

Assessment of liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs in Gaza strip

Raisa EL Massri¹, MSc., Mohammad Shubair², PhD and Mahmoud Sirdah³, PhD

Abstract

Background: many drugs affect liver and kidney functions, among these, drugs used to treat psychotic patients such as chlorpromazine (CPZ) which is used to treat schizophrenia and Trihexyphenidyl- hydrochloride (T.H.P) which is used to treat side effects of antipsychotic medication, another drug which is used to treat epilepsy is valproic acid (VPA) which may affect the liver and kidney functions.

Objective: The present study aims to assess liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs for more than one year .

Materials and methods:The present study is a case control study comprised of 220 subjects including 110 psychiatric and epileptic patients from Mental Health Clinics in Gaza and 110 healthy people as a control group. Laboratory investigations were carried out by collecting five ml blood from each subject into vacutainer plain tubes. The serum was separated and used for the assessment of gamma glutamyltransferase (GGT), aspartate aminotransferase(AST), alanine aminotransferase(ALT), urea, creatinine, uric acid, alkaline phosphatase (ALP), total and direct bilirubin (TB, DB). They were assayed biochemically using biosystem autoanalyzer At Beit Hanoun hospital laboratories.

Results: The liver and kidney function tests among epileptic patients receiving Valproic Acid (VPA) showed high statistically significant increase between cases and control groups in AST level($p < 0.01$) while There was no significant difference observed in relation to ALT, ALP,GGT levels and TB,DB,urea,creatinine and uric acid concentrations as Compared to control.

liver and kidney function tests in psychiatric patients suffered from schizophrenia who were receiving chlorpromazine (CPZ) with Trihexyphenidyl hydrochloride (T.H.P) showed, significant increase between cases and control group in relation to AST($p=0.004$), ALP($P=0.022$), GGT($P=0.005$), DB($P=0.001$), creatinine ($P 0.01$) and uric acid ($P=0.029$)tests. TB and urea concentrations were not Significant.

Conclusion: Liver and kidney functions should be monitored regularly for psychiatric patients, in particular, those who are therapeutically managed with a combined dose of CPZ and THP.

Keywords: liver & kidney function tests ,antipsychotic & antiepileptic drugs, Gaza, Palestine

2, Corresponding Author, e. mail: mohshubair@gmail.com

1,2 The Islamic University, Gaza, Palestine

3, Al-Azhar University, Gaza, Palestine

تقييم وظائف الكبد والكلى لدى المرضى النفسيين ومرضى الصرع في قطاع غزة

ملخص:

المقدمة: هناك العديد من الأدوية التي تؤثر على وظائف الكبد والكلى، ومنها تلك الأدوية التي تستخدم لعلاج المرضى الذين يعانون من الأمراض النفسية مثل كلوربرومازين الذي يستخدم لعلاج انفصام الشخصية، وتراييكسفينديل هيدروكلوريد و الذي يستخدم لعلاج الآثار الجانبية للكلوربرومازين وعقار حامض الفالبرويك الذي يستخدم لعلاج الصرع.

الهدف: تقييم وظائف الكبد والكلى لدى المرضى الذين يعانون من الأمراض النفسية ومرضى الصرع الذين يتعاطون الكلوربرومازين او حامض الفالبرويك لاكثر من سنة.

الطرق والأدوات: شملت هذه الدراسة 220 شخصاً من بينهم 110 مريضاً مصابون بالصرع أو أحد الأمراض النفسية والذين تم تجميعهم من عيادات الصحة النفسية في قطاع غزة، وكذلك 110 شخصاً سليماً كعينة ضابطة. وقد تمت الفحوصات المخبرية لهذه الدراسة بسحب 5 مل دم من كل مريض وإجراء عليها فحوصات تقييم وظائف الكبد والكلى بواسطة تقنية التحليل الآلي، وتم استخدام برنامج SPSS في تحليل البيانات التي حصلنا عليها.

النتائج: أظهرت نتائج الفحوصات الخاصة بوظائف كلا من الكبد والكلى لدى مرضى الصرع الذين يتناولون حامض الفالبرويك ارتفاعاً في فحص الأسبرتيت أمينوترانسفيريز، عند مقارنته بنتائج العينة الضابطة وهذا الارتفاع ذو دلالة إحصائية ($p < 0.01$)، بينما لا يوجد أي دلالات إحصائية في الفحوصات الأخرى وهي الجاما جلوتيميل ترانسفيريز، والألنين أمينوترانسفيريز، والبولينا، والكرياتينين، و حامض البوليك، والالكالين القاعدي، والبليروبين الكلى والمباشر.

