Retrospective Study of Hepatic Enzyme Elevations in Children Treated With Olanzapine, Divalproex, and Their Combination

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ABSTRACT

Objective: To evaluate hepatic enzyme elevations during treatment with olanzapine, divalproex, and their combination. **Method:** Fifty-two children, aged 4 to 18 years, with hepatic enzyme levels measured during treatment with olanzapine (n = 17), divalproex (n = 23), or their combination (n = 12), were identified in the computerized records at a pediatric medical center. Clinical characteristics as well as serial alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase levels were collected. **Results:** Mean and peak hepatic enzyme levels were significantly higher for the combined treatment group compared to the olanzapine or divalproex groups. All 12 patients who received combined treatment had at least one peak enzyme elevation during the treatment. For 42% of these patients, at least one enzyme level remained elevated during the time for which values were available (mean 8 ± 6 months). For those treated with divalproex either alone or in combination, the findings were not explained by variations in divalproex plasma levels. Two patients receiving combined treatment had the combination treatment discontinued because of medical complications (pancreatitis in one and steatohepatitis in the other). **Conclusions:** Combined treatment with olanzapine and divalproex was associated with more elevations of hepatic enzymes than treatment with either agent alone. The long-term significance of this is unknown but warrants study. *J. Am. Acad. Child Adolesc. Psychiatry,* 2003, 42(10):1227–1233. **Key Words:** divalproex, olanzapine, polypharmacy, hepatic function, pancreatitis.

Olanzapine and divalproex are commonly used separately and in combination for the treatment of bipolar disorder, psychosis, and severe aggression in children and adolescents, whether or not there is a comorbid seizure disorder (Chang and Ketter, 2001; Frazier et al., 2001; Kumra et al., 1998; Potenza et al., 1999). Both agents are extensively metabolized in the liver.

Olanzapine is metabolized by CYP1A2 and CYP2D6 (Prior et al., 1999). There is more information on the effect of olanzapine on hepatic enzymes in adults than in children. Nemeroff (1997) reviewed four studies of olanzapine use in adults, representing a total of 2,914 patients. He reported that asymptomatic transaminase elevations were occasionally noted in patients treated with olanzapine, but these were transient, were not dose-dependent, and were not associated with any signs or symptoms of hepatic dysfunction. Similarly, Beasley et al. (1997) examined data from 2,500 adult patients and found that transient elevations in alanine aminotransferase (ALT) occurred in 9.4% of these patients. These elevations usually began in the second week of treatment, with a median time to peak of 28 days. The median ALT elevation was 34 IU/L. Absolute values over 200 IU/L occurred in only 0.2% of patients. This rate of "substantial" elevation was half that observed in a comparison group receiving haloperidol.

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Olanzapine's effect on hepatic enzymes has been examined in pediatric clinical trials where it was used as monotherapy. While Potenza et al. (1999) did not find any abnormalities in the liver functions of eight patients (four youths and four adults) after 12 weeks of olanzapine treatment, Kumra et al. (1998) found transient liver function abnormalities in seven of eight patients. These patients were maintained either on olanzapine alone or on olanzapine and lorazepam. Both these studies excluded children with significant medical illnesses, including seizure disorders, as well as children on multiple medications. By examining the Food and Drug Administration spontaneous adverse events reporting postmarketing surveillance database, Woods et al. (2002) found that the relative risk of having a report of liver function abnormalities was highest in children, followed by adolescents taking olanzapine, with both having a statistically higher relative risk than adults.

For divalproex, glucuronide oxidation and mitochondrial ß-oxidation are the major metabolic pathways of elimination. Divalproex has also been found to be a weak inhibitor of some CYP isoenzymes, glucuronyltransferases, and epoxide hydrase (Abbott, 2002). There is a long history of divalproex use in children for epilepsy, and thus its effects on liver functions have been well described when used as monotherapy and in combination with other antiepileptic drugs. The incidence of reversible, dose-dependent, asymptomatic elevations in hepatic enzyme levels has been estimated to be about 11% of patients receiving divalproex. Divalproex has also been associated with hepatic failure in children. In children over the age of 2 years, the rates have been found to be 1/45,000 for those receiving monotherapy and 1/12,000 for those receiving polytherapy (Wyllie and Wyllie, 1991).

