
Question: Is ecallantide more effective than placebo for the treatment for Angiotensin-converting enzyme inhibitor-induced angioedema (ACEIA)?

Introduction: ACEIA accounts for up-to one third of patients treated for angioedema in the Emergency department. Briefly the pathophysiology depends on the structural similarity of Angiotensin-converting enzyme (ACE) to kininase II, an enzyme involved in the breakdown of bradykinin. When ACE-inhibiting medications are administered, kininase function is also blocked leading to an accumulation of bradykinin. Excess bradykinin, an inflammatory mediator, causes endothelial leak as well as activation of downstream mediators all leading to the development of angioedema. Risk factors associated with the development of ACEIA include age greater than 65, concomitant use of ASA or NSAIDs and cigarette usage – all factors highly prevalent in a typical ED patient cohort. ACEIA tends to not respond to antihistamines, steroids or epinephrine- therapies which are typically effective for other inflammatory-mediated vasodilatation. In the emergent setting angioedema leading to airway compromise can present a challenging and potentially life-threatening scenario. Therapies that directly target the bradykinin pathway may succeed where other traditional therapies have failed. Ecallantide is an upstream inhibitor of bradykinin production. This study hypothesized that ED use of ecallantide in patients presenting with ACEIA would decrease the production of bradykinin and help to improve the angioedema.

Methods: This was a double-blind randomized placebo controlled trial that took place in multiple Emergency Department settings in the United States. Patients 18 years or older presenting to the ED within 12 hrs of ACEIA onset and ACEI use in the preceding 36 hrs were considered for inclusion. Pregnancies, breastfeeding, h/o angioedema not associated with ACEI use or the need for immediate intubation or surgical airway were excluding factors. Patients who met inclusion criteria were randomized into one of four treatment arms; placebo or one of three ecallantide dosing regimens. Primary effective endpoint was defined as meeting the following criteria within 6 hours of medication administration: improvement in edema as assessed by the investigator with a 5-point Likert-type scale, stable vital signs, absence of stridor, absence of dyspnea or drooling, no use of accessory muscles during respiration and the ability to drink without difficulty.

Results: A total of 176 patients (44 per treatment arm) were needed to provide a power of 90% with α=0.05 to detect a treatment response of 30% between the control group and all treatments groups. An interim analysis of the preliminary data, after the first 57 patients were enrolled showed a higher than expected response rate to placebo. Because of this placebo response the study was terminated. With a higher than expected placebo response rate the number of patients enrolled in the study would have needed to be much higher than the original goal of 176 to provide a power sufficient to ultimately achieve a p-value of statistical significance.

Discussion: While there is little value gained in this study that can be directly applied to practical clinical medicine I found it to be a good exercise for the review of the basic tenants of evidence based medicine. When a study is looking at a difference between a treatment and a placebo group there needs to be a predetermined difference in response rate. In this particular study a difference of 30% between placebo group and treatment groups was the predetermined goal. A 30% difference is a big difference and this initially allowed them to have a relatively small number of subjects (176). Once it was recognized that placebo response was higher than expected and the difference between placebo and treatment groups was going to be much lower than 30% it was apparent that the original study design could not produce statistically significant results. Why is this? It’s all about accounting for the random fluctuations that are inherent in any system. Big dramatic differences between two treatments are less likely to be due to random fluctuations. With less concern for random differences skewing your data you can test a much smaller group of subjects. With small differences between treatment results the opposite is true – you need to repeat the experiment many-many times to overcome the risk of random events convoluting your data. This is where the concept of α or type I error and β or type II error comes into play. In a type I error you believe that your study has demonstrated a real difference between two treatments when in reality the only difference seen was due to random fluctuation (in fancy statistics talk – you have incorrectly rejected the null hypothesis). In a type II error your data set does show a real difference between treatments, but you fail to recognize this and chalk it up to random changes (you have failed to reject an incorrect null hypothesis). Type I and II errors are
inversely proportional, meaning as you design your study you have to decide if you want to risk a higher rate of type I or type II error. In medicine it is typically preferred to design for a lower type I error rate at the risk of a higher type II error rate – the rationale being that it’s preferable to tell a healthy patient that they might have a disease than to tell a sick person that they probably don’t have a disease. Because there tends to be more of an emphasis on rejecting the null hypothesis when it is incorrect (i.e. the difference shown between two treatments groups is legitimate and not due to random flux) the power of a study is dependent on the type II error rate (power = $1-\beta$).

Conclusion: This study was underpowered and therefore was unable to show a statistically significant difference between the treatments of ACEIA with placebo vs escallantide.