Divalproex Sodium Oral Loading During Combination Drug Therapy in Children

Candace R. Good, M.D.; Christopher A. Petersen,M.D.; Valentins F. Krecko; M.D.
Division of Child and Adolescent Psychiatry, The Penn State College of Medicine

Abstract

Objective: To identify variables (i.e., drug preparation or combinations) that may alter dosage requirements during rapid titration of divalproex sodium in children.

Method: A retrospective chart review revealed that divalproex was initiated in 45 inpatients (mean age 9 years) over a 1-year period. Initiation dose of divalproex approximated 15 mg/kg/day. Trough blood levels were obtained at steady state following initiation/dose adjustment.

Results: Initial drug levels were 37 – 121 µg/mL. Dose titration occurred in 20/45 patients. Divalproex was used most frequently with an atypical antipsychotic (29/45 patients, 13 patients also received a stimulant). No significant differences in discharge dose or drug level were apparent during co-administration with an antipsychotic. Patients administered the divalproex sprinkles formulation (n=6) required significantly higher doses to achieve comparable blood levels.

Conclusions: Combination drug therapy with divalproex does not appear to precipitate toxicity at clinically effective doses. Divalproex formulation may alter dosage requirements acutely.

Introduction

Multiple open trials support the use of divalproex sodium for the treatment of mood disorders in children and adolescents[1-3]. Divalproex sodium significantly decreased mood swings and explosive temper outbursts in children with disruptive behavior disorders in a double-blind placebo controlled trial[4]. Twenty outpatient children and adolescents (ages 10 – 18 years) with oppositional defiant disorder (ODD) or conduct disorder received six weeks of divalproex treatment and six weeks of placebo in a randomized crossover design. At the conclusion of the study, 12/15 patients had a superior response to divalproex. There are no double-blind, placebo-controlled trials of valproate for the treatment of mania in children.

Mood stabilizers are often used in combination with an antipsychotic to enhance symptom stabilization[5]. A recent study examined the acute use of adjunctive antipsychotic medication during the treatment of acute psychotic mania with lithium[6]. Combination therapy raises concerns regarding drug interactions, especially following a report of a possible pharmacokinetic interaction between valproic acid and risperidone (Wattum, 2001). Combination therapy is most likely to occur while on an inpatient psychiatry unit where children exhibit severe mood instability and aggression. In general, this is also the setting where medications are adjusted more rapidly with the goal of achieving therapeutic response earlier in the course of hospitalization. This patient population is therefore at significant risk for drug interactions resulting in acute toxicity.

The goal of this study was to examine dosage requirements for the initiation phase of divalproex sodium on an inpatient unit and to identify variables that may alter requirements such as drug preparation or co-administration with an antipsychotic. This study is necessary as the majority of trials do not address dosing issues specific to children or establish the reliability of such procedures during combination therapy. We previously reported that 15 mg/kg/day is a reasonably tolerated oral load of divalproex that quickly and reliably achieves therapeutic drug levels in child psychiatry inpatients (Good, et al.).

Methods

A retrospective chart review revealed that during a 1-year period, divalproex therapy was initiated in 52 child psychiatry inpatients. This study was approved by the Institutional Review Board at the Penn State College of Medicine. Six patients were excluded from analysis (5 because initial dose <12 mg/kg and 1 because the chart was not available for review). The remaining 45 patients had normal baseline hematologic indices and liver function tests. Age, sex, diagnoses, drug preparation (regular or sprinkle formulation), concurrent medications, and reported side effects were recorded. The final diagnoses were determined clinically by one of two board certified attending child psychiatrists in accordance with the current criteria outlined in the DSM-IV. Additional clinical criteria for a divalproex trial included an explosive temper (as evidenced by multiple episodes of destruction or verbal/physical aggression) as well as mood lability (distinct periods of worsening mood without a clear trigger). Symptoms of course were clinically significant to warrant inpatient hospitalization.