In vitro studies have found little potential for a pharmacokinetic interaction between olanzapine and divalproex (Abbott, 2002; Lilly, 2002). In a prospective controlled study comparing the addition of divalproex or placebo to either olanzapine or risperidone for treatment of adults with schizophrenia, Casey et al. (2001) found that hepatic transaminase levels were decreased in the patients receiving divalproex augmentation compared to those receiving monotherapy with olanzapine or risperidone. Given the increased use of combined pharmacotherapy, including the combination of olanzapine with divalproex in youths who have comorbid medical or psychiatric conditions, the evaluation of the hepatic effects of this combination in pediatric populations in a naturalistic clinical setting is warranted. As a first step to this end, we conducted a chart review where we evaluated the relationship between the use of olanzapine, divalproex, or their combination with hepatic enzyme elevations in children and adolescents as they were treated in actual practice. We hypothesized that there would be more frequent and higher hepatic enzyme elevations associated with combined treatment with olanzapine and divalproex than with treatment with either agent alone.

METHOD

Institutional review board approval was obtained for this study. The computer database at a major pediatric medical center was searched for patients prescribed olanzapine, divalproex, or their combination over a 2-year period from January 1998 and December 1999. Seventy-five patients prescribed olanzapine and 61 prescribed divalproex were initially identified. Patients were included for further study if they had serum levels of ALT, aspartate aminotransferase (AST), or lactate dehydrogenase (LDH) documented while receiving olanzapine or divalproex treatment and if they were younger than 18 years of age at the time of these hepatic enzyme measurements. Patients with a history of liver disease or those concurrently prescribed the following medications were excluded from further study: pemoline, phenytoin, tiagabine, imipramine, lamotrigine, phenobarbital, risperidone, carbamazepine, and topiramate, as these medications could also lead to hepatic enzyme elevations. After applying these inclusionary and exclusionary criteria, 52 children were identified. Of these, 17 patients received olanzapine, 23 received divalproex, and 12 received both medications.

In addition to hepatic enzyme levels, information about patient age, gender, race, duration of olanzapine or divalproex treatment, dose of olanzapine or divalproex, and weight was recorded. Presence or absence of other medical disorders, concomitant medications, psychiatric diagnoses, and side effects were also noted.

All the recorded levels of ALT, AST, and LDH during treatment with olanzapine or divalproex or their combination were recorded (n = 555 hepatic enzyme measurements). These were all measured in the laboratory of a major pediatric teaching hospital. The interassay coefficients of variation for these measurements within the normal range of values are ALT 3.9, AST 4.6, and LDH 1.5. Children were categorized as having abnormally elevated peak or mean hepatic enzymes if one or more of the three indices ALT (normal range 3–30 IU/L), AST (normal range 2–40 IU/L), or LDH (normal range 100–210 IU/L) were elevated according to the hospital laboratory standards. For the sample as a whole, 28 children had at least one peak enzyme level elevation, and 22 children had at least one mean enzyme elevation during treatment.

In line with our initial hypothesis, our objective was to ascertain both the frequency and the degree of hepatic enzyme elevations in response to treatment with olanzapine, divalproex, and their combination. To accomplish this, first we determined if in fact there were differences in the frequency of hepatic enzyme elevations as a function of medication treatment status using the χ^2 statistic. Subsequently, using analysis of variance (ANOVA), we examined the differences in hepatic enzyme elevations across the three treatment groups, controlling for age, and where indicated, valproic acid plasma levels. All statistical tests were two-tailed. Since for each patient multiple measurements were available for each of the three hepatic enzymes studied, both peak enzyme levels and mean enzyme levels during the course of observed treatment were used for comparative purposes.