وأظهرت فحوصات الكبد والكلى لدى المرضى الذين يعانون من الأمراض النفسية والذين يتناولون علاج الكلوربرومازين مع تراييكسفينديل هيدروكلوريد بوجود ارتفاعات ذات دلالة إحصائية في فحوصات الجاما جلوتيميل ترانسفيريز ($p = 0.005$)، والأسبرتيت أمينوترانسفيريز ($p = 0.004$)، والكرياتينين ($p < 0.01$)، و حامض البوليك ($p = 0,029$)، والألكالين القاعدي ($p = 0,022$)، والبليروبين المباشر ($p = 0.001$)، عند مقارنتها بنتائج العينة الضابطة، بينما لا توجد أي ارتفاعات في فحوصات الألنين أمينو ترانسفيريز، والبولينا، والبليروبين الكلي.

الاستنتاجات: أظهرت هذه الدراسة وجود تأثيرات سلبية على وظائف كلا من الكبد والكلى خاصة لدى المرضى الذين يتعاطون عقار الكلوربرومازين وعليه فاننا نوصي بعمل فحوصات دورية لوظائف الكبد والكلى لهذه المجموعة.

الكلمات المفتاحية: تقييم وظائف الكبد والكلى، الأدوية المضادة للذهان و الادوية المضادة للصرع

غزة - فلسطين

Assessment of liver and kidney functions in patients receiving

Introduction

Psychosis: from the Greek "psyche", for mind or soul, and "osis", for abnormal condition literally means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality" (1) . People suffering from psychosis are said to be psychotic. People with psychosis may have one or more of the following: hallucinations, delusions, or thought disorder. The exact cause of psychotic disorders is unknown. Psychosis may appear as a symptom of a number of mental disorders including mood and personality disorders, schizophrenia, and delusional disorder. Schizophrenia is a particular type of psychosis that is, a mental disorder caused by some inherent dysfunction of the brain. it is characterized by delusions, hallucination (often in the form of voices), and thinking or speech disturbances (2). This mental disorder is a common affliction, occurring among about one percent of the population (3). Many antipsychotic drugs are available for the treatment of schizophrenia. These drugs such as: Chlorpromazine, Haloperidol, Risperidone, exert blocking effects on a wide range of receptors including dopamine and adrenoceptor, muscarinic, H1 histaminic, and serotonin (5-HT₂). Dopamine receptor effects quickly became the major focus of interest. Dopamine receptors control neural signaling that modulates many important behaviors, such as spatial working memory (4).The epilepsies are one of the most common serious brain disorders, which can occur at all ages, and have many possible presentations and causes.

Although incidence in childhood has fallen over the past three decades in developed countries (5). It rounds 50 cases per 100 000 of the population . The aim of drug therapy is to prevent, cure or control various disease states. To achieve this, adequate drug doses must be delivered to the target tissues. After the absorption of the drug, it is metabolized in the liver,. The liver metabolizes virtually every drug or toxin introduced in the body(6). Most drugs are lipophilic (fat soluble), enabling easy absorption across cell membranes. In the body, they are rendered hydrophilic (water soluble) by biochemical processes in the hepatocytes to enable inactivation and easy excretion. Metabolism of drugs occurs in 2 phases. In the phase 1 reaction, the drug is made polar by oxidation or hydroxylation.

Cytochrome P450s play a central role in the metabolism and disposition of an extremely wide range of drugs and chemical carcinogens (7). Most of these intermediate products are transient and highly reactive. These reactions may result in the formation of metabolites that are far more toxic than the parent substrate and may result in liver injury.

Phase 2 reactions may occur within or outside the liver. They involve conjugation with a moiety (i.e., acetate, amino acid, sulfate, glutathione, glucuronic acid) that further increases solubility. Subsequently, drugs with high molecular weight may be excreted in bile, while the kidneys excrete the smaller molecules (8). Removal of a drug from the body may occur via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers. This study aims to assess liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs for more than one year. Noteworthy, this is the first study done in our area, the results reported here may alert physicians about the harmful consequences of these drugs so they could initiate early action to prevent or delay such consequences.