Initial dosing regimens approximated 15 mg/kg/day in divided doses (generally twice daily dosing). Trough blood valproate (VPA) levels were obtained on Day 5 of therapy. Therapeutic range was defined as 50 – 120 µg/mL, a current guideline for the treatment of bipolar disorder in adults (McElroy, 1992; Nemeroff). Each time the dose changed, a repeat level was obtained after 4 full days of the increased dose. In a few cases where the dose was increased just prior to discharge, the final dose for which a drug level was available was considered the discharge dose for the purpose of this study.

Statistical analyses were performed using standard two-tailed t-tests and analysis of variance (ANOVA) as appropriate to compare mean discharge dose and drug level between the medication combination subgroups. The Chi-Square test examined any differences in the proportion of untoward effects between groups. P-values less than 0.05 were considered significant.

Results

The 45 patients included in the analysis ranged in age from 4 – 13 years (mean=9 years); 40 were male, 5 female reflecting the predominately male milieu of the inpatient unit. Primary DSM IV diagnoses included bipolar disorder (27 cases 4 of which included psychotic feature specifiers), mood disorder N.O.S. (10 cases), ODD (3 cases), depressive disorder N.O.S. (3 cases), psychotic disorder N.O.S. (1 case) and mood disorder secondary to lead intoxication (1 case). Attention deficit hyperactivity disorder was a comorbid diagnoses in 25 cases; ODD in 22 cases. In 13 cases patients met criteria for a mood disorder, ADHD, and ODD.

Initial trough levels of divalproex on Day 5 of therapy (steady state) ranged from 37 – 121 µg/mL; all but three patients were within the therapeutic range. The dose was titrated in 20/45 patients (44%) to the mean discharge dose listed in Table 1.

Divalproex was used most frequently with an atypical antipsychotic (29/45 patients, 13 patients also received a stimulant). A smaller number received monotherapy, concurrent stimulant and/or antidepressant. No significant differences in discharge dose or drug level were apparent while receiving combination therapy with an antipsychotic (Table 1). Patients administered the divalproex sprinkles formulation (n=6) required significantly higher doses to achieve comparable blood levels (Table 1).

