# Ursodeoxycholic Acid Can Improve Liver Transaminase Quantities in Children with Anticonvulsant Drugs Hepatotoxicity: a Pilot Study

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**Abstract-** The present study has been directed to investigate Ursodeoxycholic Acid (UDCA) effect in children, to reduce the high Liver transaminases induced by Anticonvulsant drugs (drug induced hepatitis). This idea has been driven from Cytoprotective and antioxidant properties of UDCA to be used in drug induced inflammation in Liver. Twenty two epileptic patients aged between 4mo – 3yr whom were under anticonvulsant therapy with drugs such as valperoic acid, primidone, levetiracetam, Phenobarbital or any combination of them and had shown Liver transaminases rise , after rule out of Viral-Autoimmune, Metabolic and Anatomic causes, have been prescribed UDCA in dose of 10-15 mg/kg/day, at least for 6 months. Any patient who have shown confusing factors such as genetic disorders with liver involvement or spontaneous decline in enzymes or had not treatment compliance has been excluded from the study. Transaminases range changes as well as Probable side effects of the drug have been monitored. The results indicated that UDCA is effective and well tolerable in the children with drug induced hyper transaminasemia. No side effect has been seen and recorded in this study. Based on this study and its results, we recommend UDCA as a safe and effective choice in drug induced hepatotoxicities.



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**Keywords:** Ursodeoxycholic acid; Liver transaminases; Drug induced hepatitis; Anticonvulsant drugs

## Introduction

Drug induced hepatotoxicity is a common concern in Anticonvulsive therapy. In liver metabolism, activation and detoxification are two stages should be passed to activate the medicine to show the pharmacologic effects and then evacuate its metabolite safely through the urine or bile (1). UDCA has been widely used in cholestatic liver diseases (1,2).

It has been suggested that in drug induced liver disease characterized by a prolonged course, therapy with UDCA or steroids may be helpful (3,4).

UDCA also can improve hypertransaminasemia in chronic hepatitis (5).

Anticonvulsants are one of the most important and popular drugs that might show their adverse effects on the liver (mostly in the form of cytotoxicity on the hepatocytes or cholangiocytes) during hepatic metabolism (1).

During the first phase of drugs hepatic metabolism (activation) mostly cytochrome P450 – the mono oxygenase enzymes are playing an important role. The active metabolite is hydrophobe and will be toxic for cells thus must be changed to hydrophil and nontoxic molecule during the second phase (Detoxification) to be excreted with the urine or bile (1).

UDCA is a primary bile-acid that's synthesized lightly in the human body (1).

UDCA has direct cytoprotective effects, due to the stabilization of hepatocyte membrane and improve mitochondrial oxidative phosphorylation and prevent the mitochondrial membrane permeability transition. Also, it has immunomodulatory effects due to a reduction in expression of HLA Class I proteins in hepatocytes and anti apoptotic effects through reduction of reactive oxygen species products. UDCA may have direct antioxidant effects in vivo specially by blocking the biomolecular oxidative damage dependent on Fe3+ and OH- radicals (1,6,7).

There are few case reports of beneficial effects of

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UDCA therapy in toxic hepatitis (8-12).

There are also experimental trials indicating preventive effects of UDCA in drug induced liver damage based on its hepatoprotective and antioxidant properties (13,14).

It has been recommended to prescribe UCDA in the treatment of chronic hepatitis and drug induced cholestasis because of its efficacy and tolerability (3-5).

In this prospective trial, we have prescribed Ursodeoxycholic acid (UDCA) and evaluated its effects on decreasing the ALT (alanine aminotransferase), AST (aspartate aminotransferase) and γGT (γ-glutamyl transpeptidase) for children with anticonvulsant therapy whom were showing significant Liver transaminase raise.

## Materials and Methods

### Trial organization

This is a 22 patient clinical trials at the Vali-Asr pediatric ward of Tehran University of Medical Sciences since April 2009 to October 2010 Tehran, Iran.

