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ORIGINAL ARTICLE

Cytotoxicity of Metoprolol on Leukemic Cells in Vitro

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ABSTRACT

Background: β-Blockers have shown considerable cytotoxic, anti-tumor and anti-angiogenic effects. Metoprolol, a β-Blocker with anti-inflammation, anti-tumor and anti-angiogenic properties has been widely used for treatment of some cardiovascular diseases such as angina, hypertension, heart failure and myocardial infraction. Limited data exist about the cytotoxic effects of metoprolol on human cancer cells. The aim of this study was to investigate the cytotoxic effect of metoprolol on U937 and MOLT-4 cells in vitro.
Methods: Human leukemic T cell (MOLT-4) and monocyte (U937) were cultured in Roswell Park Memorial Institute (RPMI) 1640 complete medium. Then, the cultured U937 and MOLT-4 cells were treated with different concentration of metoprolol (1, 10, 50, 100, 500 and 1000 µg/ml) for 24, 48 and 72 hours. The cytotoxicity of metoprolol was determined by using MTT (3-[4, 5 dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide) assay.
Results: Metoprolol significantly decreased the viability of U937 and MOLT-4 cells at 1000µg/ml (3740.14µM) concentration after 48 hours incubation time ($P<0.01$). In addition, metoprolol significantly reduced the viability of U937 cells at ≥500 µg/ml (≥1870.07µM) concentrations after 72 hours incubation time ($P<0.001$). Moreover, metoprolol significantly decreased the viability of MOLT-4 cells at ≥100 µg/ml (≥374.01µM) concentrations after 72 hours incubation ($P<0.001$).
Conclusion: According to the results of this study, metoprolol showed cytotoxic effect on U937 and MOLT-4 cells dose and time dependently. Therefore, metoprolol might have potential implication in therapy of leukemia as well as other malignancies.

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Introduction

β-Blockers are known as the most important and widely prescribed cardiovascular medications in cardiovascular diseases including angina, hypertension, heart failure and myocardial infraction.[1] Metoprolol is a β_1-selective antagonist which has therapeutic applications in certain doses, while its overdose may cause toxicity with adverse manifestations such as bradycardia, hypotension and cardiac failure.[2]

Over the past few decades, cancer is a serious life threating problem and is the second leading cause of mortality in many papulations.[3] Leukemia is a prevalent malignant disorder due to uncontrolled proliferation of blood cells.[4] A successful treatment for leukemia requires a multi-disciplinary approach including multi-drug chemotherapy, monoclonal antibody therapy in some cases, radiotherapy and stem cell transplantation.[5] Unfortunately, due to pharmacogenomics differences, the efficacy of the treatments is variable and their common side effects such as fatigue, hair loss, increased risk of infectious and bleeding complications could terminate in some degrees of morbidity in leukemic patients.

It is well established that beta blockers have considerable anti-tumor and anti-angiogenic properties,[6-9] which might have beneficial effects in response to chemotherapy and survival of the patients.[10, 11] Previous studies have shown

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that propranolol and other beta blockers have favorable anti-tumor and anti-angiogenic effects in several cancers including leukemia via inhibition of cancer cell proliferation and reduction of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) production.[8, 12-15] There are also numerous reports of anti-inflammatory,[16-18] anti-tumor and anti-angiogenic effects of metoprolol.[8] Moreover cytotoxic effects of metoprolol on different cancer cells such as melanoma and neuroblastoma have been shown.[10, 19] However, the effect of metoprolol on viability of leukemic cell lines has not yet been reported. The aim of the present study was to evaluate cytotoxic effects of metoprolol on monocyte U937 and T-cell MOLT-4 leukemic cells in vitro.

Materials and Methods

Reagents

Roswell Park Memorial Institute (RPMI) 1640, penicillin and streptomycin were purchased from Sigma company (USA) and MTT (3-[4, 5dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide) from Merck company (Germany). Fetal bovine serum (FBS) was obtained from Gibco (USA). Metoprolol was provided by Pursina Pvt. Co. Ltd (Tehran, Iran). Microtiter plates, flasks and tubes were obtained from Nunc Company (Falcon, USA).

Preparation of Metoprolol

RPMI was used for dissolving metoprolol to prepare the stock. The stock was stored at -20°C to be used during the study. Before use, the stock was diluted in RPMI complete medium to be prepared for different concentrations of metoprolol.

