World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.com/
Research Article

Anticancer effects of cimetidine

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Received: 09-03-2014 / Revised: 24-03-2014 / Accepted: 29-03-2014

ABSTRACT

Cancer continues to be a major health problem for those in developed countries being a leading cause of death worldwide**.** Chemotherapy is able to kill some cancer cells especially the more rapidly replicating tumor cells, but they were nonspecific, characterized by low therapeutic index and associated with a wide range of side effects. Therefore the anticancer field still searching for treatments to avoid these side effects**.** The in vitro method was used to investigate the effect of pure cimetidine on four types of tumor cell lines [HeLa (human cervical cancer cell line, Passages 18-25), Rhabdomyosarcoma (RD, at 75 passages), Ahmad-Majeed-Glioblastoma-Multiform-2005 (AMGM-5, human cerebral glioblastoma multiform at passages 75-84), Ahmed-Mohammed-Nahi-2003 (AMN-3, spontaneous mammary adenocarcinoma at 158 passages) and normal cell line Rat Embryo Fibroblast (REF, at 87 passages)] in different concentrations and at different exposure times by MTT assay. The results showed that cimetidine exerted significant cytotoxic effects with all concentrations used (31.25-1000 µg) on all types of cell lines. Because of cytotoxic activity, good pharmacokinetic characteristics and the safety of drug which used for many years in the treatment of peptic ulcer disease, we can conclude that these characteristics make cimetidine a valuable treatment for many types of cancer.

Key Words: Cimetidine, Anticancer, Cell Line, Cervical Carcinoma, Rhabdomyosarcoma, Cerebral Glioblastoma, Mammary Adenocarcinoma

INTRODUCTION

Cancer continues to be a major health problem for those in developed countries being a leading cause of death worldwide and accounting for 7.9 million deaths in 2007. That number is slated to increase to 11.5 million by the year 2030. Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year [1]. Cancer is a complex set of more than 200 diseases with many causes and multiple stages and histological grades of malignancy [2-4]. This disease takes life's thousands of people of different age and sex every year in Iraq [5]. It has been estimated that approximately 15000 people have been died of cancer in 2005 in Iraq, this number represents 22.8% of the total deaths, moreover, it is expected that such percentage can be increased up to 35.4% in 2030 [6]. Cancer treatments continue to represent a major challenge to medical research [7]. Traditional therapies of cancer (surgery, radiation therapy, and chemotherapy) brought a limited success in treating this disease [8]. Chemotherapy is able to kill some cancer cells especially the more rapidly replicating tumor cells, but they were nonspecific, characterized by low therapeutic index and associated with a wide range of side effects [9-10]. Therefore the anticancer field still searching for treatments to avoid these side effects [11]. Cimetidine, the first histamine type 2 receptor antagonist to be used clinically, is commonly prescribed to treat gastro esophageal reflux disease, gastric and duodenal ulcers [12]. It has been reported that cimetidine improves the survival of patients with malignant tumors [13-14], including gastric [15], and colorectal carcinomas [16]. The mechanisms involved are incompletely understood. Previous studies showed that cimetidine stimulated the immune response, inhibited the adhesion , invasiveness and metastasis of cancer [13-16], however, the current study was carried out to investigate, if cimetidine exerts direct cytotoxic effect. The direct cytotoxicity of cimetidine in addition to its previously recorded effects will give it an additional value in cancer therapy.