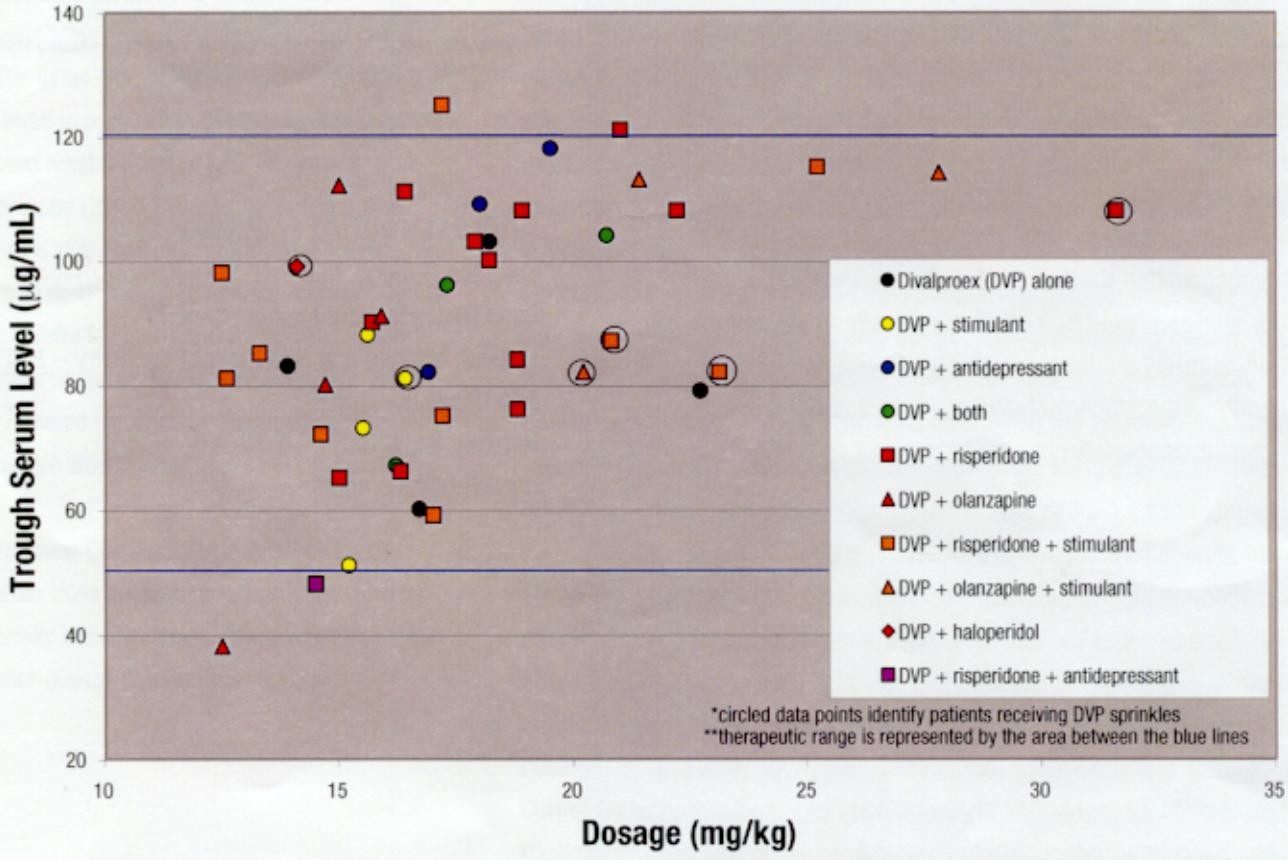
Side effects were reported in 26/45 (58%) patients. Sedation was by far the most common side effect (21 cases, 17 of which were receiving an antipsychotic), followed by nausea (8 cases), vomiting (5 cases), diarrhea (3 cases); drooling, tremor, and rash were each reported in one case. The mean length of recorded sedation was 1.4 days. Side effects can be considered mild in that symptoms resolved without a change in divalproex dosage in ~4 days. Only 7 patients received medication adjustments related to side effects. In the majority of cases the antipsychotic dose was decreased. 20/26 (77%) of those experiencing side effects were receiving an antipsychotic. This represents a significant difference in the occurrence of side effects as compared to those not receiving antipsychotics (chi square=4.18, $p<0.05$).

Table 1

	Mean dose (mg/kg)	Mean level (µg/mL)
Initiation	15.3 ± 2.43	76.8 ± 19.8
Discharge	18.1 ± 4.05	89.0 ± 20.2
Regular (n=39)	17.4 ± 3.4	88.5 ± 22.0
Sprinkles (n=6)	21.0 ± 6.1†	89.8 ± 11.1
No antipsychotic (n=14)	17.3 ± 2.3	85.3 ± 19.2
Antipsychotic (n=31)	18.1 ± 4.5	90.2 ± 21.6

†=significantly increased in comparison with regular preparation, F=2.46, df=43, p<0.04.

