IN VITRO-IN VIVO STUDIES OF BENZOTHIAZINES AGAINST LYMPHOCYTIC LEUKEMIA P388 CELLS

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Abstract : Seven benzothiazines have been screened for in vitro-in vivo cytotoxicity for the surviving cell fraction of lymphocytic leukemia P388 cells. Benzothiazines tested exhibit a slight direct cytotoxic activity.

Introduction

Benzothiazines possesses an anticancer activity (1) and resemble structurally to phenothiazines (2,3) due to the presence of a fold along nitrogen-sulfur axis which is one of the structural specificity to impart biological activities (4). In vitro and in vivo evaluation (bioassay) of the surviving cell fraction has been used to investigate the direct cytotoxic activity (5).

Experimental

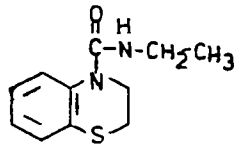
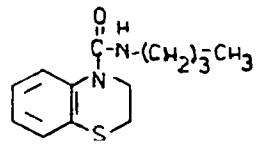
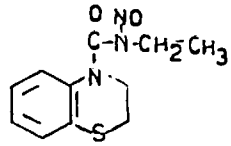
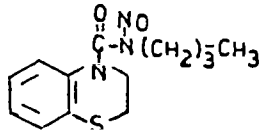
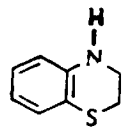
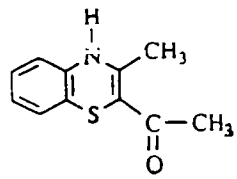
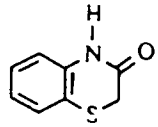
Six benzothiazines 1-5 and 7 have been prepared as described previously (6). Benzothiazine 6 has been prepard by adopting the method reported elsewhere (7). Tumor cells of P388 ascitic lymphocytic leukemia were taken from BDF mice. The P388 mouse leukemia cells were incubated in vitro at 37°C in a water bath with different concentrations of tested benzothiazines.

Benzothiazines were dissolved in small volume of DMSO and then added to Eagle tissue culture medium during 2 hrs. Cell suspansion (containing 1 x 10^6 cells) was inoculated intraperitoneally in each healthy recipient mice (male BDF_1 hybrids, weighing 22-24 g, 8 mice in each group). The inoculated mice were kept in animal rooms and observed for 60 days for their surviving time. The control group of 14 mice was inoculated with the same number untreated tumor cells and kept under identical conditions. The criterion of T/C (%) value on the increasing of the survival time for a direct cytotoxic activity was calculated by the mean survival time of treated mice (days) (T) versus the mean survival time of control mice (days) (C). In the present in vitro-in vivo experiments each benzothiazine have been tested at a dose level of 1, 10, 100 and 200 μg/ml respectively.

Results and Discussion

Among seven tested benzothiazines the most potent direct cytotoxic activity (increasing T/C % value to 20%), is exhibited by compound 1. The present study reveales that benzothiazines induces the direct cytotoxic activity in mice to various extents (Table 1). Phenothiazines, benzo[a]phenothiazines and benzo[c]acridines with similar structures induce anti-Escherichia coli activity in mice (8) and anti-Escherichia coli activity in vitro (9). These studies suggest that lymphocytic leukemia P388 cell activity of benzothiazines might be produced by immunopotentiation of the host animals.

Table 1 : Direct cytotoxic activity of benzothiazines on lymphocytic leukemia P388 cells

Comp. No.	Structure	T/C %			
		Dose (μg / ml)			
		1	10	100	200
Control		0	0	0	0
1		101.0	102.0	121.0	109.3
2		108.5	104.0	103.3	103.0
3		111.1	114.0	106.6	103.8
4		104.2	107.1	104.9	119.3
5		117.0	106.9	120.3	107.0
6		103.5	106.1	107.2	111.1
7		119.0	116.0	104.2	103.9

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