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MATERIALS AND METHODS

The in vitro method was used to investigate the growth inhibitory effect of pure cimetidine on four types of tumor cell lines [HeLa (human cervical cancer cell line at 18-25 passages), Rhabdomyosarcoma (RD, at 75 passages), Ahmad-Majeed-Glioblastoma-Multiform-2005 (AMGM-5, human cerebral glioblastoma multiform at passages 75-84) , Ahmed-Mohammed-Nahi-2003 (AMN-3, spontaneous mammary adenocarcinoma at passages 158) and normal cell line Rat Embryo Fibroblast (REF, at passages 87)], in different concentrations and at different exposure times by MTT assay. These cell lines were kindly supplied by experimental therapy department, tissue culture unit/ Iraqi centre for cancer and medical genetics research (ICCMGR) maintained in RPMI- 1640 with 10% FCS and MEM with 10% FCS. Cell lines used in this study were subcultured when the cells in the flask formed confluent monolayer, using the previously described protocol [17-18]. The cell viability was determined before studying the cytotoxic effect of the drug on each cell line. Seeding of tryptinized and suspended cells for any cell line in a microtiter plate should be in the range of (10^4–10^5) cell /well for the growth cytotoxic assay [19]**.** Viable cell counting for the study cells were accomplished using trypan blue exclusion. Dead cells take up the dye within a second making them easily distinguishable under the microscope from viable cells which remain unstained. The following protocol was conducted [20].

a) Cell suspension was prepared (HeLa, AMN3, AMGM and RD cancer cell, REF normal cell).

b) Clean hemocytometer with its cover slip fixed on its place, was prepared.
c) One part of cell suspension (0.2 ml) to one part of trypan blue (0.2ml) to eight parts of PBS (1.6 ml) was mixed. Then 20 µl samples were transferred to the edge of the cover slip, allowed to run into the counting chamber.
d) After 1-2 minutes counting started with light microscope under 40X objective lens. Separate counts for viable and nonviable cells were recorded.
e) Cell concentration (cell/ml), total cell count, and cell viability (%) were calculated according to the following equations.

1) C= n × d ×10000

Where C= Cell concentration (cell/ml), n= number of counted cells, d= dilution factor=10

2) Total cell count = C (cell/ml) × the original volume of fluid from which the cell sample was taken.

3) Cell viability (%) =

$$\frac{\text{total viable cells (unstaind)}}{\text{total cells counted (staind \& unstaind)}} \times 100$$

Cytotoxicity assay:

Preparation of drugs stock solution: Pure cimetidine was obtained from state company for drug industries & medical appliances (SDI) - Samarra /Iraq. Stock solutions of this drug were prepared for cytotoxic assay (cell growth inhibition assay), by dissolved 0.01 g of cimetidine in 1ml triple distal water and filtered by 0.22µm syringe filter.

Preparation of cell lines for cytotoxic assay: Cell cultures in microtiteration plate (96 wells) were exposed to cimetidine at six concentrations during the log phase of growth and the effect was determined after the end of exposure time. The following method was used for cytotoxic assay:

a. Seeding: After cells in the incubated falcon became monolayer, the confluent monolayer was trypsinzed, then 200 µl of cell suspension seeds in microtitration plates were dispensed into each well, except wells at edges of plate to reduce the edge effect, that every well contain about 10^4 -10^5 cells/well and then coved by plate lids and sealed with self adhesive film then shacked gently and returned to the incubator.

b. Incubation: Microtitration plates were then incubated at 37˚c until the cells reached confluence (i.e., vary according to the types of cell line). After cells attachment, the plate was checked out for contamination.

c. Exposure: When the cells are in the exponential phase exactly in population doubling time (PTD),which the cells in full of its activity (depending on the growth curve of each cell lines), cells were exposed to six concentration of cimetidine (1000, 500, 250, 125, 62.5 and 31.25 µg/ml) (Four replicates for each tested concentration). 200µl of maintenance medium added to each well of control group (twelve wells were used).

d. Staining: Cell viability was measured after 24, 48 and 72 hrs of exposure by removing the medium, adding 28 µl of 2 mg/ml solution of MTT and incubating for 1.5 hrs at 37°C. After removing the MTT solution, the crystals remaining in the wells were solubilised by the addition of 130 µl of

Dimethyl Sulphoxide (DMSO) followed by 37°C incubation for 15 min with shaking.

