PHYSIOLOGICAL AND BIOCHEMICAL CHANGES FOR 5-FLUOROURACIL DRUG (ANTI-CANCER) IN CANCER PATIENTS

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ABSTRACT

The study was conducted to determine the effect of the 5-Fluorouracil (5-FU) drug is a medication used to treat cancer or the knowledge of 5-FU drug(anticancer) effect might help to attribute these side on physiological and biochemical parameters in human by injection into a vein it is used for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer and cervical cancer. 80 blood samples were obtained adult human divided into two groups for each group (n = 40), the first group (control) and the second group treatment with drug 5-fluorouracil.

There are a significant decrease (P <0.05) in the blood parameters included parameters Red blood cells count, the total number of white blood cells, platelets , hemoglobin and packed cell volume in men treatment with 5-fluorouracildrugcompared with control group. Causing the 5-FU drug significant decrease(P<0.05) in Triglycerides, cholesterol levels and total protein in the treatment group compared with control group. Also, the result showed a significant increase in Creatinine level of second group in compared with control group, while the results showed non- significant in urea level in human treatment when compared with control group.

The results showed a significant decrease (P <0.05) in the level of liver enzymes, (ALT AST and ALP) in the treatment group with 5-FU when compared with the control group.

INTRODUCTION

Fluorouracil (5-FU) drug is a medication used to treat cancer. By injection into a vein it is used for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer and cervical cancer. Common side effects include inflammation

of the mouth, loss of appetite, low blood cell counts, hair loss. The liver and kidneys serve as the major pathways for drug metabolism and elimination, A variety of renal disease can result from the drugs that are used to treat malignant disease. Chemotherapeutic agents can affect the glomerulus, tubules, interstitial, or the renal microvasculature, with clinical manifestations that range from an asymptomatic elevation of serum Creatinine to acute renal failure[1]. .

Cancer is a destroyed healthy tissues in the body and that the cases has increased rapidly and continuously, and the longer the disease from growing problems in the world in spite of the great development and progress in the level of science and technology[2]. Cancer is known being growth abnormal of some body's cells and these cells are characterized by antagonistic as grow, divide to multiply without stopping to be a mass of tumor malignancy and have the ability invasion nearby tissue and destroy it, or move to tissues distant and these capabilities are the characteristics of a malignant tumor Malignant tumor Unlike Benign tumor, which is characterized by a specific growth and the inability to invasion and moving. Cancer occurs as a result of a defect in the gene that controls cell proliferation and differentiation and death. Its characterized by tumor cells possessing enough energy for growth and avoid the cell Apoptosis [3].

Cancer drugs have been demonstrated to cause nephrotoxicity via direct tubular injury, tubular obstruction, injury to the tubulo -interstitium and glomerular damage, such as 5-FU drug widely in the treatment of many types of malignant tumors including liver, colon, rectal cancer, lung, stomach, intestines, breast, bladder, pancreas, cancer of the uterus and ovaries and urogenital channel[4].

Chemotherapy is used to express Cytotoxic Drugs that affect all cells distinct rapid division such as generating stem cells, as there are chemical drugs have the ability to target cancer cells, called targeted drugs, Chemotherapy interferes with cell division in various regions, such as the overlap in double Duplication DNA or

Chromosomes when configured. Usually toxic drugs target rapidly dividing cells, a non-specific target and can target cancer cells and healthy alike [5].

Appear toxicity 5-FUdrug in infectious Channel later usually so be careful and complicated drug treatment, and the effects of early toxicity of the drug nausea, loss of appetite, diarrhea and inflammation of the oral [6]. The late toxic effects would be in form of sore and necrosis and of the stomach other parts of the gastrointestinal canal [7].

Induces 5-FU drug immune suppression and strongly inhibits the primary and secondary immune responses, and the effects are immediate strongest toxicity in Central peripheral lymphocytes. The single dose of 5-FU drug able to eradicate 90% of lymphocytes of type B (B lymphocytes) and 98% of Medullary cells and 90% of the cells thymus and 50% of the total spleen cells, The effects attributed immunosuppressive medication by its ability to decrease the selective cell lymphoma B, T and macrophages phagocytic cells show resistance to the 5-FUdrug. As well as toxic effects are directly to the lymphatic cells of the resulting cell to mediate. Also cause 5-FUdrug inhibition constant growth in the common cells in the humoral immune and maturation [8].

Increased warnings by the pharmaceutical Drug Information of the United Nations (FAO) United stated pharmacopoeia drug information in order to protect the profession of health that 5-FUdrug and metabolites have the possibility of induction of secondary cancers owns and despite the probability that they will be less influential than alkylating agents used in the treatment of cancer[9].