Cell Lines

Human leukemic T cell [MOLT-4 (NCBI C149)] and monocyte [U937 (NCBI C130)] lines were purchased from National Cell Bank of Iran, Pasteur Institute of Iran, Tehran (NCBI). RPMI-1640 complete medium was used for maintenance of the cells at 37°C.

Cell Culture and Treatment

The detail of the methods has been described previously by Hajighasemi et al.[20] In brief; U937 and Molt-4 leukemic cells were cultured in RPMI-1640 medium supplemented with 10% FCS, penicillin (100 IU/ml) and streptomycin (100 µg /ml) at 37°C in 5 % CO_2. The cells were divided in 96 wells plates at of 3×10^4 cells per well and treated with different concentrations of metoprolol including: 1, 10, 50, 100, 500 and 1000 µg/ml for 24, 48 and 72 hours. Cell viability was assessed by MTT assay.

Viability Assay

Viability of the cells was assessed by using MTT assay based on reduction of yellow water soluble MTT by mitochondrial dehydrogenase of intact cells to blue insoluble formazan products. [21] The MTT assay was performed after 24, 48, and 72 h of treatment. At the end of the incubation times, 20 µL of MTT solution (5 mg/ml) was added to each well and incubated for 4 h at 37°C. Subsequently, 100 µL of Isopropanol hydrochloride solution was added to each well and was shaken to dissolve the crystals. Absorbances were measured by using an ELISA microplate reader at 492 nm.

IC50 Determination

50% inhibitory concentration (IC50) of metoprolol was calculated by constructing a dose-response curve based on MTT assay. The IC50 was defined as a concentration of metoprolol which is needed to inhibit half of leukemic cells viability relative to untreated cells.

Statistical Analysis

In this study, we used the software SPSS 24 package (SPSS Inc, Chicago, IL) for data analysis and statistical calculation. The effect of metoprolol on viability of leukemic cells was assessed in 5 independent experiments. Normal distribution of the numerical variables was assessed using Kolmogorov-Smirnov Z-test. After investigation of the normality of data, one-way analysis of variance (ANOVA) was used to compare mean of leukemic cells viability between different groups. Tukey post hoc test was applied for multiple comparisons between the groups. P value<0.05 was considered significant. Data are presented as mean ± standard error of the mean (SEM).

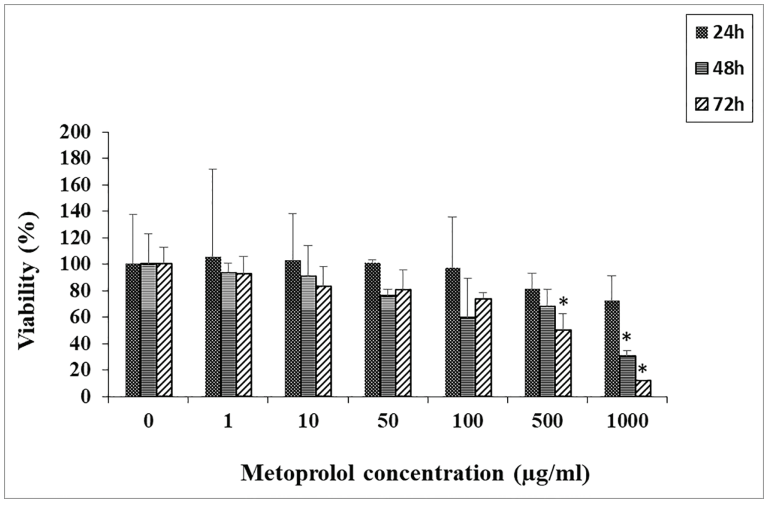


Figure 1: Cytotoxicity of metoprolol on *U937* cells. The U937 cells were treated with different concentrations of metoprolol (1-1000 µg/ml) for 24, 48 and 72 hours. Cell viability was determined by using MTT assay. Data are presented as mean±SEM. *P<0.05 was defined as statistical significant.

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Results

Figures 1 and 3 show the effect of different concentrations of metoprolol on the viability of U937 and MOLT-4 leukemic cells after 24, 48 and 72 hours treatment.