Materials and Methods

Study Sample

Study sample comprised 220 subjects including 110 psychiatric and epileptic patients from Mental Health Clinics in Gaza and 110 healthy people as a control group. Sample size was calculated according to standard formula(9). Patients were selected randomly from those who visit Outpatient clinics regularly. Clinics included three from northern area, two from Gaza city and one from each of the following areas; middle, khanyounis and Rafah. Control samples matched patients for sex and age, all of them were apparently healthy individuals. Average age of the study group who were receiving CPZ was 37 years, while for those receiving VPA it was 8 years. Ethical considerations were observed strictly and the approval of Helsinki committee was obtained before conducting this research.

Drugs were administered orally, CPZ dose was 25mg thrice daily in addition to 5mg THP. The dose of VPA was calculated according to weight; 15mg/kg.

The biochemical quantization data were tabulated, encoded and were statistically analyzed using SPSS version 15. Comparisons between the mean values of the selected biochemical parameters were made using the independent t-test analysis. P-value of less than 0.05 was considered statistically significant.

Laboratory Investigations:

Venous blood specimens(5ml) were collected from individuals and delivered into serum vacutainer tubes. Sera were obtained by centrifugation at 3000 rpm for 15 min and were used for the following assays:

1. Determination of serum urea

Serum urea was determined using LABKIT.

Assessment of liver and kidney functions in patients receiving

Method : Urease – GLDH. Kinetic (10).

2. Determination of serum creatinine

Serum creatinine was determined according to Jaffe using LABKIT .

Method : Jaffe Colorimetric- Kinetic (11).

3. Determination of serum uric acid

Serum uric acid was determined according to Globe Diagnostics S.R.I

Method : Enzymatic colorimetric (12)

4. Determination of serum Alanine aminotransferase (ALT)

Serum ALT was determined according to Globe Diagnostics S.R.I

Method: Optimized UV test according to Scandinavian Committee on Enzymes (SCE) (13).

5. Determination of serum Aspartate aminotransferase (AST)

Serum AST was determined according to Globe Diagnostics S.R.I

Method: Optimized UV test according to Scandinavian Committee on Enzymes (SCE) (14).

6. Determination of serum Alkaline phosphatase (ALP)

Serum ALP was determined according to Cromatest

Method : Kinetic (15).

7. Determination of serum Gamma glutamyltransferase (GGT)

Serum GGT was determined according to International Federation of Clinical Chemistry (IFCC) by Diasys Diagnostic Systems GmbH

Method : Kinetic photometric test (16).

8. Determination of serum Bilirubin (Total and Direct)

Serum bilirubin was determined according to diazotized sulfanilic method by Biosystem S.A, **Method** :Colorimetric (17)

Results

Distribution of patients according to disease

As shown in Table 1 among the cases, the percentage of patients suffering from schizophrenia was 44.5%, while those suffering from epilepsy represented 47.3% and those having mental retardation represented by 8.2% .

Table 1: Type of disease

Disease	Number (n=110)	Percent (%)
Schizophrenia	49	44.5
Epilepsy	52	47.3
Mental Retardation	9	8.2

Distribution of patients according to residency

Table 2 reveals that there were 33.6% of cases from north governorate, while 30.9% were from Gaza, 27.3% from middle zone and 8.2% from South governorate .

Table 2: Distribution of patients according to residency

Governorate	Number (n=110)	Percent (%)
North	37	33.6
Gaza	34	30.9
Middle	30	27.3
South	9	8.2

Effect of Valproic acid administration on liver function of epileptic patients and control

Table 3 shows the results of liver function tests among epileptic patients receiving VPA as antiepileptic drug. There was no significant difference ($t = -1.320$, $p = 0.190$) between cases (26.60 ± 12.03 u/l) and control (24.07 ± 7.54 u/l) in ALT level. There was highly statistic significant increase ($t = -4.306$, $p = 0.000$) between cases (34.38 ± 14.06 u/l) and control (25.13 ± 7.52 u/l) in AST level. There was no significant difference observed in ALP level ($t = 1.470$, $p = 0.145$) in cases as compared to control (472.1 ± 168.3 u/l) and (519.1 ± 167.5 u/l) respectively, For GGT level no significant values were obtained ($t = -1.678$, $p = 0.096$) between cases (17.4 ± 6.2 u/l) and control (15.9 ± 3.3 u/l) There was no significant difference ($t = 0.585$, $p = 0.560$) between total bilirubin in cases (0.79 ± 0.28 mg/dl) and control (0.82 ± 0.16 mg/dl). In direct bilirubin there was no significant difference ($t = -1.127$, $p = 0.262$) between cases (0.24 ± 0.15 mg/dl) and controls (0.21 ± 0.09 mg/dl).