The impact of a range of anticancer drugs in the blood standards, as the researchers found a significant decrease in each of the following blood parameters RBC count, WBC count, Hb, Platelets when treating patients drug Anticancer Busulphan, and continued to this effect to the day 60 to give potions different, as shown in this study that the drugs cause residual damage in bone marrow cells, as for other drugs used in this

study, which included both anti-cancer drugs Doxorubicin, Cisplatin, Cyclophosphamide showed to tara morally in the same blood criteria previously mentioned[10].

Therefore many anti-cancer drugs have been used. Among the most important drugs used is 5-FU which is used in the treatment of many malignant tumors. Therefore, this study was designed to investigate and identify physiological and biochemical changes and effects.

MATERIALS AND METHODS

Blood samples collected from man patients in Habboubi hospital in a province Thi-Qar, Iraq. during the period of study from 01/11/2015 to 01/03/2016.80 blood samples were obtained adult human divided into two groups for each group (n = 40), the first group (control) and the second group treatment with drug 5-fluorouracil. The blood parameters were measured by using coltter in the laboratory of Habboubi hospital in Thi-Qar, Iraq. 5 ml of blood samples were collected and divided in to two parts the first part was 2 ml in EDTA tubes, and analyzed to determine of hematological parameters such as a red blood cell count (RBC), the packed cell volume (PCV), hemoglobine (Hb), white blood cells(WBC) and platelets by using an automatic hematological assay analyzer (Nihon Kohden corporation, Japan), and the second part was 3ml blood was collected from each adult men into plain centrifuge tubes, at room temperature for clotting. Serum was separated by centrifugation at 3000g for 30 min and analyzed, for the concentration of Urea, Creatinine, Total protein, cholesterol, Triglycerides, Alanine transaminase (ALT), Aspartate transaminase (AST) and Alkaline phosphatase (ALP).

Statistical Analysis

The samples for study data collection and statistical analysis using the system (SPSS 14) to the Windows system, as was the use of the contrast between the totals analysis of analysis of variance (ANOVA), to know the Least significant differences (L.S.D).

RESULT

Table (1) there were a significant decrease(P<0.05) in red blood cells, the blood compact volume (PCV), hemoglobin, platelets and white blood cells in the second group (patients treated with 5-fluorouracil) compared with the first group (the control).

Table (1): Effect of 5-fluorouracil on some hematological parameters of male

Parameters groups	RBC $10^6/mm^3$	WBC $10^3/mm^3$	PCV %	HB %	Platelets $10^5/mm^3$
First group (control)	5.19 ± 0.30[a]	8.3 ± 0.23[a]	42.0 ± 0.9[a]	12.08 ± 0.32[a]	190.0 ± 11.21 [a]
Second group Treatment 5-FU	3.40 ± 0.12[b]	3.8 ± 0.26[b]	29.7 ± 0.99[b]	9.5 ± 0.34[b]	115.58 ±8.08 [b]
LSD	0.96	1.65	2.987	1.163	12.817

*Values are means ± S.E.

*Different letters refer to a significant difference (P<0.05)

*Same letters refer to none a significant differences (P<0.05)

Table (2) showed   significantly an increase (P<0.05) in creatinine level in the blood of patients treated with serum 5-fluorouracildrug, while non-significant decrease in the level of urea when compared with the control group.

Table (2) the effect of the drug 5- FU in kidney function

Parameters groups	Urea mg/dL	Creatinine mg/dL
First group (control)	34.10 ±1.26^a	0.73 ±0.03^b
Second group Treatment 5-FU	33.56 ±1.02^a	1.37 ±0.09^a
LSD	1.41	0.59

*Values are means ± S.E.

*Different letters refer to a significant difference (P<0.05)

*Same letters refer to none a significant difference (P<0.05)

a significant decrease in the level of the probability (P<0.05) in concentration of Triglycerides and cholesterol, and also significant decrease in the total protein concentration in the blood serum male treated in drug 5-fluorouracil that compared with the control group (table 3).

Table (3) the effect of the drug 5- FU in Triglycerides, cholesterol and total protein

Parameters Groups	Triglycerides mg/dL	Cholesterol mg/dL	Total protein g/dL
First group (control)	98.17 2.80^a±	80.52 3.35^a±	7.82 0.54^a±
Second group Treatment 5- FU	87.23 2.17^b±	68.13 1.52^b±	5.39 0.11^b±
LSD	7.771	9.511	0.940

*Values are means ± S.E.
*Different letters refer to a significant difference (P<0.05)
*Same letters refer to none significant differences (P<0.05)

Table (4) Explain a significant decrease(P<0.05) in the level of liver enzymes in the Treatment in comparison with the control group.