Effect of Metoprolol on Viability of U937 Cells

As is shown in figure 1, metoprolol decreased viability of U937 cells in every three time periods. However, these cytotoxic effects were only statistically significant after 48 and 72 hours of treatment. After 48 hours treatment of U937 cells with metoprolol, cell viability was decreased in all concentrations. But the decrease was only significant at 1000 µg/ml (3740.14µM) concentration of the drug (P=0.009) (Figure 1). Meanwhile, following 72 hours of treatment, metoprolol decreased cell viability in all concentrations. However, metoprolol cytotoxicity was only significant at ≥500 µg/ml (≥1870.07µM) concentrations of the drug in this time period (P<0.001) (Figure 1).

The IC50 of metoprolol on U937 cells at three time points is illustrated in Figure 2. Our data based on MTT assay represented a dose-response curve for each time point. The IC50 value after 24, 48 and 72 hours of treatment were 1628.09, 800.7356 and 565.3322 µg/ml, respectively (Figure 2).

Effect of Metoprolol on Viability of MOLT-4 Cells

Similar to U937 cells, metoprolol decreased MOLT-4 cells viability in the three time periods (Figure 3). However, again the cytotoxicity of metoprolol on MOLT-4 cells was only statistically significant after 48 and 72 hours of treatment. In addition, the same as for U937 cell line, metoprolol was significantly cytotoxic at 1000 µg/ml (3740.14µM) concentration (P≤0.001) after 48 hours of treatment; whereas, after 72 hours, the toxicity was significant at ≥100 µg/ml (≥374.01µM) concentration (P<0.01).

The IC50 of metoprolol on MOLT-4 cells at three time points of treatment is illustrated in Figure 4. After constructing a dose-response curve, the IC50 value was

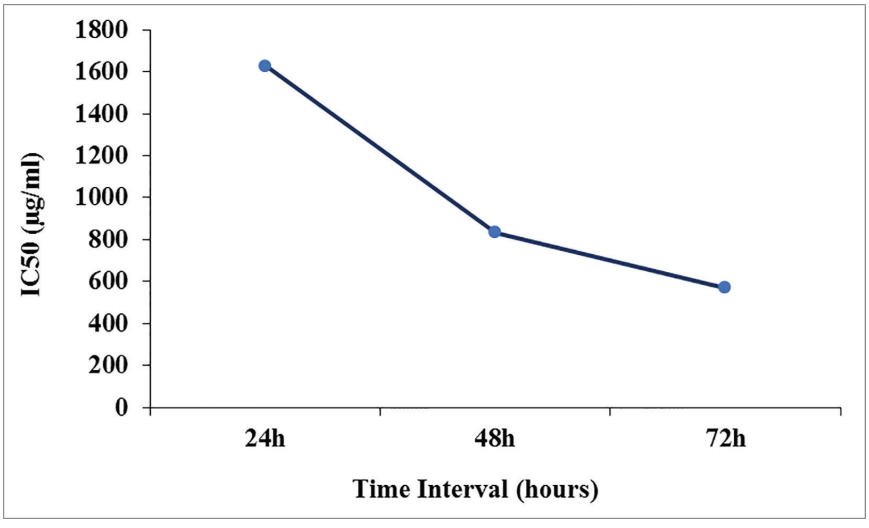


Figure 2: The IC50 value of metoprolol in different time intervals on human U937 cells based on MTT data and dose response curve.

