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MEETING REPORT

PROGRESS IN EPILEPSY RESEARCH

65TH ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY, DECEMBER 2-6, 2011, BALTIMORE, MARYLAND, USA

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SUMMARY

The 65th Annual Meeting of the American Epilepsy Society (AES) was held in Baltimore, Maryland, USA, on December 2-6, 2011. The society also celebrated its 75th year of existence during the annual meeting. Three major benchmark areas were highlighted during the current meeting. These included the prevention of epilepsy and its progression, the development of new therapeutic strategies and optimization of current approaches to cure epilepsy, as well as prevention, limitation and reversal of the comorbidities associated with epilepsy and its treatment. Epilepsy is a neurological disorder that affects approximately 50 million people worldwide, and there is a need for novel treatment strategies to treat it. The 65th Annual Meeting of the AES discussed the most recent findings in the area of epilepsy and also presented some novel molecules that are in late stages of approval for the disorder. Some of the highlights of the meeting were the AES Fellows Program, Special Interest Group Meetings, Presidential Symposium, Investigator's workshop and poster or platform presentations. The present report also discusses some of the deliberations held at the meeting.

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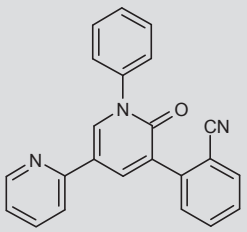
INTRODUCTION

The American Epilepsy Society (AES) is a premier organization of both basic and clinical healthcare professionals working in the area of epilepsy. Epilepsy is a chronic neurological disorder that affects a large population worldwide. Most of the seizures are managed by available antiepileptic drugs, but some patients are resistant to these available therapies and continue to have seizures. This has led to exploration of novel treatment strategies with unique mechanisms of action for such patients. The AES aspires to advance the understanding of epilepsy by providing professionals insight into the disorder's exact pathophysiology and by providing funding to explore novel drug candidates with the aim of eliminating seizures and underlying neurological defects. The society also promotes research and education among professionals engaged in the field of epilepsy. It holds its meeting every year with a plan to disseminate novel outcomes in the field of epilepsy among professionals all over the globe. This year, the annual meeting was held in Baltimore, Maryland, on December 2-6, 2011. It was attended by more than 4,000 epilepsy professionals. Interestingly, the society also celebrated its 75th anniversary this year and a special video showed its historical advancement and views of different professionals working in the epilepsy field. For the first time, the society arranged the special session "AES Fellows Program", whereby junior fellows or residents working on epilepsy were paired with senior mentors and given a chance to discuss their research outcomes, career plans and clinical endeavors.

The meeting covered preclinical and clinical findings in the field of epilepsy. The promising molecules perampanel (E-2007, ER-155055-90; Eisai), ezogabine (known as retigabine in the E.U.; Asta Medica, GlaxoSmithKline and Valeant Pharmaceuticals) and VX-765 (Vertex Pharmaceuticals) were extensively discussed during the meeting. These molecules are important in understanding epilepsy



Perampanel

as they act through novel and unique mechanisms of action. **Perampanel** has completed clinical studies and is awaiting FDA approval for marketing. Ezogabine has already been approved in the E.U. as *Trobalt*® and in the U.S. as *Potiga*®. VX-765 has completed phase IIa testing and requires phase IIb evaluation with an extended administration and observation time.

Sudden unexpected death in epilepsy (SUDEP) is a topic of debate these days. The topic is still in its infancy and the exact mechanism is not yet known. Various controversial issues in the field of SUDEP that were discussed at the meeting are presented here in this report.

Another major issue in the treatment of epilepsy is the occurrence of comorbid neurological problems in patients suffering from epilepsy. There has always been a constant debate on the association of migraine, Alzheimer's disease and depression with epilepsy pathophysiology. Therefore, it is also very important to treat these comorbid disorders in addition to managing convulsions.

SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

An acronym for sudden unexpected and unexplained death in epilepsy (as defined by Nashef in 1997), SUDEP is the sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom postmortem examination does not reveal a structural or toxicological cause for death (1). As explained by Tomson and colleagues (2005), SUDEP is more commonly associated with generalized tonic–clonic seizures and its incidence is higher in patients with chronic and refractory epilepsy than in those with new-onset epilepsy (2). Improvement of seizure control is a key factor to avoid SUDEP. During the 65th Annual Meeting of the AES, a special interest group session on SUDEP was arranged. Different controversies in the field were debated during this session. Several eminent speakers presented their thoughts on the topic.

One of the major issues discussed during this session was whether or not to inform patients and families about the possibility of SUDEP. This was a very important question and researchers had different viewpoints on it. For instance, if a patient with uncontrollable epilepsy is told about the possibility of SUDEP, this might create a great sense of anxiety and worsen the situation. Conversely, informing patients and their families about the possibility of SUDEP might help them take necessary measures to prevent it. Therefore, risks and benefits should be properly assessed before informing patients and families about SUDEP. It is very important to answer why and when patients and families should be informed about its consequences.

An interesting debate was held regarding the role of nocturnal supervision in preventing SUDEP. Nocturnal supervision could be helpful in SUDEP, as it may enable the caretaker to take appropriate steps during the night. These appropriate steps may be enabling correct positioning of the patient, stimulating them and clearing their respiratory tract (3). Therefore, having another person in the bedroom may prevent the risk of SUDEP. The researchers did not reach a conclusion on whether nocturnal supervision is necessary at this time, however, and the topic needs further investigation.

Another extensive debate was held on the exact mechanism of SUDEP. It is not yet clear which organ is totally responsible for SUDEP. Researchers discussed the involvement of three major organs: the brain, heart and lungs. No conclusion was reached and the subject requires more investigation.

Data were presented from one study in which five patients who were on electrographic sensing and recording underwent SUDEP. SUDEP occurred during a period of frequent epileptiform discharges and during time of a seizure. Four of the five subjects had epileptiform activity preceding SUDEP (4).

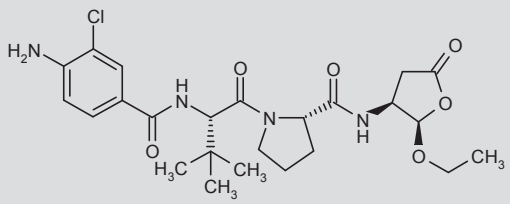
In conclusion, research on SUDEP is gaining momentum and the day is not far when the exact pathophysiological basis for SUDEP will be completely understood and different measures will be chalked out for its prevention.

VX-765

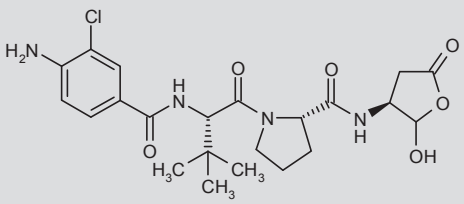
Previously, coworkers and I demonstrated the anticonvulsant action of various nonsteroidal antiinflammatory drugs in animal models of epilepsy, especially the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx®; Merck & Co., Galderma Pharma). We concluded that inflammation plays a role in the pathophysiology of epilepsy and antiinflammatory drugs may be novel therapeutic agents for the treatment of epilepsy (5).

VX-765 is an orally active prodrug of **VRT-43198** and is being developed by Vertex Pharmaceuticals for the treatment of epilepsy. VRT-43198 is a potent and selective inhibitor of caspase-1 (6) and reduces the production of interleukin-1 beta (IL-1 beta). Ravizza and colleagues reported the protective effect of VX-765 in kindling epilepsy and suggested its antiepileptogenic activity (7). Maroso and coworkers reported both an acute and chronic antiepileptic effect for VX-765 (8).