RESULTS

Sample Characteristics

Summary demographic and treatment characteristics of the sample are presented in Table 1. The use of olanzapine was directed at a wide variety of problems, including aggression, hyperactivity, mania, psychosis, and anxiety. Divalproex treatment was directed toward a similar range of problems, as well as for treatment of epilepsy. Pretreatment hepatic enzyme levels were available for 8 of the 17 olanzapine patients, 4 of the 12 olanzapine + divalproex patients, and 14 of the 23 divalproex patients.

Of the 17 patients receiving olanzapine (without divalproex), 10 (59%) were also receiving concomitant medications, including 3 patients each on paroxetine and clonidine, 2 patients each on trazodone and sertraline, and 1 patient each on lithium, gabapentin, venlafaxine, fluoxetine, fluvoxamine, dextroamphetamine, and methylphenidate. Eighteen percent of the olanzapine group was on one concomitant medication and 41% were on two. Of the 12 patients receiving combined olanzapine + divalproex treatment, 9 (75%) were also receiving concomitant medications, including lithium (3 patients), bupropion and sertraline (2 patients each), and nortriptyline, guanfacine, and nefazodone (1 patient each). Sixty-seven percent of the olanzapine + divalproex group were receiving one concomitant medication and 8% were on two. Of the 23 patients receiving divalproex (without olanzapine), 15 (65%) were also receiving concomitant medications, including dextroamphetamine, methylphenidate, and trazodone (3 patients each); fluoxetine and buspirone (2 patients each), and L-carnitine, lithium, clonazepam, mirtazapine, nefazodone, paroxetine, sertraline, citalopram, and nortriptyline (1 patient each). Of the divalproex (without olanzapine) group, 43% were on one concomitant medication, 13% were on two, and 4% were on three, and 4% were on four. When more than one concomitant medication was being given, the most common combination was an antidepressant plus either a stimulant, clonidine or guanfacine (69% were one of these combinations). Only one patient in the divalproex group was on L-carnitine. Differences in rates of concomitant medications between the groups were not statistically significant. Also, concomitant treatment with a neuroleptic (other than olanzapine), antidepressant, or anxiolytic medication was not associated with higher hepatic enzyme levels. The two patients on concomitant nefazodone did not have elevated hepatic enzyme levels.

Peak Enzyme Levels

Peak enzyme levels were defined as the highest ALT, AST, and LDH levels observed during the treatment period. At least one of these was elevated above the normal range in 100% of the olanzapine + divalproex group, 59% of the olanzapine alone group, and 26% of the divalproex alone group. These findings were examined statistically using frequency counts and the χ^2 statistic. This revealed that there were more than the expected number of children in the elevated hepatic enzyme group who were taking olanzapine + divalproex (12 observed versus 6 expected), and fewer than the expected number of children in the elevated hepatic enzyme group who were taking only divalproex (6 observed versus 12 expected) ($\chi^2_2 = 16.9$, $p < .0002$). In fact, all the children in the combined treatment group ($n = 12$) were in the elevated hepatic enzyme group. For 42% of these children, the elevated peak hepatic enzyme(s) did not return to normal during the observed course of treatment. For these patients the mean period of time for which hepatic enzyme levels were observed after the peak level was 8 ± 6 months.

Comparing the three groups for differences in peak ALT, AST, and LDH levels using multivariate ANOVA, we found the following. Medication treatment status explained variations in peak ALT levels (model $F_{2,48} = 11.4$, $p < .0001$; $R^2 = 0.32$). Post hoc comparisons indicated that combined olanzapine + divalproex treatment was associated with higher peak levels than either monotherapy (olanzapine + divalproex >

TABLE 1
Demographic and Treatment Characteristics

	n	Male	Age (yr)	Mean DPK Level (mg/L)	DPK Duration (Months)	OLZ Dose (mg/day)	OLZ Duration (Months)	% Con. Med.
OLZ	17	11	13.4 ± 3.1	NA	NA	9.7 ± 3.0	9.2 ± 9.7	53
OLZ + DPK	12	6	12.2 ± 2.7	85.8 ± 25	10.3 ± 14.1	10 ± 4.1	3.4 ± 3.2	75
DPK	23	14	12.3 ± 3.6	87.7 ± 27.2	18.5 ± 20.2	NA	NA	65

Note: OLZ = olanzapine; DPK = divalproex; Con. Med. = taking concomitant medications; NA = not applicable.

olanzapine, $t = 3.7$, $p = .0006$; olanzapine + divalproex > divalproex, $t = 4.6$, $p < .0001$). There were no significant differences between the two monotherapies (Table 2).