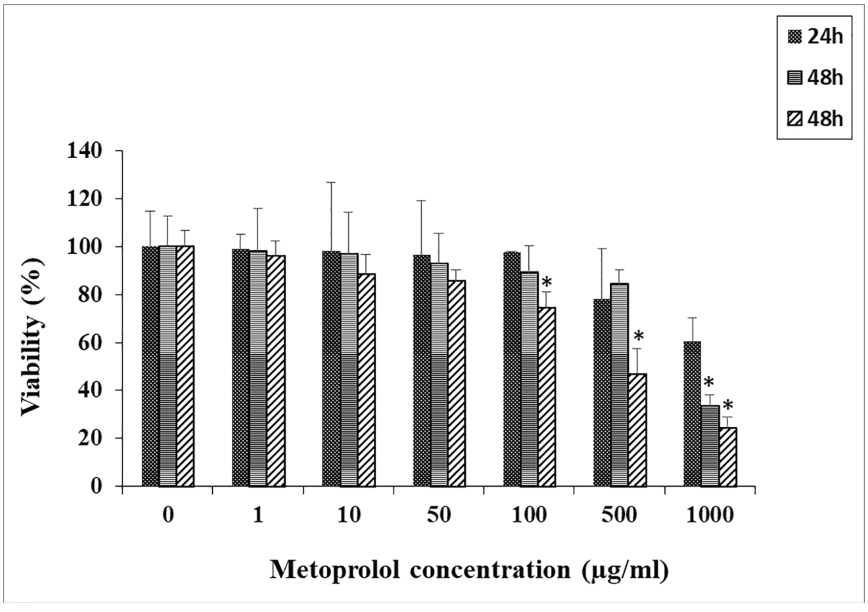


Figure 3: Cytotoxicity of metoprolol on MOLT-4 cells. The MOLT-4 cells were treated with different concentrations of metoprolol (1-1000 µg/ml) for 24, 48 and 72 hours. Cell viability was determined by MTT assay. Data are presented as mean±SEM. *P<0.05 was defined as statistical significant.

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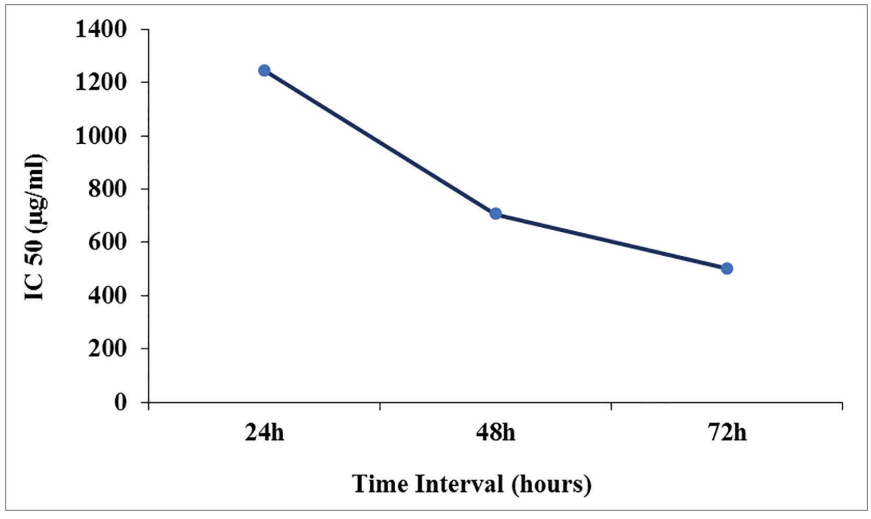


Figure 4: The IC50 value of metoprolol in different time intervals on human MOLT-4 cells based on MTT data and dose response curve.

calculated for each time. The IC50s after 24, 48 and 72 hours was 1243.199, 704.9659 and 501.5088 µg/ml, respectively (Figure 4).

Discussion

In this study, the effects of metoprolol on viability of human leukemic U937 and MOLT-4 cells was assessed. Our results showed that metoprolol had a cytotoxic effect on the mentioned leukemic cells in a dose and time dependent manner. This cytotoxicity was shown for both of U937 and MOLT-4 cells after 48h incubation time. The cytotoxicity on U937 cells was detected at 1000 and ≥500µg/ml concentrations of metoprolol after 48 and 72h incubation, respectively. Also, the cytotoxic effect of metoprolol on MOLT-4 cells was shown at 1000 and ≥100µg/ml concentrations of drug after 48 and 72h incubation, respectively. Accordingly, it seems that in shorter incubation times (24h & 48h), the sensitivity of both cell lines to metoprolol is the same. However, in longer incubation time (72h), MOLT-4 cells exhibited more sensitivity to metoprolol (cytotoxicity at ≥100µg/ml) than U937 cells (cytotoxicity at ≥500µg/ml).

Based on our results, the IC50 of metoprolol for MOLT-4 were lower than U937 cells. This may approve the more sensitivity of MOLT-4 cells to metoprolol than U937 cells. This once again indicates that various cell types have different sensitivities to metoprolol.

Wrobel and colleagues investigated the effect of β-blockers including metoprolol on growth and survival of melanoma cells such as A357, Mewo, MEL-CLS-3 cell lines.[19] He observed that metoprolol was cytotoxic for A357 cells at 100 µM (26.7 µg/ml) concentration after 72 h.

The discrepancy between our results and Wrobel et al. may be partly due to a number of facts, including the type and number of the cells, the methods used for assessment of cytotoxicity and the incubation time. They had used melanoma cells seeded 20,000 cells/well, incubated for 72 h and cytotoxicity was measured by cytotox assay.