Table 3 : Effect of valproic acid administration on liver function tests of cases and control

Parameter	Control (n=55) mean±SD	Case (n=55) mean±SD	T	P-value
ALT(u/l)	24.07±7.54	26.60±12.03	-1.320	0.190
AST(u/l)	25.13±7.52	34.38±14.06	-4.306	0.000
ALP (u/l)	519.1±167.5	472.1±168.3	1.470	0.145
GGT(u/l)	15.9±3.3	17.4±6.2	-1.678	0.096

Assessment of liver and kidney functions in patients receiving

Total Bilirubin (mg/dl)	0.82±0.16	0.79±0.28	0.585	0.560
Direct Bilirubin (mg/dl)	0.21±0.09	0.24±0.15	-1.127	0.262

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase .SD: standard deviation; $p>0.05$ non significant, $P<0.05$ significant; $p<0.01$ highly significant.

Effects of valproic acid administration on kidney function of epileptic patients and control

Table 4 illustrates that there was no significant difference ($t = -0.179$, $p = 0.858$) between epileptic patients(25.69 ± 9.2) who were receiving VPA and control (25.42 ± 6.6) in urea concentration. Likewise there was no significant difference between cases and control mg/dl) in creatinine and uric acid concentrations, $p=0.38$ and $p=0.564$ respectively.

Table 4: Effects of valproic acid administration on kidney function of epileptic patients and control.

Parameter	Control (n=55) mean±SD	Case (n=55) mean±SD	T	P-value
Urea (mg/dl)	25.42±6.6	25.69±9.2	-0.179	0.858
Creatinine (mg/dl)	0.64±0.14	0.66±0.15	-0.871	0.386
Uric acid (mg/dl)	4.11±1.03	4.24±1.21	-0.579	0.564

SD: standard deviation; $p>0.05$ non significant; $p<0.05$ significant; $p<0.01$ highly significant.

Effects of chlorpromazine with Trihexyphenidyl hydrochloride administration on liver function of psychiatric patients and control.

Table 5 illustrates the liver test among psychiatric patients suffered from schizophrenia who were receiving CPZ with T.H.P. There was no significant difference ($t = -1.799$, $p = 0.075$) between cases (28.06 ± 12.8 u/l) and control (24.31 ± 8.6 u/l) in ALT level. While there were significant increase in AST,ALP and GGT levels($p=0.004$, $p=0.022$, $p=0.0050$ respectively as compared to control. There was no significant difference($t =$

- 1.477, p=0.143) in total bilirubin between cases (0.94±0.38 mg/dl) and control (0.85±0.17 mg/dl). In direct bilirubin there was significant difference (t = -3.485, p = 0.001) between cases (0.35±0.32 mg/dl) and controls (0.19±0.05 mg/dl).

Table 5 : Effects of chlorpromazine with Trihexyphenidyl hydrochloride administration on liver function of psychiatric patients and control.

P-value	T	Case (n=55) Mean ± SD	Control (n=55) mean ± SD	Parameter
0.075	-1.799	28.06±12.8	24.31±8.6	ALT(u/l)
0.004	-2.965	29.73±6.9	25.31±8.7	AST(u/l)
0.022	-2.320	209.4±87.2	178.5±46.3	ALP (u/l)
0.005	-2.838	30.9±30.2	19.2±5.1	GGT(u/l)
0.143	-1.477	0.94±0.38	0.85±0.17	Total Bilirubin(mg/dl)
0.001	-3.485	0.35±0.32	0.19±0.05	Direct Bilirubin(mg/dl)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase . SD: standard deviation; p>0.05 non significant; p<0.05 significant; p>0.01 highly significant.

Effects of chlorpromazine with trihexyphenidyl hydrochloride administration on kidney function of psychiatric patients and control.

