

### The Effect of Intravenous Metoclopramide and Valproate in Acute Migraine

Headache is the most common reason for ER visits. Acute migraine is the most common type of headache among these. Even though there are multiple treatment options for acute migraine, the efficacy of these is very limited in practice.

In a study investigating the efficacy of valproate used in routine practice as prophylactic treatment, researchers divided 330 patients into 3 groups: 1000 mg intravenous (IV) valproate group, 10 mg IV metoclopramide group, and 30 mg IV ketorolac group (1). All three treatments in the study were administered within 15 minutes and the effectiveness of the treatment was scored between 0 and 10, and also qualitatively as severe, moderate, mild and painless.

The primary outcome was determined as the comparison between the groups after an hour. Secondary outcomes were determined to be requiring another medication in the ER, the patient's satisfaction with the treatment, complete painlessness within 2 hours that is maintained for a minimum of 24 hours and the improvement level of the pain within two hours.

At the end of study, valproate group improved 2.8 points (95% CI: 2.3-3.3), metoclopramide group improved 4.7 points (95% CI: 4.2-5.2), and ketorolac group improved 3.9 points (95% CI: 3.3-4.5). It is interesting that valproate was equally or less effective than the other two drugs at the secondary outcomes. In addition, despite being relatively more effective than valproate, ketorolac was seen to be less effective than metoclopramide. When the patients were asked if they could return to their jobs after 1 hour from the drug administration, 28% of valproate group, 39% of ketorolac group and 39% of metoclopramide group said yes. During the study, all drugs were tolerated without any significant side effects, except for 6% of patients that were given metoclopramide who showed some restlessness.

Being the largest study on valproate in acute migraine, this study showed that metoclopramide's effect is bigger than it was previously thought. In other studies testing valproate on acute migraine, IV salicylic acid (2), subcutaneous sumatriptan and intramuscular metoclopramide combination (3), intramuscular dihydroergotamine and metoclopramide combination (4), and prochlorperazine (5) were compared and it was found to have equal or less effect than all those other drugs.

This study suggests very clearly that even though IV valproate

is thought to be effective for acute migraine, it should not be considered as the primary option where drugs with better cost/benefit ratios such as metoclopramide and ketorolac are available. However, the fact that none of the drugs provided 24 hours of pain relief in more than 25% of the patients suggests that further drug trials are required for the treatment of acute migraine.

### References

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### Use of Acetazolamide in Idiopathic Intracranial Hypertension

Synthesized from the antibiotic sulfanilamide in 1950 by Roblin and Clapp, acetazolamide was discovered to be a powerful carbonic anhydrase inhibitor in the following years. Initially only tried in kids with hydrocephalus, this drug took its place in standard practice in treatment of intracranial hypertension (1). Despite its common use in idiopathic intracranial hypertension (IIH), acetazolamide has not been tested in a randomized controlled clinical study about this specific indication.

To fill this need, a collaborative study involving 38 centers in North America was planned (2). In this study, the researchers randomized 165 IIH patients into 2 groups and gave either placebo or acetazolamide for 6 months with significantly high doses; starting with 1 gr/day and increasing up to 4 gr/day with 250 mg increments. The first outcome measure was the improvement of Humphrey's 210 visual field examination at the 6th month of treatment. This test relies on retinal sensitivity measurement at

54 points on the central visual field. The result is reduced into a single logarithmic term perimetric mean deviation (PMD). This PMD value is 0dB in healthy individuals. A PMD value -3 dB indicates a 3-fold decrease in retinal sensitivity.

The secondary outcome measures of the study were papillary edema severity, cerebrospinal fluid pressure, visual acuity, quality of life, headache and body weight.

The mean PMD values of the patients included in the study were -3.5dB. On the sixth month, this value increased to -2.1dB in acetazolamide group and to -2.8 dB in placebo group ( $p=0.05$ ). Even though there was an improvement, the effect size was "mild", as expressed by the authors. As for the secondary outcome measures of the study, all but visual acuity seemed to improve in acetazolamide group compared to placebo group.

The presence of the placebo control prevented the recruitment of the more severe cases where the effect of treatment could more easily be observable. This situation can explain why the treatment's benefit was limited. It is worth noticing that the PMD values of patients with severe papilledema decreased more compared to those with less severe papilledema (-2.3 dB versus -0.7 dB).

Another interesting result of the study was that the weight loss in acetazolamide group was twice as much as the placebo group (-7.5 kg versus -3.5 kg;  $p<0.001$ ).

The study used an extraordinarily high dose of acetazolamide. The regular dose for practice is 0.5-1.5 gr/day globally whereas the

investigators used 2.5 gr/day (2-4 gr/day). Despite that, however, there were no significant side effects. Decrease in CO<sub>2</sub> levels, diarrhea, loss of taste, fatigue, nausea, vomiting and paresthesia were seen more commonly in acetazolamide group. In addition, it was interesting that there were no electrolyte imbalance despite the high dosage. Still, the fact that 2 patients in the active treatment group had kidney stones, one patient had elevated transaminase and one patient developed pancreatitis suggests that the drug still requires caution.

This study, which used high dosage acetazolamide in IIH, showed clearly that the drug caused moderate improvements in cases of moderate severity. Even though acetazolamide's effect for more severe cases is expected to be much greater, it is important from an evidence-based treatment perspective for IIH that this group is used in studies comparing medical and surgical treatment options.

## References

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