Therapeutic drug monitoring with valproate–Why product selection is an important factor

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ABSTRACT

There is a modest collection of literature describing the pharmacokinetic and clinical differences between the extended-release form of divalproex sodium (Depakote ER®) and the delayed-release form (Depakote®). Published articles are quick to espouse the extended-release formulation, especially in the setting of seizure control. Reasons commonly cited include a longer dosing interval, improved patient compliance, a more consistent pharmacokinetic profile, and fewer side effects. There are fewer articles discussing these differences in the context of treating mental illnesses, namely bipolar affective disorder. This article aims to compare these two formulations of divalproex with a special focus on their pharmacokinetic profiles, uses in psychiatric illness, and the role of therapeutic drug monitoring. The patient case that follows will describe a scenario in which a patient was prescribed each formulation during an acute hospitalization.

KEYWORDS

Valproate, therapeutic drug monitoring, delayed-release, extended-release

BACKGROUND

Valproic acid (VPA) has long been used as an antiepileptic agent for the treatment of various seizure disorders, with the Food and Drug Administration granting approval for its use in epilepsy in 1978. Its widespread use as an agent for treating mental illness did not occur until the 1990s. VPA and derivatives are currently available in the United States in eight dosage forms - five are of the parent drug VPA while three are formulated as the prodrug divalproex sodium. Two of the most common dosage forms of VPA used in modern practice are divalproex sodium delayed-release tablets (DR) and divalproex sodium extended-release tablets (ER). The FDA first approved DR for market in 1983 while ER was granted approval in 2002.[1] All VPA products are indicated for seizure disorders, but not all are approved for use in psychiatric illness. Both divalproex delayed-release and extended-release are indicated for the treatment of acute manic or mixed episodes of bipolar disorder and migraine prophylaxis in addition to their use in seizure control.[2,3]

The intent of developing newer controlled-release versions of VPA was to slow the rate of drug absorption thereby reducing the associated concentration-dependent side effects such as gastric irritation and nervous system effects (e.g., impaired cognition, tremors). To this end, DR was produced as an enteric-coated tablet containing both valproic acid and valproate sodium in a 1:1 ratio.[2] The enteric coating delays tablet dissolution and absorption until after the compound has progressed past the stomach.[4] In contrast, the ER tablet is comprised of a hydrophilic polymer matrix surrounded by a thin outer coating. The outer layer melts away upon ingestion and the polymer matrix subsequently becomes hydrated, forming a gel through which active drug is slowly released over several hours.[5,6] In both dosage forms, the divalproex sodium molecule released from its respective vehicle dissociates to the active valproate ion within the GI tract.

These differences in drug delivery mechanisms confer pharmacokinetic consequences. The DR formulation exerts a more robust and rapid absorption than does its ER counterpart, as illustrated by a higher maximum concentration (C_{max}) and shorter time to maximum concentration (T_{max}) in pharmacokinetic analyses.[6,7] It has been observed that the delayed-release form may cause much greater fluctuation in serum levels compared with the extended-release option.[6,7] In addition, the DR tablet has a shorter half-life than does the ER version. As a result, DR is traditionally dosed twice a day while ER is dosed once daily. The DR and ER tablets are not bioequivalent. Compared to the DR form, the ER tablet exhibits an average bioavailability of 81-89%.[6,7] This could be due to the slow, and possibly incomplete, release of active drug from the aforementioned matrix structure. To account for the differences in absolute bioavailability, the ER version may need to be dosed 10-20% higher than the DR form to achieve similar serum concentration levels of

the drug.[6,8] The divalproex extended-release package insert provides a dose conversion table for switching from DR to ER formulations.[3]

