STUDY OF THE CALCITONIN GENE-RELATED PEPTIDE-POSITIVE INTRAEPIDERMAL NERVE FIBERS IN A RAT MODEL OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

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Bortezomib (BTZ), a selective proteasome inhibitor, is a potent antineoplastic drug to treat multiple myeloma. In clinical practice, the most significant side effect of its administration, is a peripheral painful sensory neuropathy (PN), characterized by numbness and tingling in a distal stocking-glove distribution as well as distal paresthesia and generally associated with impairment of Adelta and C type primary afferent fibers. At the moment the therapies for PN are not really effective and almost only symptomatic. To evaluate if BTZ-induced sensory deficits are associated to loss of epidermal nerve fibers as is observed in other PN conditions, here we examine the effect of a well-established chronic BTZ-treatment schedule on the number of intraepidermal nerve fibers (IENF) in a rat model of BTZ-induced PN and compared the outcome of chronic BTZ-treatment followed by two-weeks of follow up with that of animals that received a 2-weeks treatment period with two analgesic drugs commonly used in clinical practice such as Gabapentin (Gaba) and buprenorphine (Bupre). To these aims, female Wistar rats were treated with BTZ 0.20 mg/kg, 3 times a week for 8 weeks (i.v.). Then analgesic were orally administered according to the following curative schedule: Gaba (100 mg/kg, daily, p.o.), Bupre (28,8 µg/kg, daily, s.c.).
At the end of treatments, the hindlimb footpad skin was examined by immunohistochemistry for the pan-neuronal marker PGP9.5 and the neuropeptide calcitonin gene-related peptide (CGRP), a neuropeptide involved in pain perception and neurotransmission. Labelled nerve fibers were distributed in the reticular and papillary dermis and within the epidermal lining. Quantitative evaluation of IENF showed that, according to the painful symptoms induced by BTZ, the mean linear density of CGRP-labelled IENF normalized by that of the PGP9.5-labelled ones shows a statistically significant decrease in BTZ-treated rats. None of the analgesics used in this study appeared to reverse the BTZ-induced loss of IENF.
Results obtained suggest that the CGRP-positive innervation is likely involved in the persistence of BTZ-induced pain and that detectability of CGRP-positive IENF appears not to be related to the effectiveness of the selected analgesics.