NCX 4016, A NITRIC OXIDE-RELEASING ASPIRIN DERIVATIVE, EXHIBITS A SIGNIFICANT ANTI-PROLIFERATIVE EFFECT AND ALTERS CELL CYCLE PROGRESSION IN LOVO COLON ADENOCARCINOMA CELL LINE


Purpose. Numerous studies demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) are useful agents for prevention and cure of cancers, especially colon and rectal cancers, but side effects are a major obstacle to their assumption. Nitric oxide releasing non-steroidal anti-inflammatory drugs (NO-NSAIDs) are reported safer than NSAIDs by their ability to decrease gastric toxicity. In our study we assessed in vitro the cytotoxic activity of a new aspirin derivative, NCX 4016, after different exposure schedules in LoVo colon adenocarcinoma cell line.

Experimental design. COX-1 and COX-2 expression was evaluated as protein expression and mRNA content by Western blot and RT-PCR respectively, cytotoxic activity was evaluated by sulforhodamine B assay and the data elaborated according to Monk’s model, cell cycle perturbations and apoptosis were evaluated by flow cytometry, mitotic index was evaluated by at microscope on hematoxylin-eosin stained cytopsin.

Results. LoVo cell line resulted positive for the presence of protein and mRNA of the two isoenzymatic form of cyclooxygenase COX-1 and COX-2. Important anti-proliferative effects were induced by NCX 4016 and GI_{50} value, ranging from 174-to 200 mM, was already reached after 24-h drug exposure. A significant cell killing was observed only at the highest concentrations and LC_{50} values were reached only after longer time exposures.

NO-aspirin compound also induced an accumulation of cells in G2-M phase in LoVo cell line with a peak after 48-h treatment which still persisted after 72-h or after 48-h exposure followed by a 24-h of wash-out. Furthermore, the block resulted be charged to G2 phase whereas mitosis phase was not affected at all.

Conclusion. Our results indicate that NCX 4016 has an in vitro antiproliferative activity superior respect to parental compound aspirin that makes it a potential important tumor chemopreventive agent and the cytotoxic effect to higher concentration with specific block in G2 phase renders it a promising candidate for drug combination regimen.