### Patients

A number of 31 Children between 4mo – 3yr, whom were under Anticonvulsant Therapy with drugs (valperoic acid [16 Patients], primidone [6 Patients], levetiracetam [5 Patients], Phenobarbital [4 Patients]) had shown significant rises (more than 2 times of the upper limits of normal range) in liver transaminases (AST, ALT and γGT) on monthly follow up. They have been checked for complete Liver function tests including AST, ALT, bilirubin (total and direct), γ-GT (gamma glutamyl transpeptidase), Alb (albumin), PT and INR (prothrombin time and international normalization ratio) and PTT (partial thromboplastin time) with the same uniform kit (Pars Azmoon Co.) and at the same laboratory unit.

After rule out of other liver damage causes such as viral hepatitis, autoimmune hepatitis, specific errors of metabolism and anatomical causes (with serologic tests including HAVIgM, HBSAg, HBCIgM, HCVAb, EBV VCA IgM, CMVIgM, ANA, AMA, ASMA, ANCA and metabolic screening by measurement of blood sugar in ortho and glucose oxidase manner, serum aminoacids chromatography, blood ammonia and lactate level, ABG and urine analysis for ketone, reducing substances and organic acids and performing complete abdominal ultrasound by the same specialist and Siemens G40 system and CH5-2 prob). Also after reducing anticonvulsant drug dose to minimal effective dose or if possible substituting it with a safer was drug in case of rising transminases for more than 2 months, in case of incompetence them were treated with ursodeoxycholic acid (UDCA).

During study 3 patients have been excluded because of the high level of ammonia and lactate and 6 others showed transaminases decline, those were excluded too. From 22 remainder patients, 10 have been on VPA (valproic acid), 6 on primidone, 2 on levetiracetam and 4 on Phenobarbital.

Duration of anticonvulsive therapy before aminotransferase rise was variable, and some have shown it in early weeks of treatment and others later. Anyone of our patients has not showed an abnormality in bilirubin, prothrombin time (PT), and albumin thus we were not faced with liver functiona insufficiency. One of our patients was still showing high transaminases level (more than 2 times of the normal range) in despite of UDCA prescription. Although the partial decline was seen in his tests, we performed liver needle biopsy for him whose pathological report was compatible with drug induced changes. This patient was on primidone therapy.

At the end of 6 month therapy with UDCA, his ALT was still higher than 2ply of normal upper limits but descending. UDCA therapy was continued and after 40 weeks, ALT decreased thus UDCA was discontinued.

In spite of transaminases increase, PT INR, PTT, Alb and serum bilirubin were in the normal ranges.

In Pars Azmoon Co. Kits those have been used in this trial, the normal ranges have been defined as following:

ALT: 0-37 IU/l

AST: 0-41 IU/l

γ-GT: $\begin{cases} 2 – 4^{mo}: 8\text{-}90 \text{ IU/l} \\ 4^{mo} – 10^{yr}: 5\text{-}32 \text{ IU /l} \end{cases}$

Any quantities higher than 2ply of upper limits were considered as a pathologic case and received UDCA after rule out of other causes.

We did not divide our patients in two groups of drug and Placebo and prescribed UDCA for all of them. Any amounts over the 2ply of upper normal limits consider hepatitis.

### Intervention

The 22 patients those were indicating significant rise in Liver transaminases during anticonvulsant therapy and neither dose reduction nor drug change has had influence in transaminases normalization, after their negative results for virologic, metabolic,

autoimmune and anatomic causes, were treated with UDCA (10-15 mg/Kg/day) assuming drug-induced hepatitis, for at least 6 months. As far as there were no previous trial with ursodeoxycholic acid in drug-induced hepatitis, we have considered 6 months duration to monitor patients responses and be sure against rebound rising of enzymes, and based on one literature , which in it has been tried UDCA in chronic hepatitis of different etiologies for 6 months (4). However, most experiences show that UDCA is safe to use in infants and children who do not have fixed obstruction to bile flow (1).

Liver enzymes were checked during treatment every 1 week up to 4 weeks; every 2 weeks up to 3 months and every 4 weeks up to 6 months and liver function tests same as bilirubin (total and direct), Alb, PT, PTT monthly by using Pars Azmoon kits and at Vali-asr hospital laboratory.

All patients have been treated with the same 250mg Capsules of UDCA made with the commercial name of Ursobil by ABC Farmaceutici of Spain. The capsules should be opened and prescribed dosage based on patient's weight, was given on orally daily basis.