Medication treatment status explained variations in peak AST levels (model $F_{2,48} = 9.2$, $p = .0004$; $R^2 = 0.28$). Post hoc comparisons indicated that combined olanzapine + divalproex treatment was associated with higher peak levels than monotherapy with divalproex (olanzapine + divalproex > divalproex, $t = 3.9$, $p = .0003$) and monotherapy with olanzapine (olanzapine + divalproex > olanzapine, $t = 3.8$, $p = .0005$). There were no significant differences between the two monotherapies (Table 2).

There was also a clear trend for medication treatment status to explain variations in peak LDH levels (model $F_{2,37} = 3.1$, $p < .055$; $R^2 = 0.14$). Post hoc comparisons indicated that combined olanzapine + divalproex treatment was associated with higher peak levels than monotherapy with divalproex (olanzapine + divalproex > divalproex, $t = 2.3$, $p < .03$). Furthermore, monotherapy with olanzapine was associated with higher peak LDH levels than monotherapy with divalproex (olanzapine > divalproex, $t = 2.0$, $p = .053$). There were no differences between the two olanzapine treatment groups (Table 2). Where divalproex was administered, valproic acid plasma levels did not explain variations in peak hepatic enzyme levels across the treatment groups for any of the enzymes.

Mean Enzyme Levels

Mean levels for ALT, AST, and LDH were defined as the average of all the measured levels for each of these enzymes observed during the treatment period. The mean of at least one of these enzymes was elevated above the normal range in 83% of the olanzapine + divalproex group, 47% of the olanzapine-alone group, and 17% of the divalproex-alone group. Similar to the results for peak enzyme levels, these findings were examined statistically using frequency counts and the χ^2 statistic. Frequency counts revealed that there were more than the expected number of children in the elevated mean hepatic enzyme group who were taking the combination of olanzapine + divalproex (10 observed versus 5 expected) and fewer than the expected number of children in the elevated mean hepatic enzyme group who were taking only divalproex (4 observed versus 10 expected) ($\chi^2_2 = 14.3$, $p = .0008$).

In comparing the three groups for differences in mean ALT, AST, and LDH levels using multivariate ANOVA, we found the following. Medication treatment status explained variations in mean ALT levels (model $F_{2,48} = 17.6$, $p < .0001$; $R^2 = 0.27$). Post hoc comparisons indicated that combined olanzapine + divalproex treatment was associated with higher mean levels than either of the monotherapies (olanzapine + divalproex > olanzapine, $t = 4.4$, $p < .0001$; olanzapine + divalproex > divalproex, $t = 5.8$, $p < .0001$) (Table 3). Medication treatment status explained variations in mean AST ($F_{2,48} = 5.2$, $p < .009$). Post hoc comparisons indicated that the combined olanzapine + divalproex treatment was associated with higher mean levels than either of the monotherapies (olanzapine + divalproex > olanzapine, $t = 3.0$, $p < .005$; olanzapine + divalproex > divalproex, $t = 2.7$, $p < .01$) (Table 3). Medication treatment status did not explain variations

TABLE 2
Mean ± Standard Error of Patients' Peak Hepatic Enzyme Levels

Group	ALT (IU/L)[a]	AST (IU/L)[b]	LDH (IU/L)[c]
Normal range	3–30	2–40	100–210
DPK	16 ± 5	28 ± 4	183 ± 14
(observed range)	(6–57)	(13–58)	(140–270)
OLZ	22 ± 6	27 ± 5	224 ± 14 (E)
(observed range)	(4–68)	(13–55)	(128–362)
OLZ + DPK	53 ± 6 (E)	53 ± 5 (E)	232 ± 16 (E)
(observed range)	(4–125)	(8–127)	(187–308)

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; DPK = divalproex; OLZ = olanzapine; E = mean elevated.

