THE ACUTE TREATMENT OF HEADACHES WITH INTRAVENOUS VALPROATE

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ABSTRACT

An open-label, nonrandomized, and noncontrolled study was conducted to pilot the use of intravenous (IV) valproate sodium in the management of patients with moderate to severe primary headaches (≥4 on 0-10 visual analog pain scale [VASpain]). The study evaluated 130 patient encounters that included transformed migraine, chronic tension-type headaches, episodic migraine (including status migrainosus), episodic cluster, and uncharacterized, chronic daily headache. Because of its design, the study was of limited validity. However, results suggest that the use of IV valproate is statistically associated with improvement in VASpain scores in the treatment of primary headaches, both acute and acute exacerbation of chronic headaches. A randomized double-blind, controlled study of IV valproate for severe primary headaches is warranted.

Oral valproate has proven efficacy in preventing episodic and chronic migraine, controlling seizures, and modulating mood swings in bipolar illness. The introduction of intravenous (IV) valproate has been successful in the treatment of status epilepticus, as well as in acute mania. Several possibilities may explain this efficacy. Pharmacokinetically, IV valproate may cause a rapid saturation of plasma binding proteins, resulting in high concentration of this free drug, and therefore, high cerebral levels of the drug. Spinal cord and cortical neuronal cell culture studies conducted in the mid-1980s demonstrated that at therapeutic concentrations between 60 mcg/mL and 100 mcg/mL, IV valproate inhibits the voltage-dependent sodium channel in an activity-related manner, meaning that the hyperactive cells were the cells for which the action potentials were most suppressed. Also, at high concentrations, valproate increases gabapentin GABA concentrations through activation of GABA-synthetic enzymes and inhibition of GABA degradation. Therefore, this drug, administered at doses of approximately 120 mcg/mL, should be tested in the abortive treatment of acute headache disorders.

The objective of the study was to describe the use of IV valproate in the management of outpatients with moderate to severe primary headaches. In a nonrandomized, open-label and prospective fashion, 130 consecutive valproate-naïve patients were treated with a solution of valproate and 150-cc saline, infusing the solution over 10 to 15 minutes, waiting 15 minutes, then repeating the dose until the total dose reached 15...
Valproate does range from 300 to 1200 mg.

Indications for treatment were moderate to severe primary headaches (≥4 on 0-10 visual analog pain scale (VASpain)). Headache pain was measured before treatment and at time of discharge. Positive response was defined as a ≥50% reduction at discharge in baseline headache. Patient demographic data were collected, as well as information regarding the type of headache (utilizing IHS criteria and the criteria recently proposed for chronic headaches by Silberstein et al.). Also measured were observation time, time spent in the infusion suite, cumulative dose of valproate, and use of concurrent medication. The association among categorical variables and reduction in VASpain was assessed using \( \chi^2 \) analysis, and the association among continuous variables and VASpain reductions was assessed using the \( t \) test. Logistic regression analysis was used to identify univariate and multivariate correlates of pain relief. In each of these measures, \( P < 0.05 \) was considered significant.

The study evaluated a total of 130 patient encounters: 54 (42%) chronic daily headaches with migrainous features; 4 (3%) chronic tension-type headaches (CTTH); 39 (30%) ... were reported: 2 episodes of transient dizziness and 1 pseudoseizure in a patient with a history of pseudoseizure.

For all treatments, 82/130 (63%) responded with ≥50% reduction in VASpain (\( P = 0.003 \)). Classifiable headaches fared much better than unclassifiable headaches. Longer stays in the infusion unit and the need for additional analgesics were associated with a poorer outcome. Positive responses were unrelated to cumulative doses of valproate (range 300-1200).

Twenty-seven (21%) were headache free by the time of discharge. Thirteen (10%) had 76% to 99% reduction in VASpain scores. Forty-two (32%) had 50% to 75% reduction in VASpain scores. Forty-eight (37%) negative responses were observed.

These results are of limited validity because the study was open-label, nonrandomized, and noncontrolled. A limited window of observation without follow-up for delayed responses or headache recurrence may have resulted in an underestimation of the efficacy of IV valproate among late responders. Other limitations include the use of VASpain scale only and not headache relief as an endpoint. No evaluation of associated headache symptoms was conducted.

In conclusion, in this study, use of IV valproate is statistically associated with improvement in VASpain scores and in the treatment of primary headaches, both acute and acute exacerbation of chronic headaches. IV valproate is a safe, rapidly effective, and easily administered IV agent for aborting moderate to severe headaches. Investigators found that the more easily classified the headache, whether it was chronic or episodic, the more effective the response to IV valproate. Moreover, this therapy was extremely effective for episodic migraine and episodic cluster headaches; all patients in these 2 groups left the IV unit within 1 hour, headache free. A randomized, double-blind, controlled study of IV valproate for severe primary headaches is warranted. --GB

REFERENCES

