P05-018
Bupivacaine myotoxicity and neurotoxicity after laser therapy

S.M.M. Matheus[1,*], C.A. Pissulin[2], F. Codina[1], A.A. Fernandes[3]

[1] *Bioscience Institute/Unesp, Anatomy, Botucatu, Brazil*
[2] *Botucatu Medical School, UNESP, Botucatu, Brazil*
[3] *Bioscience Institute/Unesp, Chemistry and Biochemistry, Botucatu, Brazil*

Local anesthetics are commonly used to provide peripheral nerve blocking for surgical anesthesia or postoperative analgesia. Some of them are neurotoxic, and cause myotoxicity and inflammation. Bupivacaine is a widely used amide local anesthetic. There is a strong evidence that low level laser therapy (LLLT) helps in muscle and nerve repair. The objective of this study was to assess the myotoxicity and neurotoxicity of bupivacaine in rats after LLLT application. 20 adult male Wistar rats (CEEUA/IBB n° 509) received bupivacaine 0.5% application on right antimere, and sodium chloride 0.9% on left antimere (control). After 24 h, the animals were divided into two groups. One group received a daily application of LLLT on both antimeres for 5 days (laser group). After the animals were euthanized and had sternomastoid muscles and the associated nerves removed. The following aspects were evaluated: Myotoxicity – quantification of Creatine Kinase (CK) and Lactate Dehydrogenase (LDH) and morphological analysis (HE staining); Neurotoxicity – morphological (osmium tetroxide staining) and morphometric nerve analysis. The biochemistry data showed a decrease of CK in the LLLT group (310.20 ± 38.51 nmol/mg) when compared to the other (401.55 ± 40.41 nmol/mg) $p < 0.01$. In LDH data there were no statistical differences between the groups although the value of LLLT group (1.09 ± 0.24 nmol/mg) was less than in the other (1.20 ± 0.30 nmol/mg). The muscle morphological analyses showed that bupivacaine promoted considerable muscle injury with polygonal shape loss and a lot of central nuclei (signal of degeneration)were present. Large areas of inflammatory cell infiltrated and fibrous tissue formation were found. In the LLLT group there was a considerable decrease of myonecrosis with characteristics of immature cells such as large nuclei. The morphological nerve analyses showed a similar pattern between the groups and there were no statistical differences in relation to the G ratio (control 0.574 ± 0.048 and LLLT 0.568 ± 0.047) $p > 0.05$. These data indicate that LLLT can be used after local anesthesia to reduce inflammation, minimizing myotoxicity. It also suggests that although the bupivacaine binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, no neurotoxicity was observed.

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Induction of CYP3A4 by omeprazole and lansoprazole enantiomers in human hepatocytes and cell lines via glucocorticoid receptor and pregnane X receptor axis

A. Novotna*, Z. Dvorak

Palacky University Olomouc, Faculty of Science, Department of Cell Biology and Genetics, Olomouc, Czech Republic

Benzimidazole drugs lansoprazole and omeprazole act as proton pump inhibitors and are used for treatment of various gastrointestinal disorders. Both compounds cause drug-drug interactions because they activate aryl hydrocarbon receptor and induce CYP1A genes. In the current study, we examined the effects of lansoprazole and omeprazole enantiomers on the expression of key drug metabolizing enzyme CYP3A4 in human hepatocytes and human cancer cell lines. Lansoprazole enantiomers were equipotent inducers of CYP3A4 mRNA in HepG2 cells but we did not observed this effect by omeprazole enantiomers. All forms (S-, R-, rac-) of lansoprazole and omeprazole induced CYP3A4 mRNA and protein in human hepatocytes, and this CYP3A4 induction by individual forms of both drugs exerted enantiospecific patterns. In gene reporter assay, lansoprazole caused dose-dependent activation of pregnane X receptor (PXR) and slight increase of rifampicin-inducible PXR, with similar potency for each enantiomer. Omeprazole caused dose-dependent activation of PXR and inhibition of rifampicin-inducible PXR activity. The effects of S-omeprazole were much stronger as compared to those of R-omeprazole. All forms of lansoprazole caused slight activation of glucocorticoid receptor (GR) and enhancement of dexamethasone-induced GR transcriptional activity. All forms of omeprazole and lansoprazole induced expression of tyrosine aminotransferase (TAT), a GR target gene, in HepG2 cells, but we found decrease of TAT expression in human hepatocytes. Overall, we demonstrate here that omeprazole and lansoprazole enantiomers induce CYP3A4 in HepG2 cells and human hepatocytes. The induction comprises differential interactions of omeprazole and lansoprazole with transcriptional regulators PXR and GR, and some of the effects were enantiospecific. The data presented here might be of toxicological and clinical importance, since the effects occurred in therapeutically relevant concentrations.

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Evaluation of folate and Vitamin B12 status in lead exposed workers

C. Bal[1,*], A. Hocaoglu[2], M. Büyükşekerci[3], M.E. Alagüney[4], O.H. Yılmaz[5], E. Tutkun[6]

[1] *Ankara Occupational Disease, Biochemistry, Ankara, Turkey*
[2] *Ankara University Institute of Forensic Science, Ankara, Turkey*
[3] *Ankara Occupational Disease Hospital, Pharmacology, Ankara, Turkey*
[4] *Hacettepe University, Internal Medicine, Ankara, Turkey*
[5] *Yıldırım Beyazıt Üniversity, Public Health, Ankara, Turkey*
[6] *Ankara Occupational Disease Hospital, Toxicology, Ankara, Turkey*

Question: Lead (Pb) is a well known toxic metal. Pb enters the body either through gastrointestinal or respiratory tracts. After inhalation 35–45% of Pb reaches the blood stream and binds to red cells. Its distribution occurs mainly to liver, kidneys, brain, bones and teeth. About 90% of the Pb burden is stored in bones and can latterly release in blood that causes toxic effects. Among these; neurobehavioral, hematologic, nephrotoxic and reproductive effects have been observed in humans and animals. Folate takes many roles in human organism such as DNA and RNA synthesis, production of red blood cells and maintenance of nervous system. Folate also acts as a co-enzyme in many of the reactions of the metabolism of amino acids. Vitamin B12 or cyanocobalamine takes role as a co-factor in folate metabolism and it is necessary for DNA synthesis especially for red blood cell development. Vitamin B12 is also required for the