[a] DPK < OLZ + DPK, $p < .0001$; OLZ < OLZ + DPK, $p = .0006$.

[b] DPK < OLZ + DPK, $p = .0003$; OLZ < OLZ + DPK, $p = .0005$.

[c] DPK < OLZ + DPK, $p = .028$; DPK < OLZ, $p = .053$.

TABLE 3
Mean ± Standard Error of Patients' Mean Hepatic Enzyme Levels

Group	ALT (IU/L)[a]	AST (IU/L)[b]	LDH (IU/L)
Normal range	3–30	2–40	100–210
DPK	11 ± 2.3	23 ± 2.4	177 ± 61
(observed range)	(7–23)	(12–58)	(140–245)
OLZ	15 ± 2.8	21 ± 2.8	204 ± 43
(observed range)	(4–40)	(13–38)	(128–270)
OLZ + DPK	34 ± 3.2 (E)	34 ± 3.3	205 ± 60
(observed range)	(14–76)	(8–66)	(158–316)

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; DPK = divalproex; OLZ = olanzapine; E = mean elevated.

[a] DPK < OLZ + DPK, $p < .01$; OLZ < OLZ + DPK, $p < .0001$.

[b] DPK < OLZ + DPK, $p < .01$; OLZ < OLZ + DPK, $p < .005$.

in LDH levels ($F_{2,48} = 1.8$, $p = .17$). Where divalproex was administered, valproic acid plasma levels did not explain variations in mean hepatic enzyme levels across the treatment groups.

In the case of both peak and mean enzyme levels, in most instances the observed hepatic enzyme elevations were less than three times the upper limit of the normal range, and thus do not meet the threshold for immediate heightened concern (Wyllie and Wyllie, 1991). However, two patients in the olanzapine + divalproex group had peak hepatic enzyme elevations greater than three times the upper limit of the normal range. In one patient the elevations occurred during an episode of acute pancreatitis that began while receiving the combination. The second patient developed steatohepatitis while on the combined treatment, and it resolved following the discontinuation of olanzapine. These two patients are described more fully in the following paragraphs.

The first patient was a 13-year-old boy who was being treated with divalproex, olanzapine, and nortriptyline for bipolar depression. He presented with abdominal discomfort, tenderness, nausea, and vomiting. A computed tomography scan of his abdomen revealed pancreatitis, and his amylase was elevated to 634. He had been on divalproex for 2 months and on olanzapine for 1 month. The divalproex and olanzapine were discontinued, but his hepatic enzymes began to rise and peaked 6 days later at an ALT of 125, an AST of 127, and an LDH of 234, with normal bilirubin levels. By day 10 off medication his mood started destabilizing and olanzapine was restarted. His last set of laboratory studies was on day 8 and showed an ALT of 84 and an AST of 45. He was subsequently lost to follow-up.

The second patient had been on divalproex for many years with normal liver function before being placed on olanzapine 41 weeks prior to the measured elevation. At the time of his peak ALT, his valproic acid level was 31. His ALT decreased from 122 to 64 in 8 weeks with diet and weight loss. The olanzapine was then switched to risperidone, with the ALT subsequently returning to the normal range. Workup of his elevated liver function revealed steatosis/steatohepatitis, perhaps caused by the 7-kg weight gain he experienced during the time olanzapine was added to divalproex.

DISCUSSION

The principal finding of this retrospective study is that elevations in hepatic enzyme levels occurred more frequently and to a greater degree in patients treated with the combination of olanzapine + divalproex than in patients treated with either agent alone. In fact, all of the patients being treated with this combination had at least one elevated peak hepatic enzyme level during the course of treatment, and 10 of 12 had at least one mean hepatic enzyme level that was elevated. The only patients in the study who required discontinuation of medication because of the emergence of a clinically significant problem (pancreatitis, steatohepatitis) were receiving the combined treatment.