While it is recommended for clinicians to increase the total daily dose when converting from DR to ER dosage forms, it remains unclear whether such a dose adjustment is necessary to achieve targeted clinical outcomes.[3] Stoner and colleagues published a trial in 2004 comparing clinical outcomes in the setting of a 1:1 conversion versus a regimen compensating for the expected difference in bioavailability. The study enrolled 10 patients ages 21-65 who carried a diagnosis of bipolar disorder, schizoaffective disorder (bipolar or depressed type), chronic paranoid schizophrenia, chronic disorganized schizophrenia, or chronic undifferentiated schizophrenia. The authors utilized the 18-item Brief Psychiatric Rating Scale (BPRS) to assess clinical efficacy. Over a 4-week follow-up period, no statistically significant differences were detected in BPRS scores between the study groups.[9] Davis and colleagues published similar findings in 2007. The authors conducted a crossover study comparing a direct 1:1 conversion from DR to ER dosage forms with a regimen including a compensatory higher ER dose. The authors compared the results of several validated rating scales such as the Young Mania Rating Scale (YMRS), the 17-Item Hamilton Rating Scale for Depression (HAM-D17), and the Clinical Global Impression scale (CGI). The results of a 1:1 conversion reflected the expected differences in serum concentrations between the two dosage forms but did not yield any significant changes in YMRS, HAM-D17, or CGI measures.[10]

In many patients who are prescribed a form of VPA for the treatment of bipolar disorder, therapeutic drug monitoring (TDM) is utilized as a tool for efficacy assessment and dose adjustment. This is true for patients who are new-starts in an inpatient facility as well as outpatients on maintenance therapy. In general, a range of 50-125 mcg/mL is targeted in the treatment of bipolar disorder.[2,3] However, evidence provided by Allen et al suggests that in the treatment of acute mania serum concentrations greater than 94 mcg/mL may provide clinical benefit.[11] There are key monitoring pearls that exist for both the DR and ER dosage forms regarding the timing of serum concentration assays that are often overlooked. Steady-state levels are usually achieved within 3-5 days of therapy initiation or dosage change.[2,3] Trough concentrations are generally used for all forms of VPA when assessing efficacy; peak levels are rarely utilized but may be helpful if dose-related toxicity is suspected. It is recommended that trough levels for the DR version be drawn immediately prior to the morning dose, assuming a twice-daily dosing strategy. For once-daily divalproex ER regimens, the ideal time to draw serum levels is immediately prior to the next scheduled dose. However, logistical barriers such as variations in laboratory operating hours and hospital collection times may make this impractical. For this reason, facilities may prefer to draw morning levels 12 hours post-dose, regardless of dosage formulation.

It is unclear whether a serum concentration drawn 12 hours after administration of the ER version can be extrapolated to give an estimated trough level. The Davis study may provide some insight as the authors measured serum levels every four hours from 12 hours post-dose to 24 hours post-dose in patients receiving ER. They reported that 24-hour levels were 18-25% lower than the measured 12-hour levels.[10] However, there are few, if any large population-based pharmacokinetic models utilized to predict such measures. Also, much of the available literature regarding kinetic modeling for VPA is based on studies of patients with seizure disorders. There is limited evidence suggesting that VPA behaves differently in patients with bipolar disorder compared to patients with seizure disorders, which may render such PK analyses unreliable when applied to psychiatric patients.[12]

CASE

The case involves a 40-year-old, 117 kg female patient admitted to inpatient psychiatric facility following a deliberate overdose on her antidepressant medication. This patient had an extensive psychiatric history including diagnoses of bipolar affective disorder-currently depressed, post-traumatic stress disorder, borderline personality disorder, as well as alcohol and cocaine dependence (in remission). Additionally, her medical history included frequent headaches, asthma, fibromyalgia, and a seizure disorder of unknown classification. Her home medications at the time of admission were divalproex ER 1250 mg at bedtime, gabapentin 400 mg three times a day, topiramate 100 mg twice a day, venlafaxine XR 75 mg daily, clonazepam 0.5 mg at bedtime, naproxen EC 500 mg twice a day, and trazodone 150 mg at bedtime.