UDCA treatment period was 24 weeks (about 6 months) for all patients except for one who took the drug for 40 weeks. Transaminases were checked one month after treatment cessation. In 8 patients partial transaminases rise not higher than 2 ply of the upper limit of normal, were detected. Theirs follow-up is continued.

**Ethical consideration**

We explained completely for patients parents about transaminases raise due to anticonvulsant drugs. They have been offered UDCA for controlling the transaminases rise, considering high transaminases is an evidence of active inflammation in the liver which must be controlled. Expected side effects of UDCA like gastrointestinal disturbances, rash, arthralgia, anxiety, headache and elevated liver enzymes have been explained and received written inform concept from parents to prescribe it.

According to the Helsinki Declaration this study was approved by the Medical Ethics Committee of Medicine School-Tehran University of Medical Sciences, as a medical student thesis with registration ID: 1391-1075.

**Outcome**

In this study, subsidence of liver transaminases has been considered as an indicator of improvement in hepatic inflammation and involvement. UDCA a probable side effect was our concern that no any of our 22 patients were showing any undesirable results and no interfering factor has occurred. Routine and correct usage of the drug has been followed and supervised.

**Statistical analysis**

All findings have been recorded in Information bank of SPSS 15 (the Statistical analysis program). Based on the trial objectives, Descriptive statistics has been considered as a percentage and average factors. On the other hand analytic statistics has been used to describe the liver enzyme changes before and after treatment using Pearson correlation test and repeated measure methods. Confidence interval percentage of the study was 95% and the P value less than 0.05, has been considered significant.

## Results

Our patients' age range is between 4mo to 36mo, the average of 14.04 ± 8.27 months. 73% of them were male (16 boys) and 27% female (6 girls).

Valproic acid had been prescribed in 45.5%(10 patients), primidone in 27.5% (6 patients), Phenobarbital in 18% (4 patients) and levetiracetam in 9%(2 patients)of cases. Pre-treatment and 1 wk to 6 mo post treatment aminotransferase changes and Pearson's correlation are showed in table 1 and figures 1-3.

Findings show a significant decline in liver transaminases levels after the intervention.

**Table 1. Transaminase changes before and after treatment**

| | Before treatment | 1 w | 2 w | 3 w | 1 m | 1.5 m | 3 m | 6 m |
|---|---|---|---|---|---|---|---|---|
| **ALT** Mean ± SD | 266.8 ± 86.5 | 216.0 ± 93.0 | 153.2 ± 85.2 | 99.7 ± 68.7 | 64.7 ± 60.0 | 41.0 ± 62.4 | 35.6 ± 41.0 | 27.5 ± 15.8 |
| **AST** Mean ± SD | 161.3 ± 44.9 | 150.5 ± 63.2 | 110.8 ± 63.0 | 85.3 ± 57.3 | 57.2 ± 39.8 | 41.0 ± 62.4 | 33.8 ± 42.2 | 24.3 ± 6.8 |
| **γ GT** Mean ± SD | 22.5 ± 22.4 | 22.8 ± 19.3 | 18.0 ± 14.3 | 12.5 ± 5.4 | 11.7 ± 5.2 | 11.2 ± 4.9 | 10.2 ± 3.6 | 10.2 ± 4.7 |

