ETHOXYQUIN IS EFFECTIVE IN PREVENTING CISPLATIN-INDUCED PAINFUL PERIPHERAL NEUROPATHY IN RATS

Carozzi VA [(1)], Chiorazzi A [(1)], Marmiroli P [(1)], Oggioni N [(1)], Ceresa C [(1)], Zhu J[(2)], Hoke A [(2)] , Cavaletti G [(1)].

[(1)]Department of Surgery and Translational Medicine, University of Milan-Bicocca, Monza (MB), Italy.

[(2)] Departments of Neurology and Neuroscience, Johns Hopkins School of Medicine, Baltimore (MD), USA.

Ethoxyquin (EQ) is a synthetic potent antioxidant approved by Federal Drug Administration for use in animal food in order to protect it against lipid peroxidation and stabilize fat soluble vitamins. It was found that diet supplemented with EQ allowed mice to live longer than littermates. Antimutagenic effect was observed in mice and rats treated with cancer chemotherapy. However, these observations were never carried out to human studies and the primary use of EQ is still as a supplement in animal food.

EQ should be considered a potential neuroprotective drug against platinum-based chemotherapy, a cornerstone of the current antineoplastic treatment limited by the onset of peripheral nervous system dysfunction in cancer patients. In fact platinum-induced oxidative stress contributes to dorsal root ganglia (DRG) and peripheral nerves damage. Intriguing preliminary *in vitro* data demonstrated that EQ can prevent platinum toxicity on primary DRG culture.

In this study we tested *in vivo* neuroprotective properties of EQ through Nerve Conduction Velocities (NCV) studies, morphological and morphometrical analysis of DRG, caudal and sciatic nerves and behavioral assessment of neuropathic pain.

Cisplatin (i.p, 2 mg/Kg, twice weekly) and/or EQ (i.p, 75 micrograms/kg, daily) were administered in female Wistar rats for four weeks. When co-administered, EQ was injected 1 hour after cisplatin. A group of control animals was left untreated. At the third week of treatment, cisplatin alone determined piloerection, kyphosis and hypokinesia while co-treated animals had only piloerection. Neurophysiological measurements showed that cisplatin induced functional abnormalities in caudal nerve evident as a significant decrease in NCV ($p<0.001$ vs controls) while, if EQ was co-administered, the NCV impairment was significantly prevented ($p<0.05$ cisplatin alone vs cisplatin+EQ). Similarly, cisplatin-induced mechanical allodynia ($p<0.05$ vs controls) and thermal hypoalgesia ($p<0.01$ vs controls) were avoided when EQ was co-administered ($p<0.001$ and $p<0.05$ cisplatin alone vs cisplatin+EQ for mechanical and thermal tests). Qualitative and quantitative analysis of DRG damage demonstrated that cisplatin alone induced somatic, nuclear and nucleolar atrophy in sensory neurons ($p<0.001$ vs controls for somatic, nuclear and nucleolar sizes); if co-administered with EQ atrophy was not observed ($p<0.001$, $p<0.05$ and $p<0.01$ cisplatin alone vs cisplatin+EQ for somatic, nuclear and nucleolar sizes).

These data support the neuroprotective action of EQ against cisplatin-induced peripheral neurotoxicity and allow a future evaluation in tumor xenograft models of the interfering effects on the antineoplastic activity of platinum-based chemotherapy.

This work was partially supported by “Fondazione Banca del Monte di Lombardia”.