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In vitro evaluation of the genotoxicity of ritodrine and verapamil in human lymphocytes

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Abstract

The aim of this study was to investigate the genotoxic effects of ritodrine and verapamil on human peripheral lymphocytes in vitro using micronucleus (MN) test. Also, fluorescence in situ hybridization (FISH) with a centromeric probe was performed to determine the origin of the induced MN. Cells were treated with 8.4×10^{-6} M – 25.2×10^{-4} M concentrations for ritodrine and 0.56–11 $\times 10^{-5}$ M concentrations for verapamil, separately and combined. The MN frequencies showed increase after all treatments, but the difference between treated cells and untreated controls were found to be statistically significant only in the concentration range from 8.4×10^{-5} M – 4.5×10^{-4} M for ritodrine, $1.1 - 3.3 \times 10^{-5}$ M for verapamil, and in combined treatment with concentrations 8.4×10^{-5} M + 1.1×10^{-5} M for ritodrine and verapamil. The highest tested concentrations of both medicaments showed cytotoxic effect. Both medicaments decreased the nuclear division index (NDI) in tested concentrations. The results of FISH analysis suggest that verapamil, separately or combined with ritodrine, shows to a larger extent aneugenic than clastogenic effect.

Keywords

micronucleus, lymphocytes, in vitro, ritodrine, verapamil

Introduction

Micronuclei (MN) are small, round chromatin bodies in the cytoplasm of cells that originate from cell division as the result of the elimination of acentric chromosome fragments or whole chromosomes. There are several genotoxic studies on pharmaceutical compounds using this assay.[1-3] To distinguish between MN derived from acentric fragments and MN containing whole chromosomes, fluorescence in situ hybridization (FISH) with centromere-specific DNA probes is being increasingly used in monitoring studies,[3,4] and the presence of hybridization signal in an MN is a direct measure of the presence of a centromere.[5]

Ritodrine hydrochloride (ritodrine), IUPAC name 4-[2-[3-hydroxy-2-(4-hydroxyphenyl)-1-methyl-ethyl]aminoethyl] phenol, belongs to β_2 group of selective agonists that have special affinity for β_2 receptors in miometrium (Figure 1). Stimulating these receptors, they induce uterus relaxation, especially during gravidity. This property is of prominent importance in the prevention and protection from premature contractions of the uterus in gravidity.[6] Ritodrine can stop the threatening abortion or postpone premature labor. It is administered orally or intravenously. Oral dose of 3 × 40 mg in combination with intravenous transfusion of 2 × 50 mg per day is administered until the uterus contractions stop, to be followed by oral administration only. In addition to the heart stimulation (tachycardia, more forceful heart contractions and irritability), ritodrine also induces hypotension, tremor at rest, anxiety, dizziness and nausea.[7]

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