associated with a number of unwanted side effects including neuropathic pain, which is intolerable for the majority of patients (Markman, 2006; Stillman and Cata, 2006; Van Cutsem and Arends, 2005). These adverse effects are dose-dependent and reduce the therapeutic outcome of chemotherapeutic agents worsening patient quality of life (Ocean and Vahdat, 2004; Warner, 1995). Cisplatin and its analogues (oxaliplatin and carboplatin) are used clinically world-wide as a first-line treatment alone or in combination with other antineoplastic agents for malignant tumors including for example, those associated with lung, breast and colorectal cancer (He et al., 2016; Lynch et al., 2012; Marschner et al., 2015; Zhang et al., 2015). The neuropathy caused by cisplatin may persist for years (Chaudhry et al., 2003; Markman, 2003). In addition, approximately 20% of patients are unable to complete their course of treatment due to the intolerable neuropathic pain arising from the use of antineoplastic agents. The neuropathy caused by such drugs is managed by reduction of the cumulative dose, individual doses or sometimes by complete cessation of chemotherapy upon the appearance of neuropathic symptoms (Ocean and Vahdat, 2004).

Despite cisplatin combined treatment with a variety of drugs including calcium and magnesium infusions, amifostine, antioxidants (glutathione, vitamin E, α-lipoic acid and *N*-acetylcysteine) and anticonvulsant or antidepressant drugs (carbamazepine, lamotrigine, gabapentin, pregabalin or venlafaxine, duloxetine), clinical outcomes have not been totally satisfactory (Albers et al., 2014; Cavaletti and Marmiroli, 2010; Kaley and DeAngelis, 2009). There is therefore a need for an effective treatment to prevent or limit the occurrence and severity of chemotherapy-induced peripheral neuropathy.

* Corresponding author.
E-mail addresses: nisarahmadsatal@yahoo.com (N. Ahmad), fazal_subhan@upesh.edu.pk (F. Subhan), islanaz@yahoo.com (N.U. Islam), shahidsalim_2002@hotmail.com (M. Shahid), faizurrahman@fudan.edu.cn (F.U. Rahman), sewell@cardiff.ac.uk (R.D.E. Sewell).

http://dx.doi.org/10.1016/j.ejphar.2017.08.040
Received 8 May 2017; Received in revised form 3 August 2017; Accepted 24 August 2017
Available online 01 September 2017
0014-2999/

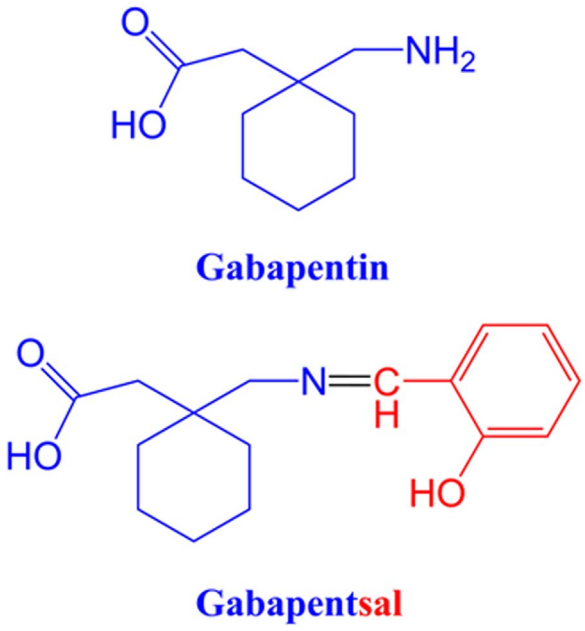

Fig. 1. Chemical structures of gabapentin and gabapentsal.

Gabapentin (Fig. 1) was first approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in 1993 as an oral add-on therapy for the treatment of partial seizures and later in 2000 for peripheral neuropathy. It is probably one of the most effective agents of the newer generation of antiepileptics used for the treatment of neuropathic pain. The efficacy of gabapentin has been demonstrated in clinical trials and in several preclinical models of neuropathic pain (Ali et al., 2015; Field et al., 1997; Rowbotham et al., 1998). However, there is a meager scientific evidence demonstrating gabapentin efficacy against cisplatin-induced preclinical neuropathic pain although a previous study has demonstrated that it does produce a dose dependent relief of mechanical allodynia in cisplatin-induced neuropathic rats (Han et al., 2014). Moreover, gabapentin has been shown to be effective in the treatment of cancer-related neuropathic pain, by producing a meaningful reduction in pain scores in patients receiving radiotherapy, surgery or chemotherapy (Ross et al., 2005). Unfortunately, the effectiveness of systemic GBP in patients suffering from neuropathic pain may be limited by the occurrence of side-effects such as dizziness, somnolence, ataxia, lethargy and convulsions (Rose and Kam, 2002). Accordingly, the discovery of new drugs with enhanced analgesic propensity associated with a reduced side effect profile is warranted (Ahmad et al., 2017).