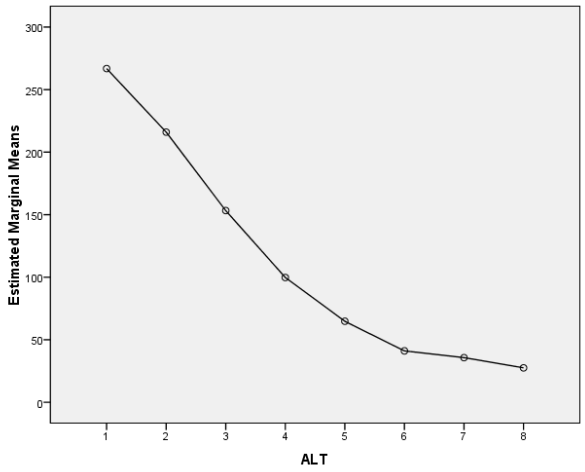


**Figure 1.** ALT trend after intervention
*P*<0.0001

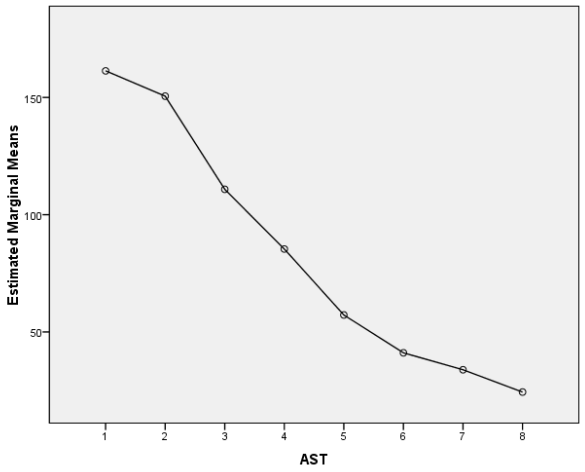


**Figure 2.** AST trend after intervention
*P*<0.0001

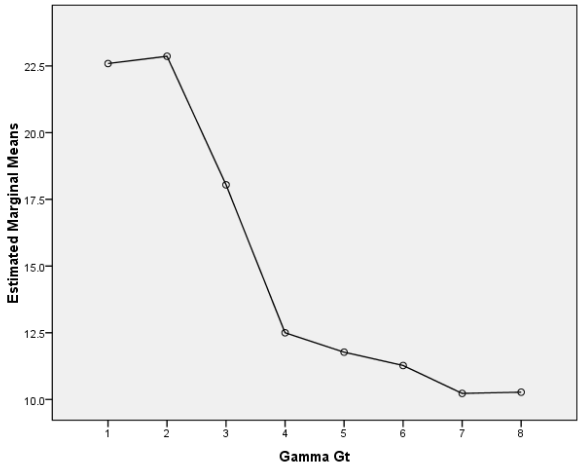


**Figure 3.** γGT trend after intervention
*P*<0.0001

## Discussion

In this 18 months prospective study in children who were under anticonvulsive therapy, consist of VPA, primidone, phenobarbital and levetiracetam, in those suffering from hepatotoxicity; we used ursodeoxycholic acid to control transaminases rise. UDCA is a primary and non-toxic bile acid which obviously has direct cytoprotective and antioxidant effects in vivo (1,6,7).

UDCA is the major bile acid of the black bear and has been used for centuries in traditional Chinese and Japanese medicine for the treatment of gallbladder and liver diseases (1,2).

Its therapeutic effects have been proven in cholestatic liver disease, alcohol induced liver damage, non-alcoholic steatohepatitis (NASH), cholesterol gallstone and probably in better control of high transaminases in chronic hepatitis (C and autoimmune) (2,3,5).

Also it has been suggested by Teschke for drug-induced liver disease (4).

We have used UDCA to control the high transaminases due to drug hepatotoxicity, considering its antioxidant and cytoprotective properties and obtained its effective role (6,7).

There are five case reports by Soza *et al*., Dandakis *et al.*, Manolakopoulos *et al*., Cicognani *et al*., and Stickel *et al*., based on therapeutic effects of UDCA in management of toxic hepatitis arising from Amoxicillin-clavulanic acid, flutamide and cyproterone acetate sequential administration, flutamide and herbalife respectively, which emphasizes its potential efficacy in toxic hepatitis (8-12).

Also the preventive effects of UDCA have been experimentally proven in amoxicillin + clavulanic acid and in methotrexate induced Liver toxicity (13,14).

The therapeutic effects of UDCA in drug-induced and toxic hepatitis could be as a result of its cytoprotective and antioxidant properties, which has been proven in an *in vivo* investigation (6,7).

We did not find any adverse reaction or intolerance of drug in our patients.

Our study is not a randomized and placebo–controlled trial. On the other hand, liver synthesis function was not affected in our patients, so we were unable to judge about UDCA effect on liver functions and we can consider it as another limitation.

This study has been shown that UDCA treatment in liver toxicity caused by anticonvulsant drugs, may be effective to control the increased amount of

transaminases, it's safe and tolerable. Performing a randomized and Placebo-controlled trial with UDCA in drug-induced hepatitis is strongly recommended.

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