Divalproex Dosage Requirements to Achieve Target Drug Levels



Discussion

- 15 mg/kg appears to be an adequate dose of divalproex sodium to reach therapeutic range (50 – 120 µg/mL). However, a large number of patients will require further dosage adjustment on this regimen prior to discharge from an inpatient psychiatry unit. Those taking the sprinkle preparation of divalproex required significantly higher doses of divalproex. Although the bioavailability of the sprinkle preparation of divalproex is assumed to be the same as the regular preparation, there appears to be a significant difference in bioavailability during oral loading. Further studies are indicated to determine whether this effect persists in steady state.
- In this study we chose to focus on the initiation phase only and excluded patients already taking divalproex. These patients should be examined in the future, especially as the current drug interaction report was of a case where riperidone was initiated in a patient already therapeutic on divalproex (Wattum). Much is published regarding cytochrome P450 interactions in psychiatry; however, less than 10% of the total dose of valproic acid is metabolized by this system (Levy, et al.) and risperidone is only believed to be a weak inhibitor of the 2D6 enzyme (reference). It is proposed that at higher concentrations of valproic acid competition for protein binding sites between these two highly bound drugs could become more significant. It is therefore important to compare valproate levels in patients receiving a variety of drugs that have differing levels of effect on the cytP450 system and protein binding. The limited sample size in some subgroups limited the power of some analyses in this study; future studies should look more specifically at the effects of individual drugs on divalproex sodium levels. Also, this study does not address the efficacy of divalproex as a combination therapy nor does it establish timeframe to onset of drug effect.
- This study does establish safe administration guidelines that should allow future studies to proceed. The 20 – 30 mg/kg oral load recommended for adults (Hirschfeld, Keck, 1993; McElroy, 1993) likely exceeds the doseage requirements necessary to achieve a degree of stabilization necessary for discharge from an inpatient child psychiatry unit, especially in children receiving combination therapy. The children in this study who received antipsychotics were significantly more likely to experience side effects, especially sedation during oral loading of divalproex which emphasizes the need to titrate medications more conservatively in children.

References

1. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder, *J Am Acad Child Adolesc Psychiatry*, 2000, 39:713-720.
2. Papatheodorou G, Kutcher SP, Katic M, Szalai JP. The efficacy and safety of divalproex sodium in the treatment of acute mania in adolescents and young adults: an open clinical trial, *J Clin Psychopharmacol*, 1995, 15:110-116.
3. West SA, Keck Jr. PE, McElroy SL, Strakowski SM, Minnery KL, McConville BJ, Sorter MT. Open trial of valproate in the treatment of adolescent mania, *J Child Adol Psychopharm*, 1994, 4:263-267.
4. Donovan SJ, Stewart JW, Nunes EV, Quitkin, FM, Parides, M, Daniel W, Susser E, Klein DF: Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design, *Am J Psychiatry*, 2000, 157:818-820.
5. McClellan J, Werry JS, Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder, *J Am Acad Child Adolesc Psychiatry*, 1997, 36:157S-176S.
6. Kafanteris V, Coletti DJ, Dicker R, Padula G, Kane JM, Adjunctive antipsychotic treatment of adolescents with bipolar psychosis, *J Am Acad Child Adolesc Psychiatry*, 2001, 40:1448-1456.
7. Wattum, PJ. Valproic acid and risperidone (letter), *J Am Acad Child Adolesc Psychiatry*, 2001, 40:866-867.
8. Good CR, Feaster CS, Krecko VF, Tolerability of oral loading of divalproex sodium in child psychiatry inpatients, *J Child Adol Psychopharm*, 2001, 11:need #.
9. McElroy SL, Keck Jr. PE, Pope Jr. HG, Hudson JI: Valproate in the treatment of bipolar disorder: literature review and clinical guidelines, *J Clin Psychopharmacol*, 1992, 12S:42-52.
10. Nemeroff CB: An ever-increasing pharmacopoeia for the management of patients with bipolar disorder, *J Clin Psychiatry*, 2000, 61(suppl 13):19-25.
11. Hirschfeld FM, Allen MH, McEvoy JP, Keck PE, Russell JM, Saftey and tolerability of oral loading of divalproex sodium in acutely manic bipolar patients, *J Clin Psychiatry*, 1999, 60:815-818.
12. Keck Jr. PE, McElroy SL, Tugrul KC, Bennett JA, Valproate oral loading in the treatment of acute mania, *J Clin Psychiatry*, 1993, 54:305-308.
13. McElroy SL, Keck Jr. PE, Tugrul KC, Bennett JA, Valproate as a loading treatment in acute mania, *Neuropsychobio*, 1993, 27:146-149.

Address reprint requests to:

Candace R. Good, M.D.
Penn State Hershey Medical Center
Division of Child and Adolescent Psychiatry – H073
500 University Drive
Hershey, PA 17033
dgood17@juno.com