Table 6 illustrates the kidney test among psychiatric patients suffered from schizophrenia who were receiving CPZ with T.H.P drugs. There was no significant difference (t = - 0.891, p = 0.375) between cases (28.71±10.22 mg/dl) and control (27.24±6.8 mg/dl) in urea test. There was statistically significant difference (t = - 6.681, p = 0.000) between cases (1.03±.18 mg/dl) and control(0.81±0.17 mg/dl) in creatinine test. There was significant difference in uric acid test (t = -2.208, p=0.029) when compared between cases (6.25±5.70 mg/dl) and control (4.53±.95 mg/dl) .

Assessment of liver and kidney functions in patients receiving

Table 6: Effects of chlorpromazine with trihexyphenidyl hydrochloride administration on kidney function of psychiatric patients and control.

P-value	T	Case (n=55) Mean ± SD	Control (n=55) mean ± SD	Parameter
0.375	-0.891	28.71±10.22	27.24±6.8	Urea(mg/dl)
0.000	-6.681	1.03±0.18	0.81±0.17	Creatinine(mg/dl)
0.029	-2.208	6.25±5.70	4.53±0.95	Uric acid(mg/dl)

SD: standard deviation; $p > 0.05$ non significant; $p < 0.05$ significant; $p < 0.01$ highly significant

Discussion

Assessment of liver function in epileptic patients receiving Valproic Acid

The present study assessed the liver function test in epileptic children receiving (VPA) for more than one year, the results show that ALT, GGT, ALP, Total and Direct bilirubin were not statistically significant when these results were compared with those of control group. On the other hand AST activity was statistically significant. These findings are in agreement with other researchers (18) Other researchers obtained the same results with the exception of AST where they found no difference between patients and control groups (19). This controversy between our results and theirs may be due to small sample size and the fact that their target group might have administered the drug for longer periods than ours. Our results showed a significant difference in relation to AST, this may be explained based on the fact that AST is distributed in many other organs beside liver. Muscle cells contain appreciable amounts of this enzyme. It is well known that antiepileptic drugs affect muscles causing their relaxation, which may be the cause of elevated activity of AST in such patients. Among our patients, eight of them had elevated levels in ALT and nine with GGT. This could be explained on the basis that they administered high doses over a long period of time which leads to this result. Other researchers (20,21) correlated high doses with abnormal liver functions. We expect that these eight or nine patients did not receive special care and attention from their families in relation to drug administration.

Other studies (22) reported the same results with a slight difference in relation to ALT and AST where they significantly increased after two years

of treatment with VPA. These differences between our results and theirs may be due to the fact that their target group might have administered the drug for longer periods than ours. Elevated level in these enzymes may be due to genetic, environmental factors or preexisting of another disease which affected the liver and not discovered. Our results showed no significant difference in relation to ALP, TB, DB, and GGT which coincides with other studies (23). Other researcher (24) evaluated the relationship between plasma concentrations of VPA and the occurrence of side effects especially hepatotoxicity in patients receiving high doses of VPA. The present study showed that adverse effects and clinical signs of liver toxicity may be present in VPA concentrations generally considered in the therapeutic range especially when used in combination with antiepileptic drugs like phenobarbital or carbamazepine and benzodiazepines. This finding put more emphasis on dose adjustment, we may conclude that the patients of the present study most probably receive the correct dose of VPA. A documented study in UK (25) reported 49 cases of hepatotoxicity caused by VPA which ends in death. However, most of those children had other pre-existing problems in addition to epilepsy. This is not the case of our target group. Other researcher looked for more sensitive indicators than GGT and ALP for liver damage such as serum protein F (26), so we should think of performing more sensitive indicators to detect the signs of liver damage progression as early as possible.

Assessment of kidney function in epileptic patients receiving VPA.

The present study showed no significant differences between patients and control group in relation to kidney function. All parameters (urea, creatinine, and uric acid) proved to be normal in both groups. This result is in agreement of Altunbasak et al (22, 27). It seems that the kidney is not affected by the metabolites of VPA and these molecules do not cause nephrotoxicity. The dose of VPA is considered to be in the therapeutic range. that's mean VPA is safe for long term treatment and not toxic to liver or kidney when used in suitable dose.

Assessment of liver function in psychiatric patients who were receiving Chlorpromazine and Trihexyphenidyl Hydrochloride.

