PAIN-RELATED BEHAVIOUR AND ANALGESIC EFFECT OF GABAPENTIN IN AN EXPERIMENTAL MODEL OF BORTEZOMIB-INDUCED NEUROPATHIC PAIN

Meregalli C., Chiorazzi A., Sala B., Ceresa C., Oggioni N., Cavaletti G.

Department of Neuroscience and Biomedical Technologies, University of Milan Bicocca, Monza.

Peripheral tissue injury can alter somatic sensory pathways, resulting in behavioural hypersensitivity and increased responses to pain caused by noxious stimuli (hyperalgesia) and normally innocuous stimuli (allodynia). The absence of knowledge concerning mechanism of chemotherapy- induced neuropathic pain has hindered the development of new treatment strategies.
The anticancer drug bortezomib (BTZ) is a inhibitor of the 26S proteasome mainly used for treatment of multiple myeloma. BTZ modulates protein metabolism leading to the apoptosis of malignant cells. However BTZ induces a painful neuropathy that cause a significant impairement of patient's quality of life. The use of adjuvant for neuropathic cancer pain is largely empirical and their mechanisms of action is not completely know. Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA) and is a promising anticonvulsant drug with an analgesic effect in neuropathic pain. The aim of this study was to evaluate through neurophysiological, histological and behavioural methods the effect of BTZ long-term administration on the rat peripheral nervous system. Furthermore the analgesic effect of gabapentin was evaluated.
BTZ was administrated for 8 weeks at doses of 0.20 mg/kg [3q7d] i.v. In a second experimental phase, half of the animals were treated with gabapentin (100 mg/kg for 4 weeks daily) and half of the animals were left untreated. General toxicity was monitored twice a week by body weight measure. The neurotoxicity was evaluated by tail nerve conduction velocity (NCV) measures at 8 and 11 weeks after the begin of the experiment. Mechanical allodynia was assessed by Dynamic test at baseline, at 56, 57, 67, 70, 77, 84 days of treatment.
BTZ induced a significant reduction in body weight after 8 weeks ($p<0.05$ vs CTRL) that was no longer significant at the end of follow-up period. Electrophysiological evaluation at the 8 weeks of treatment evidenced a significant reduction of NCV ($p<0.0001$ vs. CTRL). After 11 weeks BTZ and BTZ+gabapentin-treated group showed a decrease of NCV ($p<0.001$ vs. CTRL). The sensory behavioural assessment revealed a significant BTZ-induced mechanical allodynia; gabapentin induced an anti-allodynic effect only after the first oral administration.
Although gabapentin might be considered as a promising analgesic drug for the treatment of neuropathic pain, our results indicated that the decrease in pain score was minimal. This animal model will be used to improve the knowledge of mechanism underlying the neuropathic pain and also to test other potential new analgesic and neuroprotective drugs.

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