In a 6-week phase IIa study presented at the AES, VX-765 was found to be safe and tolerable. The study enrolled 60 patients with refractory partial-onset epilepsy. The most common adverse effect was dizziness and its incidence in the cohort receiving VX-765 was not significantly different from that in the group receiving placebo. One patient had to discontinue the study due to the development of rash. Regarding the efficacy of VX-765 in patients with refractory partial-onset seizures, different parameters were measured. These parameters included the percent reduction in seizure rate, the percent of



VX-765



VRT-43198

patients with a ≥ 50% reduction in seizure frequency (responder rate) and the percent of patients who were free of seizures the last 2 weeks of treatment. Although none of the parameters were found to be significantly different with VX-765 versus placebo, improvement in clinical activity with VX-765 was greater than with placebo during the last 2 weeks of treatment and the first 2 weeks of follow-up. These results suggested a need for a clinical trial of longer duration (phase IIb) to determine the product's exact efficacy in the treatment of refractory epilepsy (9).

EPILEPSY AND COMORBIDITIES

Comorbid disorders are very common in epilepsy. In one of the studies presented at the 65th AES meeting, Kosachunhanun et al. compiled the epidemiology of comorbid disorders in patients with epilepsy. The study involved analyzing the data from the Ohio Medicaid Database between 1992 and 2008. It was found that mental disorders (mainly depression, alcohol dependence and drug dependence) were commonly observed in patients with epilepsy. Other comorbid disorders listed by the group were respiratory problems, nervous system and sense organ abnormalities (excluding epilepsy and convulsions), injury and poisoning. Among nervous system disorders, migraine was the most common complaint in patients with epilepsy. Other chronic comorbid disorders observed in patients with epilepsy included hypertension, diabetes, anxiety disorders and ischemic heart disease (10).

In another study presented at the meeting, it was shown that anxiety can worsen the occurrence of depressive disorders in patients with epilepsy (11). In a preclinical study, animals with lithium/pilocarpine-induced status epilepticus displayed depression characteristics a few days after status epilepticus. This depression was not sensitive to fluoxetine treatment. It was shown that combined treatment of fluoxetine and a human recombinant IL-1 receptor antagonist reversed the depression in this animal model (12).

EZOGABINE/RETIGABINE

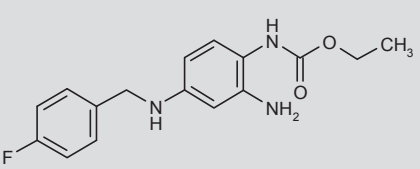
In a presentation at this year's AES meeting, Dr. Edward Faught discussed ezogabine/retigabine (13). On June 11, 2011, the FDA approved its use as an adjunctive treatment for partial-onset seizures in patients aged 18 years and older. The drug targets voltage-gated $K_V7.2$ and $K_V7.3$ potassium channels. The FDA has issued a warning regarding the possibility of urinary retention associated with the use of ezogabine. Urinary retention was observed in 2% of patients in clinical trials of the product. Dr. Faught also emphasized the drug's pros and cons as an antiepileptic. It has a novel mechanism of action in treating epilepsy. Some other advantages include few drug–drug interactions, the fact that it is excreted via the kidneys, has a low propensity to cause rash and problems with cognition, and that no apparent serious skin, blood and liver problems have been associated with its use. Cons include the agent's modest efficacy, short half-life and the fact that it can cause urinary retention, which may be a problem in elderly patients. Finally, Dr. Faught told the audience that the FDA has not yet approved the label but that the drug would be used at 600-1200 mg/day in three divided doses. The starting dose has not yet been determined, however.

CONCLUSION

The AES continues to be an important platform for dissemination of recent advances in the field of epilepsy. At its 65th Annual Meeting, the future of epilepsy research was discussed. It is hoped that we will soon be able to treat each and every patient with epilepsy.

DISCLOSURES

The author states no conflicts of interest.



Retigabine

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