The absorbency was determined on a microplate reader at 550 nm (test wavelength); the assay was performed in triplicate [21]. The inhibiting rate of cell growth was calculated as follow [22]:

Inhibition rate = $\frac{\text{mean of control} - \text{mean of treatment}}{\text{mean of control}} \times 100$

RESULTS

The results showed that cimetidine decreased the growth of AMGM5 cells significantly as compared to untreated control cells; it appeared that the growth inhibition was concentration and exposure time dependent. The results showed that the inhibition rates for the concentrations 31.25. 62.5, 125, 250, 500 and 1000µg/ml were 4.900, 11.342, 195.512, 27.125, 34.295 and 42.754% respectively after 24 hrs of exposure. When the exposure time increased to 48 hrs, the inhibition rates for these concentrations reached 15.497, 24.931, 31.912, 42.319, 50.753 and 58.587 % respectively. However after 72 hrs exposure the inhibition rates increased to 22.181, 32.617, 40.087, 48.694, 60.076 and 67.647% respectively (table 1).

As shown in the table 2, cimetidine decreased the growth of AMN3 cells significantly as compared to untreated control cells; the growth inhibition was also concentration and exposure time dependent. The results showed that the inhibition rates for the concentrations 31.25. 62.5, 125, 250, 500 and 1000µg/ml were 8.713, 16.819, 23.106, 28.910, 34.278 and 42.365% respectively after 24 hrs of exposure. After 48 hrs of exposure the inhibition rates increased to18.497, 24.126, 31.007, 37.981, 44.553 and 48.976% respectively. When the exposure period increased to 72 hrs, the inhibition rates reached 21.637, 33.137, 42.186, 50.163, 58.352 and 65.243% respectively.

Cimetidine also significantly decreased the growth of HeLa cells in comparison to untreated control cells with a concentration and exposure time dependent manner. When the HeLa cell line exposed to 31.25. 62.5, 125, 250, 500 and 1000µg/ml concentrations of cimetidine, the growth rates inhibited by 7.145, 12.567, 16.872, 24.506, 32.527 and 39.845% respectively after 24 hrs exposure. The same concentrations of the drugs exerted inhibition of growth rates 18.084, 25.251, 30.257, 40.595, 46.988 and 54.658%, when the exposure time increased to 48 hrs. However, after 72 hrs of exposure, the growth rates inhibition reached 31.740, 39.127, 48.080, 57.751, 65.141 and 73.060% for the same concentrations respectively (table 3).

The results also showed that cimetidine decreased the growth of RD cells significantly as compared to untreated control cells with a concentration and exposure time dependent manner. The inhibition rates for the concentrations 31.25. 62.5, 125, 250, 500 and 1000µg/ml were 7.145, 12.567, 16.872, 24.506, 32.527 and 39.845% respectively after 24 hrs of exposure. When the exposure time increased to 48 hrs, the inhibition rates for these concentrations reached 18.084, 25.251, 30.257, 40.595, 46.988 and 54.658% respectively. After 72 hrs exposure the inhibition rates increased to 31.740, 39.127, 48.080, 57.751, 65.141 and 73.060 % respectively (table 4).

Against normal cell line rat embryo fibroblast (REF), cimetidine in concentration of 31.25. 62.5, 125, 250, 500 and 1000µg/ml also exerted significant growth inhibition rates (5.132, 11.704, 16.931, 20.520, 26.207 and 30.908 % respectively) after 72 hrs exposure (table 5).

DISCUSSION

It has been reported that cimetidine improves the survival of patients with malignant tumors, including gastric and colorectal carcinomas [14-16, 23-24]. The mechanisms by which cimetidine improve survival rate in gastrointestinal tumors were included enhancement of the host immune response against tumor cells via blocking of histamine H2 receptors. By this mechanism, it enhanced infiltrating of lymphocytes in the tumors [16, 25-27]. Cimetidine also exerted an inhibitory effect on cancer cell migration and adhesion to endothelial cells, thus inhibiting tumor metastasis [28-32]. It was also reported that cimetidine inhibited colon adenocarcinoma cell adhesion to vascular endothelial cells and prevents metastasis by blocking E-selectin expression [31-32]. E-selectin is able to bind to certain types of complex carbohydrate chains that are frequently expressed on the surfaces of cancer cells but not by the healthy tissues from which they arise. Otherwise, cimetidine makes endothelial cells more slippery by suppressing the E-selectin adhesion protein, thus making it harder for cancer cells circulating in the bloodstream to bind to the endothelial lining of blood vessels [33-34]. However, in addition to the previously mentioned beneficial effects, this study also showed that cimetidine exerted direct cytotoxic effects on cell lines, this direct effect could be attributed to blocking of H2 receptors (H2R). Histamine regulates diverse biological responses related to tumor growth including proliferation, differentiation and apoptosis, which