Upon admission and throughout her hospitalization, the patient's laboratory values were unremarkable with some small exceptions. She had a slightly depressed serum albumin level, the lowest recorded value being 2.7 g/dL. Her serum triglycerides were slightly elevated at 210 mg/dL. There were no laboratory results suggesting any pathology that could affect valproic acid levels such as uremia, hyperbilirubinemia, severe hypoalbuminemia,

severe hypertriglyceridemia, renal or liver insult, or pregnancy.

On day one of admission, the patient was re-started on her home medication divalproex ER for bipolar disorder at a starting dose of 1250 mg (10 mg/kg) by mouth at bedtime. On day three the dose was increased to 1500 mg (13 mg/kg) at bedtime. Three days later, a serum level was drawn ten hours post-dose that measured 71.3 mcg/mL. This level, along with the patient's clinical picture, suggested that higher dosing was necessary to achieve symptom control.

On day seven of admission, divalproex ER was increased to 2000 mg (17 mg/kg) at bedtime and after six subsequent doses, a level was drawn 24 hours post-dose. On this occasion the measured VPA concentration was 56.0 mcg/mL. The rate of titration was slow early in her admission as the patient was experiencing bouts of hypotension and dizziness which the divalproex may have caused or exacerbated.

As the side effects subsided, a dose increase was again warranted based on the patient's persistent symptoms of mood lability and agitation. Two medication changes were made at this point: quetiapine was initiated for symptoms of psychosis and paranoia and divalproex was increased, as well. A regimen of 2500 mg (21 mg/kg) at bedtime was ordered on day fourteen of admission. However, upon entry into the computerized prescriber order entry system, the patient was switched to divalproex delayed-release 2500 mg at bedtime with no apparent clinical intentions to switch the formulation. The patient remained on this regimen for four days and immediately prior to the fifth dose another VPA serum level was drawn and measured at 62.9 mcg/mL.

On day nineteen of admission the care team switched the patient back to divalproex ER at a dose of 2500 mg at bedtime. At this time, the patient's antipsychotic medication was also changed to risperidone 1 mg twice daily. One week later, a 12-hour VPA level was drawn. The serum concentration was measured as 114.5 mcg/mL – falsely elevated due to the timing of the blood draw. The dose was reduced to 2000 mg nightly on day twenty-four due to concern that the level of 114.5 mcg/mL was too high for outpatient maintenance. The patient was discharged home on this regimen after a total of thirty-two days in inpatient care.

ANALYSIS

The patient case described above revealed some interesting information as well as a broad array of questions. Perhaps the most notable observation was that the patient exhibited no clinical changes such as psychiatric deterioration or side effects upon conversion between the DR and ER formulations. It may be fair to assert that, for this patient at least, the two dosage forms of divalproex sodium may have a large degree of clinical interchangeability. A more thorough study of such a theory may be warranted. To this point, much of the published literature comparing DR and ER relies on proxy measures such as serum levels. One might speculate that a study comparing the efficacy of these two formulations in the treatment of bipolar disorder may reveal that no clinically significant difference exists. This point is illustrated by an occurrence in the case; the patient was switched from 2500 mg ER nightly to 2500 mg DR nightly on day fourteen and the subsequent serum level on day eighteen was 62.9 mcg/mL. Previously in her stay, the patient had a serum level of 56.0 mcg/mL while on 2000 mg ER nightly.

This sequence of levels is remarkable in that it suggests that once-daily DR dosing did not result in reduced drug concentrations as may have been expected. In addition, the patient reported no side effects and there were no signs of toxicity that may have been associated with a higher C_{max} from the DR formulation.