Our results show that patients who were receiving CPZ with T.H.P had abnormal liver function tests namely AST, ALP, GGT, and DB. These results are in agreement with those obtained by Garcia-Unzueta et al (28, 29). TsingHua (30) studied the difference in the effect on indices of liver function in schizophrenic patients treated with CPZ. ALT level was elevated after 8 weeks of treatment but after 5 weeks, it returned to its normal level.

Assessment of liver and kidney functions in patients receiving

It is noted that the AST enzyme activity was increased highly significant, this increment may be due to the decomposition of red blood cells, especially that direct bilirubin was elevated and statistically significant, where it is known that bilirubin resulting from the break down of red blood cells, this indicates the presence of post-liver problems such as hepatocellular damage, intrahepatic and extrahepatic biliary tract obstruction which might lead to appearance of jaundice (30).

Assessment of kidney function in psychiatric patients receiving Chlorpromazine and Trihexyphenidyl Hydrochloride.

Results of the present study showed that kidney function is affected by the administration of CPZ & T.H.P. This is indicated by significant differences between cases & control groups in relation to creatinine & uric acid, on the contrary urea levels were not significant. It is well known that creatinine is a sensitive marker of kidney damage while uric acid which is another test of kidney function might be elevated- In addition to kidney impairment- due to the effect of CPZ & T.H.P on purine metabolism. Kidney impairment may be due to the fact that some CPZ is excreted unchanged in urine and due to high lipophilic characters of its metabolites, it may be detected in the urine up to 18 months which may cause long term toxicity of the kidney(32)

Recommendations

It was concluded that liver and kidney functions should be monitored regularly in psychiatric patients specially in those who are therapeutically managed with a combined dose of CPZ and THP. VPA in the current therapeutic dose is considered to be safe,

however a large scale study with and extended follow up period is recommended for better evaluation of used drugs. Other biochemical parameters should also be evaluated and considered as well.

References

1. **Wikipedia .Psychosis.** <http://en.wikipedia.org/wiki/Psychosis>, accessed on March 20, 2010.
2. **Mcclellan J., and Werry J., (2001).** Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *Journal of the American of Child & Adolescent Psychiatry*, 40 (7), 4-23.
3. **Taber KH ., Lewis DA., and Hurley RA., (2001).** Schizophrenia: What's under the microscope?. *Journal of Neuropsychiatry and Clinical Neuroscience*, 13, 1-4.
4. **Williams G., and Castner S., (2006).** Under the curve: critical issues for elucidating D1 receptor function in working memory. *Neuroscience*,139 (1).
5. **Duncan JS., Sander JW., Sisodiya SM., and Walker MC, (2006).** Adult epilepsy. *Lancet*, 367:1087-100.
6. **Abdel-Misihand S., Bloomston M ., (2010).** Liver Anatomy. *Surgical Clinics of North America*, 90 (4), 643-653.
7. **Forrester L., Henderson C., Glancey M., Back DJ, Park PK, Ball SE and Kittelingham NR (1992).** Relative expression of cytochrome P450 isoenzymes in human liver and association with the metabolism of drugs and xenobiotic. *Biochemical Journal*, 15; 281(Pt 2): 359–368.
8. **Mehta N ., Ozick L., and Gbadehan E., (2009).** Drug-Induced Hepatotoxicity, *eMedicine journal* .
9. WWW.Surveys system.com. Accessed on Feb. 12, 2011.
10. **Young DS., (2001).** Effect of disease on clinical lab. *Tests*, 4th ed AACC.
11. **Burtis A. (1999).** *Tietz Textbook of clinical chemistry*. 3rd ed. AACC.
12. **Newman DG., and Price CP (1999):** Renal function and nitrogen metabolites. In: Burtis CA., and Ashwood ER., editors. *Tietz Textbook of clinical chemistry*. 3rd ed Philadelphia: W.B Saunders company.p.1204-70.
13. **Moss DW., and Henderson AR., (1999).** Clinical enzymology. In: Burtis CA, Ashwood ER, editors. *Tietz Textbook of clinical chemistry*. 3rd ed. Philadelphia: W.B Saunders company. P.617-721.
14. **Thomas L., (1998).** Alanine aminotransferase (ALT), A spartate aminotransferase (AST). In: Thomas L., editor. *Clinical Laboratory Diagnostic*. 1st ed .Frankfurt: TH-Books veriangsgesellschaft.p.55-65.
15. **Tietz N.W., (1995).** *Clinical Guide to Laboratory Tests*, 3rd Edition . Philadelphia: W.B Saunders company. P.A.