In another similar study, Caldwell et al. showed metoprolol cytotoxicity on human hepatocytes at ≥500 µM (≥133.68 µg/ml) concentration of the drug after 3 hours of incubation. Caldwell et al. also used MTT assay for their assessment. Cytotoxicity was detected very early (at ≥133.68 µg/ml after 3h incubation) in their study. It seems that hepatocyte cells are much more sensitive to metoprolol than human leukemic cells.[22]

Consistent to our results, anti-proliferative effects of metoprolol and some other β-blockers on BE(2) C and SHEP neuroblastoma cell lines have also been demonstrated.[10] Decreased proliferation of neuroblastoma cells was detected at 10^{-3} M (267.369 µg/ml) concentration of the drug after 72 hours. Also they used 3750 cells/well and Alamar blue test for proliferation assessment.[10]

The sensitivity of human U937 and MOLT-4 leukemic cells against a number of β-blockers have been investigated by several studies.[23, 24] For example, Cheng et al. showed the cytotoxicity of carvedilol on U937 cells at ≥4.06 µg/ml concentration after 24 hours.[23] In this study, the concentration of the cells used was 5×10^5 cells/ml and trypan blue exclusion method and MTT were used for cytotoxicity assessment.[23] Carvedilol was found to be cytotoxic at much lower concentrations (at ≥4.06 µg/ml) than metoprolol (at ≥1000µg/ml) as in our study.[23] This discrepancy could be explained by the fact that β-blockers have different anti-proliferative properties.[10] β-blockers have potent (carvedilol and nebivolol), intermediate (propranolol and labetalol) and weak (atenolol, metoprolol and butoxamine) anti-proliferative potencies.[10]

In a previous study by authors, cytotoxicity of propranolol on human leukemic cells occured at concentrations ≥0.2 mM (≥50µg/ml).[24] Once again the discrepancy between two studies might be due to the fact that propranolol is an intermediate while metoprolol is a weak β-blocker. Another reason for difference in cytotoxic concentration of propranolol and metoprolol may be that propranolol is a non-selective blocker.[25]

The results of the present study along with other researches revealed that metoprolol exerts cytotoxicity at different doses in different cells.[10, 19, 22] It could be hypothesized that metoprolol and some other β-blockers could have positive impacts on survival of cancer patients partially due to direct cytotoxicity.[9-11, 26, 27] Decreased angiogenesis and rate of metastasis by β-blockers has also

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been stated.[28-30] Moreover, activation of beta adrenergic receptors in cancer cells leading to increase of angiogenic factors like VEGF and MMP-9 which are involved in tumor invasion and metastasis has been shown.[31-33]

β-Adrenoreceptor 1 and 2 (β-AR1 & 2) are expressed by all types of cancers, except neuroblastoma which only expresses β2-AR.[33] The anti-tumor and anti-angiogenic effects of β-blockers are mediated by both β1 and β2-AR related mechanisms.[33]

A proposed model has suggested that stress-induced catecholamines such as epinephrine and norepinephrine in tumor environment results in activation of protein kinase A (PKA) and exchange protein activated by cAMP (Epac) which leads to transcription of genes encoding for IL-6, IL-8, VEGF, MMP-9 and PTGS2 which are involved in inflammation, angiogenesis and tumor invasion.[34] Moreover, PKA induced activation of Bcl-2 associated death promotor (Bad) can make cancer cells resistant to chemotherapy induced apoptosis.[34] Blocking the β-ARs could reduce invasion, inflammation, angiogenesis, cell proliferation and increases the sensitivity to chemotherapy and apoptosis.[34] Decrease in cell proliferation and enhancement of apoptosis by β-adrenoreceptor blockers reported in other studies are consistent with our results that showed metoprolol cytotoxicity on leukemic cells.

Although, anti-tumoral effects of metoprolol on some cancer cell lines have been shown[10, 19] its cytotoxicity on normal cells and also its exact anti-tumoral concentrations has not been precisely declared yet. Therefore, it would be valuable to study metoprolol toxicity on other cancers as well as normal cells in vivo to find the optimum anti-tumor dose of the drug along with the least toxic effects on normal cells.

Conclusion

In present study, metoprolol showed cytotoxicity on the leukemic cells in a time and dose dependent manner. The β-blocker properties of Metoprolol plays the main contribution role in cytotoxic effects of this medication.

Conflict of Interest: None declared.

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