Our findings differ from those of Casey et al. (2001), who in their study of adult patients with schizophrenia did not find increased AST and ALT levels with the combination of divalproex and either olanzapine or risperidone. These divergent findings could be due to several factors: Casey et al.'s study was of adults, treated for shorter periods of time, and concomitant medications were strictly limited to lorazepam, chloral hydrate, and zolpidem. In contrast, the present study is of children with a variety of diagnoses and comorbidities who were treated for longer periods of time, and who were also taking a variety of other psychotropic medications. The concomitant medications and pattern of comorbidity of the present sample make our findings more difficult to interpret but also increase their ability to be generalized to actual clinical practice. Of the few studies examining hepatic enzyme levels in response to treatment of children and adolescents with olanzapine or divalproex, our findings are most consistent with those of Kumra et al. (1998), who reported transient elevations in hepatic enzymes in the majority of children treated with olanzapine as monotherapy. The present study is of hepatic enzyme elevations, and with the exception of the two patients in the combined olanzapine + divalproex group for whom the combination was discontinued, actual hepatic dysfunction was not demonstrated in the rest of this sample. However, an increased risk of hepatic dysfunction with divalproex in combination with other medications compared to divalproex monotherapy is suggested by the finding in other studies of a risk of hepatic failure of 1/45,000 with divalproex monotherapy versus 1/12,000 when it is used in combination with other antiepileptic medications (Wyllie and Wyllie, 1991). While case series of hepatic failure associated with valproic acid report AST levels at least three times normal in all cases of hepatic failure from valproic acid, the prognostic implications of asymptomatic hepatic enzyme elevations below this threshold are not known (Wyllie and Wyllie, 1991). Evidence of cirrhosis at autopsy in some cases of valproic acid-associated hepatic failure implicates gradual

hepatic damage over time. It is not known if the continued exposure to mildly increased hepatotoxic effects of combined treatment with valproic acid and olanzapine can lead to damaged hepatic architecture as is seen with chronic exposure to other agents such as ethanol (Wyllie and Wyllie, 1991).

The long-term clinical significance of the observed elevations in the present study is not known. However, the lack of systematic study of the safety of the combination of olanzapine + divalproex is made more concerning by the finding that even within this relatively small group of patients who received combined treatment with olanzapine + divalproex, one patient developed pancreatitis and one developed steatohepatitis. Only the systematic long-term follow-up of sufficient numbers of patients receiving combined olanzapine + divalproex treatment will determine if this combination leads to an increased risk of significant hepatic damage.

A number of mechanisms may contribute to the elevation of hepatic enzymes when olanzapine, divalproex, or their combination is used. Obesity has been noted as a risk factor for steatohepatitis (Baldridge et al., 1995; Moran et al., 1983; Vajro et al., 1994), and weight gain is common with both olanzapine and divalproex. We did not have sufficient data concerning baseline values or changes in height and weight to examine the relationship of weight gain or change in body mass index to the hepatic enzyme elevations described in this report. The patient in the study with pancreatitis had significantly elevated hepatic enzymes and was in the olanzapine + divalproex group. The risk of pancreatitis while being treated with divalproex has been found to be elevated above the baseline rate in the population. In clinical trials there were 2 patients with pancreatitis among 2,416 patients representing 1,044 patient-years of treatment with divalproex. As a result of this accumulating evidence, the package insert for divalproex has a warning for pancreatitis. The risk of pancreatitis during valproate treatment appears to increase with concomitant anticonvulsant use (Abbott, 2002; Chapman et al., 2001; Pellock et al., 2002; Yazdani et al., 2002). Several cases of pancreatitis in patients being treated with olanzapine have also been reported. Interestingly, three of these patients were being treated with both olanzapine and divalproex (Hagger et al., 2000; Ragucci and Wells, 2001). Hepatic enzyme elevations during pancreatitis are not uncommon and are associated with biliary stasis (Anderson, 1966; Butler, 1973; Chapman et al., 2001; Pellock et al., 2002; Yazdani et al., 2002). While the bilirubin level of the patient with pancreatitis remained normal, this mechanism cannot be ruled out.

