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Is there a link between long term use of antihypertensive agents and cancer development?

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Introduction: The association between chronic use of anti-hypertensive agents and cancer development has been suggested in the literature for several years. However, this association has been trailed with much controversy with numerous epidemiological studies indicating a positive, while some negative and some indicated no association between Calcium Channel Blockers (CCBs) and increased risk of cancer. Polyamines have been found to play a crucial role in cancer pathogenesis with elevated level seen in significant number of human epithelial tumours (Paz, E.A. 2011). The role of elevated levels of polyamines in cancer have been well research and documented (Wallace, HM 2007). The aim was to investigate in mechanistic terms the link between chronic use of calcium CCBs and cancer development using the human embryonic kidney (HEK293) cell line.

Method: We used trypan blue dye exclusion (cell counting) and 3-[4, 5-Dimethylthiazol-2-yl]-2, 5-diphenyl-tetrazolium bromide (MTT) assays to determine the proliferative as well as cytotoxic effects of some selected CCBs. Furthermore, protein assay using a modified Lowry method and analysis of the intracellular concentration of polyamines using liquid chromatography - tandem Mass spectrometry (LC-MS) were performed to ascertain the mechanism through which chronic use of anti-hypertensive agents increases the risk of developing cancer.

Results: Both nifedipine and diltiazem significantly increased the proliferation of HEK293 cells concentration and time dependently. This proliferative effect after 24, 48 and 72-hour incubation period was observed at 1.0, 2.0 and 25 µM for nifedipine and 0.4, 1.5 and 25 µM for diltiazem, respectively. The increased proliferation of the cells was found to be statistically significantly ($p<0.05$), analysed using two-way ANOVA with Dunnet's post-test. Interestingly, Verapamil had a growth inhibitory rather than proliferative effect on HEK293 cells and the growth inhibition was found to be significant ($p<0.01$). Furthermore, the increased proliferation of the cells induced by nifedipine was associated with increase in the concentration of protein and intracellular polyamines.

Conclusion: Chronic use of some calcium channel blockers is associated with increased cell proliferation as well as increased concentrations of the polyamines and elevated level of polyamines have been implicated in many malignant transformations. Therefore, chronic use of calcium channel blockers is associated with increased risk of developing cancer.

References [1] PAZ, E.A., GARCIA-HUIDOBRO, J. and IGNATENKO, N.A., 2011. Polyamines in cancer. *Advances in Clinical Chemistry,* **54**, pp. 45-70. [2] WALLACE, H. and NIIRANEN, K., 2007. Polyamine analogues-an update. *Amino acids,* **33**(2), pp. 261-265.