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47 - EFFECTS OF KETOCONAZOLE ON ACTH-PRODUCING AND NON ACTH-PRODUCING NEUROENDOCRINE TUMOR CELLS

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Resumen

Introduction: Prolonged spontaneous remission of hypercortisolemia in ectopic ACTH syndrome (EAS) after long-term treatment with steroidogenesis inhibitors has been described. Some authors hypothesize a direct drug effect on the adrenal glands or effects on tumoral ACTH secretion and/or *POMC* gene expression. Medical treatment with steroidogenesis inhibitors can be used when a source of ACTH production cannot be identified, not only for control of symptoms, but also for disease control.

Methods: In human BON-1 pancreatic neuroendocrine tumor cells and ectopic ACTH-producing small cell lung carcinoma DMS-79 cells, we have evaluated the effects of ketoconazole on cell growth, apoptosis, cell cycle, chromogranin mRNA expression and ACTH secretion.

Results: In the BON-1 cell line, ketoconazole significantly suppressed cell growth in a dose and time-dependent manner. Maximal inhibitory effects by 10μM ketoconazole were 41.02% ($p < 0.0001$) and 95.23% ($p < 0.0001$) after 3 and 7 days of treatment, respectively. The IC_{50} value of growth inhibition was 7.768 μM after 7 days of treatment. Ketoconazole also induced a significant G1-phase arrest ($p < 0.001$) accompanied by a decrease in S-phase and G2-phase, as well as a significant increase in early ($p < 0.001$) and late ($p < 0.01$) apoptosis. Ketoconazole did not significantly affect the chromogranin A expression in BON-1 cells. DMS-79 cells are less sensitive to ketoconazole effects, with maximally inhibitory effects by 50μM ketoconazole of 44.02% ($p < 0.0001$) and 94.02% ($p < 0.0001$) after 3 and 7 days of treatment, respectively. The IC_{50} value of the growth inhibitory effect was 15 μM after 7 days of treatment. The highest ketoconazole (5×10^{-5}M) concentration tested induced a significant G1-phase arrest ($p < 0.001$), increased dead cells rate ($p < 0.001$) without significant effect on early or late apoptosis. ACTH secretion was suppressed only concentrations of ketoconazole of 10^{-5}M and higher.

Conclusions: These results suggest a potential direct effect of ketoconazole on cell proliferation, apoptosis and cell cycle in ACTH- and non ACTH producing neuroendocrine tumor cells. Additional studies, including experiments in human NET samples, are required to confirm and extend these results.