Pharmacokinetic interactions directly between olanzapine and divalproex are not likely; however, pharmacokinetic interactions involving their metabolites have not been excluded (Abbott, 2002; Lilly, 2002). Also, a pharmacodynamic interaction may be possible. Divalproex interferes with glutathione-mediated protection from free radicals, thus making hepatocytes more vulnerable to oxidative stress from other drugs (Glauser, 2000; Klee et al., 2000). Divalproex also inhibits fatty acid metabolism and can produce microvesicular steatosis (Rettie et al., 1987). It is not known what effect concomitant olanzapine may have on these processes.

Limitations

In addition to the retrospective nature of this study, several other limitations should be noted. Baseline hepatic enzyme levels were available for only 50% of the overall sample. Thus, we cannot exclude the possibility that some patients had elevated hepatic enzymes before beginning treatment with olanzapine or divalproex. We only know that none of the patients in this study had documented histories of liver disease or other medical conditions associated with elevated hepatic enzymes prior to starting treatment with the combination.

Although we were able to examine the relationship of divalproex levels to hepatic enzyme elevations, the absence of sufficient data on patient weights also precluded the inclusion of medication dosing on a mg/kg basis in our statistical analyses. As a result, we could not address whether higher doses of medication per unit of body weight were associated with greater elevations in hepatic enzymes.

The majority of patients in this study received medications in addition to olanzapine or divalproex. Although we eliminated from consideration those patients who were taking medications known to be associated with elevations in hepatic enzymes, these other medications could have nonetheless contributed to the hepatic enzyme elevations reported here.

Clinical Significance

Controlled, prospective studies are needed to define better the risk factors associated with abnormal hepatic enzyme elevations related to treatment with olanzapine, divalproex, and their combination in children. The clinical significance of prolonged periods of mildly elevated hepatic enzyme levels has not been determined. Such studies may be useful for developing guidelines

for monitoring liver function during treatment with olanzapine and divalproex. In the interim, our findings are in agreement with recommendations from Abbott Laboratories that periodic monitoring of liver functions be done while divalproex is prescribed (Abbott, 2002). The recommendation for periodic monitoring with divalproex is due in part to a documented significant risk of fatal hepatotoxicity (Wyllie and Wyllie, 1991).

In our sample, we found that the rates of elevation in hepatic enzymes were comparable in the olanzapine-only group and the divalproex-only group. We found the rates of elevation higher in the group receiving olanzapine + divalproex. Marked weight gain was implicated as a possible mechanism contributing to steatohepatitis in at least one patient with a clinically significant elevation in hepatic enzymes. Thus, clinicians should periodically monitor hepatic enzyme levels when treating with either olanzapine plus divalproex or olanzapine with other hepatically metabolized agents, including valproate, or when there has been marked weight gain. When olanzapine is used as monotherapy, there is less evidence to support regular monitoring of liver enzyme levels. The short-term monotherapy trials found only transient elevations in liver functions; however, there have been reports of acute hepatitis possibly due to a hypersensitivity reaction from olanzapine (Cadario, 2000; Chitturi and George, 2002). Woods et al. (2002) have also found an increase in hepatic adverse events reported for olanzapine in pediatric versus adult populations. Thus, given the lack of long-term pediatric safety data with this agent, periodic monitoring seems prudent.

While the retrospective and uncontrolled nature of our data do not let us assess the potential effectiveness of different monitoring schedules, we believe it is prudent to check AST and ALT levels every 3 to 4 months during the initial year of treatment with either olanzapine or divalproex and after the addition of other hepatically metabolized agents. For the two patients in the olanzapine + divalproex group with hepatic enzyme elevations greater than three times the upper limit of the normal range, the onset of these elevations was within the first 12 months of treatment. Thus, if there have been no elevations of AST or ALT and no marked weight gain after 1 year, then a decrease in frequency of monitoring to every 6 months can be considered.

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