indicate that histamine is a crucial mediator in cancer development and progression. [35-39]. So, overexpression of histidine decarboxylase (HDC), (the only enzyme responsible for the generation of histamine from L-histidine) at both the mRNA and protein levels, with an increased levels of histamine have been recorded in melanoma, small cell lung carcinoma, breast carcinoma, endometrial cancer and colorectal carcinoma [40-45]. In the other hand, inhibition of HDC with monofluormethyl histidine resulted in antitumoural effects on experimental tumors in rodents. Furthermore, the employment of specific HDC antisense oligonucleotides suppressed melanoma cell proliferation [42, 45-48]. Therefore the cytotoxicity of cimetidine could be related to blocking of H2R of histamine which promote tumor proliferation. Cimetidine has been in use for a number of years. It is generally well tolerated, and appears to be quite safe. Furthermore the drug characterized by a good pharmacokinetic characteristics, so, the effect of six months therapy with cimetidine (800 mg or 1600 mg/day) showed that the mean elimination half-life of cimetidine was 100±25 min, the total body cimetidine clearance was 652 + 223 ml/min, the mean volume of distribution at steady state was 65 ± 181 and the overall bioavailability was 78% [49-50]. Accordingly, we can conclude that the good pharmacokinetic characteristics, safety and direct broad anticancer effects make cimetidine a valuable additional treatment for many types of cancer.

Table 1: Growth inhibitory rate of different concentrations of cimetidine on AMGM5 cell line after 24, 48 and 72 hrs of exposure.

Conc. µg	Effects according to the period of exposure					
	24 hrs		48 hrs		72 hrs	
	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)
Control	0.605±0.030		0.606±0.015		0.594 ±0.020	
31.25	0.565±0.040*	4.900±1.194	0.480±0.032**	15.497±2.655	0.471±0.047**	22.181±3.087
62.5	0.518±0.053**	11.342±0.331	0.426±0.029***	24.931±2.816	0.408±0.036****	32.617±1.992
125	0.478±0.035***	19.512±1.504	0.386±0.030****	31.912±2.085	0.362±0.030****	40.087±1.054
250	0.434±0.049****	27.125±2.881	0.328±0.035****	42.319±4.276	0.309±0.017****	48.694±2.873
500	0.391±0.049****	34.295±2.929	0.279±0.027*****	50.753±3.194	0.240±0.018*****	60.076±3.988
1000	0.341±0.043****	42.754±3.041	0.234±0.014*****	58.587±2.503	0.194±0.024*****	67.647±5.433

In comparison with control , * (P< 0.05), ** (P< 0.01), ***(P< 0.001), ****(P< 0.0001), *****(P< 0.00001).

Table 2: Growth inhibitory rate of different concentrations of cimetidine on AMN3 cell line after 24, 48 and 72 hrs of exposure.