In this context, a rationale was adopted in this investigation using a GBP derivative (See Supplementary file) based on the premise of combining the reported antineuropathic effect of GBP (Rosenberg et al., 1997; Serpell and Group, 2002) with the antinociceptive and anti-inflammatory properties of salicylaldehyde (Rainsford, 2016) in a single molecular entity to explore any potential benefit over GBP. The study further investigated the cisplatin-induced neuropathic pain de-escalating efficacy of gabapentin in addition to its salicylaldehyde derivative [gabapentsal (GPS), Fig. 1] (Mallesha et al., 2012), synthesized herein via an exclusively novel method by incorporating a salicylaldehyde moiety at its amine functionality. Additionally, a motor coordination assessment (rotarod) was performed to evaluate its activity in comparison to GBP.

2. Materials and methods

2.1. Animals

Sprague-Dawley rats of either sex (150–200 g) bred in the Animal House of the Department of Pharmacy, University of Peshawar, Peshawar, Pakistan, were used in this study. All the experimental procedures on animals were performed in compliance with the UK Animals (Scientific Procedures) Act 1986 and according to the rules and ethics of the Institutional Ethical Committee. Approval for the study was granted with the registration number:10/EC-15/Pharm. To eliminate bias, all animal groups were coded and both the experimental behavior assessors and statistical analysts were blind to the treatments.

2.2. Acute toxicity test

For the determination of acute toxicity of GPS, mice were injected intraperitoneally (i.p) with GPS at doses ranging from 25 to 1000 mg/kg (n = 6 mice for each dose) and their behavior was observed initially for 2 h and then up to for 24 h post drug administration. The animals were observed for spontaneous activity, aggressiveness, cyanosis, ataxia, tail pinch response, righting reflex, writhing, convulsions, catalepsy and bizarre behavior (OECD guidelines, 2001)

2.3. Induction of cisplatin-induced neuropathic nociception

Animals were administered cisplatin (3.0 mg/kg i.p., once a week for 5 weeks, i.e. cumulative dose of 15 mg/kg). Sterile saline solution (2.0 ml) was administered subcutaneously (s.c.) to prevent renal damage via hyperhydration before each cisplatin dose (Authier et al., 2003a; Han et al., 2014; McKeage, 1995) and animals received less than 5.0 ml of dosing solution into the peritoneal cavity.

2.3.1. Treatment groups

2.3.1.1. Experiment 1(Treatment with GBP). GBP was dissolved in normal saline (Zeesol NS, Shahzaib Pharmaceuticals [Pvt.] Ltd. Haripur Pakistan) and was intraperitoneally administered in doses of 50, 75 and 100 mg/kg on the 37th day of the treatment protocol. The animals were randomly distributed into the following treatment groups (n = 8 rats per group).

Group 1: Saline (10 ml/kg/week for 5 weeks) + Saline (10 ml/kg on day 37)

Group 2: Cisplatin (3.0 mg/kg/week for 5 weeks) + Saline (10 ml/kg on day 37)

Group 3: Cisplatin (3.0 mg/kg/week for 5 weeks) + GBP (50 mg/kg on day 37)

Group 4: Cisplatin (3.0 mg/kg/week for 5 weeks) + GBP (75 mg/kg on day 37)

Group 5: Cisplatin (3.0 mg/kg/week for 5 weeks) + GBP (100 mg/kg on day 37)

Group 6: Saline (10 ml/kg/week for 5 weeks) + GBP (100 mg/kg on day 37)

2.3.1.2. Experiment 2 (Treatment with GPS). The GBP derivative (GPS) was dissolved in a vehicle comprising of DMSO, Tween-80 and normal saline in a ratio of 5:1:94. The animals were randomized into the following treatment groups (n = 8 rats per group), during which they were intraperitoneally administered GPS in doses of 25, 50, 75 and 100 mg/kg on the 37th day.

Group 1: Vehicle (10 ml/kg/week for 5 weeks) + Vehicle (10 ml/kg on day 37)

Group 2: Cisplatin (3.0 mg/kg/week for 5 weeks) + Vehicle (10 ml/kg on day 37)

Group 3: Cisplatin (3.0 mg/kg/week for 5 weeks) + GBP (100 mg/kg on day 37)

Group 4: Cisplatin (3.0 mg/kg/week for 5 weeks) + GPS (25 mg/kg on day 37)

Group 5: Cisplatin (3.0 mg/kg/week for 5 weeks) + GPS (50 mg/kg on day 37)

Group 6: Cisplatin (3.0 mg/kg/week for 5 weeks) + GPS (75 mg/kg on day 37)