A second crucial point that can be drawn from this case is that the utility of therapeutic drug monitoring can only be realized if levels are drawn at the appropriate time relative to dose. Trough levels should be obtained 12 hours post-dose for DR and 24 hours post-dose for ER formulations. These are not interchangeable parameters and such mistakes can lead to mismanagement of drug therapy. Such an error may have occurred in the case above – note that on day 23 of therapy the dose of divalproex ER was reduced from 2500 mg nightly to 2000 mg nightly due to a serum level of 114.5 mcg/mL. This level was drawn 12 hours post-dose rather than 24 hours post-dose and may not have been representative of a true trough. It is difficult to estimate what the predicted trough would be for this patient based on the 12-hour serum-level. The pharmacokinetic analyses available suggest that this level may be approaching the expected peak.[5,6] In applying the information garnered from the Davis study, one might predict that a 24-hour trough level would fall in the 85-94 mcg/mL range.[10]

Valproic acid and its prodrug divalproex are mainstays in the treatment of bipolar affective disorder. Despite the widespread use of these medications as treatment options, there are still areas of knowledge in which we are deficient. Topics to investigate further may involve the clinical similarities and differences that each dosage

formulation of divalproex presents, the utility of therapeutic drug monitoring in bipolar disorder, and the importance of understanding the dosing and monitoring strategies for each product.

REFERENCES

1. FDA Orange Book, 2013. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm, keywords "valproic acid" and "divalproex", accessed July 15, 2013.
2. Depakote (divalproex sodium delayed-release tablets) [Package Insert]. North Chicago, Illinios: AbbVie Inc.;2013
3. Depakote ER (divalproex sodium extended release tablets) [package insert]. North Chicago, Illinois: AbbVie Inc.; 2013
4. Zarate CA, Tohen M, Narendran R, Tomassini EC, McDonald J, Sederer M, et al. The adverse effect profile and efficacy of divalproex sodium compared with valproic acid: a pharmacoepidemiology study. J Clin Psychiatry. 1999;60(4):232-6. PubMed PMID: 10221283.
5. Stoner SC, Dahmen MM. Extended-release divalproex in bipolar and other psychiatric disorders: A comprehensive review. Neuropsychiatr Dis Treat. 2007;3(6):839-46. PubMed PMID: 19300619.
6. Dutta S, Zhang Y, Selness DS, Lee LL, Williams LA, Sommerville KW. Comparison of the bioavailability of unequal doses of divalproex sodium extended-release formulation relative to the delayed-release formulation in healthy volunteers. Epilepsy Res. 2002;49(1):1-10. PubMed PMID: 11948003.
7. Dutta S, Reed RC. Distinct absorption characteristics of oral formulations of valproic acid/divalproex available in the United States. Epilepsy Res. 2007;73(3):275-83. DOI: 10.1016/j.eplepsyres.2006.11.005. PubMed PMID: 17208410.
8. Reed RC, Dutta S, Cavanaugh JH, Locke C, Granneman GR. Every-12-hour administration of extended-release divalproex in patients with epilepsy: impact on plasma valproic acid concentrations. Epilepsy Behav. 2006;8(2):391-6. DOI: 10.1016/j.yebeh.2005.12.004. PubMed PMID: 16473558.
9. Stoner SC, Dubisar BM, Lea JW, Marken PA, Ramlatchman LV, Reynolds JB. Extended-Release Divalproex Sodium for Mood Stabilization. Pharmacotherapy. 2004;24(9):1147- 1153. DOI: 10.1592/phco.24.13.1147.38088.
10. Davis LL, Li X, Bartolucci AA, Williford RB, Lowe JS. A pharmacokinetic and clinical evaluation of switching patients with bipolar I disorder from delayed-release to extended-release divalproex. J Clin Psychiatry. 2007;68(10):1546-51. PubMed PMID: 17960970.
11. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry. 2006;163(2):272-5. DOI: 10.1176/appi.ajp.163.2.272. PubMed PMID: 16449481.
12. Mohammadpour AH, Foroughipour M, Azarpazhooh MR, Khayat MH, Rezaee S, Aghebati T, et al. Comparison of Valproic acid Clearance between Epileptic Patients and Patients with Acute Mania. Iran J Basic Med Sci. 2011;14(6):546-50. PubMed PMID: 23493631.

How to cite this article
McGraw D. Therapeutic drug monitoring with valproate–Why product selection is an important factor. Ment Health Clin [Internet]. 2014;4(1):31-4. Available from: http://dx.doi.org/10.9740/mhc.n186966