Con. µg	Effects according to the period of exposure					
	24 hrs		48 hrs		72 hrs	
	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)
Control	1.053 ± 0.088		1.053± 0.073		1.105±0.074	
31.25	0.904±0.046*	7.145±6.832	0.879±0.0974**	18.084±4.604	0.727±0.141****	31.740±11.832
62.5	0.846±0.042**	12.567±7.184	0.790±0.090***	25.251±1.802	0.649±0.168****	39.127±15.950
125	0.804±0.041***	16.872±6.641	0. 54±0.137****	30.257±3.458	0.553±0.144****	48.080±13.939
250	0.731±0.033***	24.506±5.599	0.643±0.139****	40.595±4.691	0.449±0.095*****	57.751±7.786
500	0.654±0.042****	32.527±4.229	0.578±0.147****	46.988±8.165	0.370±0.080*****	65.141±6.575
1000	0.584±0.074****	39.845±7.448	0.498±0.155*****	54.658±10.386	0.286±0.064*****	73.060±6.456

In comparison with control , * (P< 0.05), ** (P< 0.01), ***(P< 0.001), ****(P< 0.0001), *****(P< 0.00001).

Table 3: Growth inhibitory rate of different concentrations of cimetidine on HeLa cell line after 24, 48 and 72 hrs of exposure.

Conc. µg	Effects according to the period of exposure					
	24 hrs		48 hrs		72 hrs	
	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)
Control	0.685±0.075		0.610±0.014		0.657±0.066	
31.25	0.584±0.095*	8.713±9.180	0.480±0.032**	18.497±11.631	0.471±0.047***	21.637±9.712
62.5	0.532±0.084**	16.819±8.036	0.426±0.029***	24.126±3.696	0.408±0.036****	33.137±4.083
125	0.491±0.072***	23.106±6.037	0.386±0.030****	31.007±2.621	0.362±0.030****	42.186±1.843
250	0.453±0.056***	28.910±2.591	0.328±0.035****	37.981±1.085	0.309±0.017*****	50.163±1.306
500	0.436±0.050****	34.278±2.988	0.279±0.027****	44.553±1.176	0.240±0.018*****	58.352±2.365
1000	0.368±0.059****	42.365±3.963	0.234±0.014****	48.976±3.281	0.194±0.024*****	65.243±5.758

In comparison with control , * (P< 0.05), ** (P< 0.01), ***(P< 0.001), ****(P< 0.0001), *****(P< 0.00001) .

Table 4: Growth inhibitory rate of different concentrations of cimetidine on RD cell line after 24, 48 and 72 hrs of exposure.

Conc. µg	Effects according to the period of exposure					
	24 hrs		48 hrs		72 hrs	
	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)	Optical density (mean±SD)	Inhibition rate (mean±SD)
Control	0.588±0.014		0.593±0.017		0.588±0.008	
31.25	0.551±0.061*	5.957±5.638	0.553±0.040*	8.399±5.761	0.477±0.033**	21.622±5.555
62.5	0.527±0.054*	8.996±7.899	0.509±0.030**	15.664±3.721	0.434±0.030***	28.638±5.623
125	0.491±0.063**	15.363±10.243	0.471±0.048***	21.869±10.038	0.393±0.029****	35.450±4.635
250	0.445±0.053**	23.264±7.984	0.423±0.058****	29.869±10.038	0.337±0.024****	44.660±4.804
500	0.412±0.060***	28.972±9.395	0.388±0.056****	35.766±9.690	0.304±0.019*****	50.065±2.584
1000	0.358±0.063****	38.155±6.933	0.348±0.051****	42.295±8.873	0.260±0.033*****	57.932±4.957

In comparison with control , * (P< 0.05), ** (P< 0.01), ***(P< 0.001), ****(P< 0.0001), *****(P< 0.00001).

Table 5: Growth inhibitory rate of different concentrations of cimetidine on REF cell line after 72 hrs of exposure.

Concentration µg	Effect after exposure for 72 hrs	
	Optical density (mean±SD)	Inhibition rate (mean±SD)
Control	0.859±0.028	
31.25	0.790±0.073*	5.132±1.675
62.5	0.735±0.064**	11.704±2.916
125	0.692±0.068**	16.931±3.465
250	0.663±0.070***	20.520±3.701
500	0.610±0.081***	26.207±5.213
1000	0.578±0.092****	30.908±6.973

In comparison with control, * (P< 0.05), ** (P< 0.01), *** (P< 0.001), **** (P< 0.0001).

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