Table (4) the effect of drug 5FU in testing liver function male treated

Parameters Groups	AST IU/L	ALT IU/L	ALP IU/L
First group (control)	52.62 ±0.41[a]	189.80 ±0.49[a]	138.61 ±2.01[a]
Second group Treatment 5-FU	49.18 ±0.96[b]	155.08 ±0.33[b]	115.03 ±3.56[b]
LSD	0.96	0.68	9.46

*Values are means ± S.E.
*Different letters refer to a significant difference (P<0.05)
*Same letters refer to non a significant differences (P<0.05)

DISCUSSION

The results of the current study showed a reduction in physiological and biochemical levels due to use of 5- Fluorouracil drug (anticancer) in man. The main reasons for decrease blood standards are acute toxic effect of 5-FUdrug on the bone marrow cells that generate blood cells through the occurrence of pharmacological suppression of these cells [4].

There is a clear reduction in blood cells of patients treated with 5-fluorouracil, because the 5-fu drug is caused to suppress severe immunization caused by the reduction of white blood cells, in particular central and peripheral lymphocytes that are directly affected by the drug, which could lead to the result of the significance decrease of the number of white cells in the peripheral blood. Also, the drug affects in the lymphocytes type of T and B in the spleen and lymph glands[11].

The results of the present study were agreed with[12]showed that the cause of this decrease is due to the degree of suppression of bone marrow cells that resulting due to treatment with anti-cancer cells from the bone marrow stem cells which established the blood cells.

Also The 5-FU drug affects the Platelet - activating factor (PAF), which has a role in the regulatory impact of the proliferation and differentiation the cells, as well as it presence in the spleen and thymus gland which has a regulatory role in the blood-forming organs so the low level of this factor by the drug 5-FU causes a decrease in the number of blood cells types[13].

The present study showed a significant increase in Creatinine level due effect of anticancer drugs in various places of the nephron, which is the basic unit and functional structural of kidneys and especially the glomeruli and proximal and distal tubules, This cause dysfunction of the glomeruli reduction of glomerular filtration resulting in an increase in the level of concentration of creatinine in the plasma, and the dysfunction in the proximal tubule lead to a reduction of the levels of Na, K, Ca, Mg, P, Cl in the plasma, while causing dysfunction in the distal tubule increase at acidic pH level and urea[14].

There is significant decrease in the level of liver enzymes (AST, ALT and ALP) in the serum of patients treated with 5-FU drug and this decrease is an indication and evidence of hepatotoxicity occurs causing from hydropic degeneration of most of hepatic cells and necrosis.

The results were agreed with [15]who studied the effect of 5-FU in human patients. It is believed that such pathological damage could be attributed to the toxic effects of the drug on the hepatic cells. The drug 5-FU cause toxicity in the liver cells and this may significantly decrease in these enzymes due drug damage in liver cells, as the[16]referred to that giving chemotherapy caused significant changes in the level of enzymes AST and ALT in patients' blood serum. In addition to that 5-FU drug cause disintegration and

Inhibition in the manufacture of RNA through drug interferes with nucleotides of the RNA. This causing a decrease in functional synthesis of proteins in the liver cells and this may cause a decrease in the enzymes AST, ALT and ALP in liver cells [17, 18].

In conclusion, the 5-FU human therapeutic regime is safe to blood cells (WBC, RBC, PCV, HB, Platelets) and the kidney and liver for a large extent while the higher doses and for time long are not safe and must be used carefully under close medical supervision.

التغيرات الفسلجية والكيموحيوية لعلاج 5- فلورويوراسيل (المضاد للسرطان) في مرضى السرطان

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أجريت الدراسة الحالية لمعرفة تأثير دواء 5- فلورويوراسيل (5-FU) وهو دواء يستخدم لعلاج السرطان او لمعرفة تأثير علاج 5- فلورويوراسيل (المضاد للسرطان) على الجوانب الفسلجية والكيموحيوية عن طريق الحقن في الوريد ويستخدم لعلاج سرطان القولون، المريء، المعدة، البنكرياس، الثدي و سرطان عنق الرحم.جمعت (80) عينة وقسمت الى مجموعتين كل مجموعة تحتوي على (40) عينة المجموعة الاولى هي مجموعة السيطرة اما المجموعة الثانية هي مجموعة المرضى المعالجين ب5- فلورويوراسيل.

لوحظ انخفاضا معنويا عند مستوى احتمال (0.05> P) في المعايير الدموية (كريات الدم الحمراء، خلايا الدم البيضاء، الصفيحات الدموية، الهيموكلوبين وحجم الخلايا المضغوط وكذلك انخفاضا في مستوى الدهون الثلاثية، الكولسترول والبروتين الكلي في مجموعة المرضى المعالجين ب(5-FU) مقارنة مع الكونترول، كما لوحظ ارتفاعا معنويا في مستوى الكرياتنين في مجموعة المرضى المعالجين ب (5-FU)، ولم تظهر النتائج وجود فارق معنوي في مستوى اليوريا.

كما اظهرت النتائج انخفاضا معنويا في مستوى انزيمات الكبد (ALT AST and ALP)في مجموعة المرضى المعالجين ب (5-FU) مقارنة مع الكونترول.

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