Digitoxina e paclitaxel. Ambos inibem a Na+ / K+ ATPase e juntos aumenta efeitos adversos

Digitoxin activates EGR1 and synergizes with paclitaxel on human breast cancer cells
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Received May 21, 2010; Accepted September 29, 2010.

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Abstract
Background:
Numerous studies have suggested that digitalis derivatives promise to be superior to existing adjuvant therapy for breast cancer as to effects and side-effects. In the present study, we have used gene expression analysis to determine the molecular action of digitoxin on breast cancer cells and assessed digitoxin’s ability to synergize with the chemotherapy agent paclitaxel with respect to inhibition of cell proliferation

Materials and Methods:
We treated (Her2 overexpressing, ER low) MDA-MB-453 human breast cancer cells with digitoxin at four doses {20 ng/ml (26 nM) to 1 μg/ml} and collected RNA at 6 h and 24 h for gene expression analysis. To examine the effects on ER positive cells, we treated MCF7 cells with digitoxin at 1 μg/ml and collected RNA for RT-PCR analysis. In addition, we assayed the growth inhibitory effect of low doses of digitoxin combined with paclitaxel and determined combination index values.

Results:
To reveal primary effects, we examined digitoxin’s effect 6 h post-treatment with the highest dose, 1μg/ml, and found upregulation of the stress response genes EGR-1 and NAB2, lipid biosynthetic genes and the tumor suppressor gene p21, and downregulation of the mitotic cell cycle gene CDC16 and the replication gene PolR3B. RT-PCR analysis validated effects on stress response, apoptotic and cell cycle genes on MDA-
MB-453 and MCF7 cells. Western blot analysis confirmed induction of EGR1 protein at 1 h and ATF3 at 24 h. Paclitaxel, as well as digitoxin, inhibited the in vitro activity of the purified Na\(^+\)-K\(^+\)-ATPase; digitoxin enhanced the growth inhibitory effects of paclitaxel on Her2 overexpressing breast cancer cells.

**Conclusions:**

Our studies show the potential of digitoxin to prevent and treat breast cancer and indicate that the combination of digitoxin and paclitaxel is a promising treatment for ER negative breast cancer. These findings are the first to alert physicians to the possible dangers to patients who take a combination of digitoxin and paclitaxel. The potential dangers ensuing when paclitaxel and digitoxin are combined are dependent on the dose of digitoxin.

**Keywords:** Cardiac glycosides, microarrays, paclitaxel, stress response, synergy