Assessment of liver and kidney functions in patients receiving

16. Schumann G., Bonora R., Ceriotti F., Terard G., Ferrero CA., Franck PF., Gell FJ., Hoelzel W., Jorgensen PJ., Kanno T., Kessner A., Klauke R., and Kristiansen N., (2002). IFCC primary reference procedure for the measurement of catalytic activity concentration of enzymes at 37°C. Part 5: Reference procedure for catalytic concentration of γ -glutamyltransferase. **Clinical Chemistry and Laboratory Medicine** 40:734-8.
17. Young DS., (1997). Effects of drugs on clinical laboratory tests, 3th ed. AACC Press.
18. Cepelak I., Zanić Grubisić T., Mandusić A., Rekić B., and Lenicek J., (1998). Valproate and carbamazepine comedication changes hepatic enzyme activities in sera of epileptic children. *Clinica Chimica Acta; international journal of clinical chemistry.* 28;276(2):121-7.
19. Sonmez FM., Demir E., Orem A., Yildirmis s., Orhan F., Aslan A., and Topbas M., (2006). Effect of antiepileptic drugs on plasma lipids, lipoprotein (a), and liver enzymes. *Journal of Child Neurology.* 21(1):70-4.
20. Willmore L., Wilder B., Bruni J., and Villarreal HJ., (1978). Effect of valproic acid on hepatic function. *Neurology.* 28(9):961.
21. Lackmann GM., (2004). Valproic-acid-induced thrombocytopenia and hepatotoxicity: discontinuation of treatment? *pharmacology.* 70(2):57-8.
22. Attilakos A., Voudris KA., Garoufi A., Achilleas A., Konstantinos A., Anastasia G., Sotiria m., stamatia D., Alexia P., and Eustathia K., (2006). Effect of sodium valproate monotherapy on serum uric acid concentrations in ambulatory epileptic children: a prospective long-term study. *European Journal of Paediatric Neurology.* 10(5-6):237-40.
23. De-ming L., and Mei-rong LU., (2008). The influence of antipsychotic drug on liver function of schizophrenia patients. *Hainan Medical Journal*
24. Ghozzi H., Hakim A., Sahnoun Z., Ben Mahmoud L., Atheymen R., hammami S., and Zeghal K., (2011). Relationship between plasma concentrations of valproic acid and hepatotoxicity in patients receiving high doses. *Revue Neurologique.* 167(8-9):600-6.
25. Green., (1978). sodium valproate and routine liver function tests. *Archives of Diseases in childhood.* 59,813-814.
26. Altunbaşak S., Yildizaş D., Anarat A., and Burgut H., (2001). Renal tubular dysfunction in epileptic children on valproic acid therapy. *Pediatric Nephrology.* 16(3):256-9.
27. Callaghan N., Majeed T., O'Connell A., and Oliveira D., (1994). A comparative study of serum F protein and other liver function tests as an

- index of hepatocellular damage in epileptic patients. *Acta Neurologica Scandinavica*. (89), 4, p237–241.
28. **Garcia-Unzueta M., Herran A., Biddle D., Amado J., Carrera M., Ramirez M., Ayestaran A., Hoyuela F., (2003).** Alterations of liver function test in patients treated with antipsychotics. *Journal of Clinical Laboratory Analysis*. 17(6) p216-218
 29. **Demircioğlu S., Soylu A., and Dirik E., (2000).** Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. *Pediatric Neurology*. 23(2):142-6.
 30. **Tsinghua., (2004).** Comparison of Chlorpromazine, Clozapine and Risperidone in the effect on indices of liver function. *Journal of Practical Medical Techniques*.
 31. **Lomas J., Boardman R. H., and Markowe M., (1955).** CHLORPROMAZINE (LARGACTIL) JAUNDICE. *Lancet*, 1, 1144.
 32. **Yeung PK., Hubbard JW., Korchinski ED., and Midha K., (1993).** "Pharmacokinetics of chlorpromazine and key metabolites". *European Journal of Clinical Pharmacology*. 45 (6): 563–9.