Eradicating seizures

Dr Ilo Leppik, a professor of pharmacy and neurology, is conducting pioneering research into the development of novel drugs for the long-term treatment of prolonged, life-threatening seizures.

Could you clarify the terms epilepsy and status epilepticus (SE) and explain the complications involved with SE?

Epilepsy is a condition that is characterised by seizures. It affects all age groups, although it is most common in children and the elderly. At any given time, approximately 1 per cent of the human population will have epilepsy. The most convulsive (generalised tonic-clonic or grand mal) seizures are self-limiting and even without immediate treatment only last a few minutes. Convulsions lasting more than five minutes indicate that the processes that limit a seizure are not working and constitute SE. Convulsions lasting more than 30 minutes often cause permanent brain damage and can be fatal.

Why are current treatments for human status epilepticus (HSE) only about 50 per cent effective?

The drugs currently used for HSE were initially developed to treat people with chronic epilepsy. Only later when intravenous preparations became available were they adapted for treating HSE. These drugs work best when the person is free of seizures most of the time, but has sporadic seizures that may be prevented by using antiepileptic drugs (AEDs), so that a constant level of medicine is present. This helps supplement the brain’s normal ability to limit seizure activity. In HSE, however, these mechanisms do not work and the person develops a prolonged seizure. It is well known that in this situation, the brain becomes resistant to the most commonly used class of drugs, the benzodiazepines, as well as to other AEDs. Because the response rate is so low, novel drugs that work specifically for HSE are badly needed.

The jump from drug discoveries based on small animals to human testing is great and has limited progress. What are some of these restrictions?

Developing new drugs for epilepsy has become increasingly costly. The potential efficacy of new agents is first evaluated in rodent models. There are three limitations to these studies. First, most of this testing involves artificially induced seizures using electrical or chemical stimulation. These tests, although useful, are not always able to predict success in treating human epilepsy. Secondly, there are a number of side-effects that cannot be detected in these small animals, including cardiac toxicity and behavioural changes such as depression. Lastly, the prediction of doses needed is difficult due to variance in drug metabolism and the approximately 8,000-fold difference in body size between small animals and humans.

What makes the development of new drugs so costly?

Once promising agents have been identified, companies must plan for extensive and expensive testing. First, safety in humans must be evaluated for factors that cannot be tested in rodents, such as cardiac and behavioural effects. Some drugs will inevitably fail these initial tests in phase I clinical trials. However, if they pass, dose ranges will then need to be tested in phase II trials because the extrapolation of dose from rodent to human is not precise. Many drugs fail in phase I and II trials and add to the overall cost of developing drugs. Using naturally occurring epilepsy and SE in dogs to evaluate toxicity and efficacy will screen out drugs which have properties that would cause them to fail in phase I and II studies. In addition, obtaining information regarding therapeutic drug levels in dogs will allow human studies to be designed to attain effective drug levels without the need to perform extensive dose-ranging studies in humans.

To what extent could the use of naturally occurring epilepsy and SE in dogs reduce the cost of drug development?

We estimate that screening potential drugs in naturally occurring epilepsy and SE for efficacy and tolerability would eliminate a number of drugs that appear to be promising in small animals but are found to be cardiotoxic or have other intolerable side effects when tested in humans. Testing in dogs is much less expensive and we estimate that a drug can be screened in dogs at a fraction of the cost of a phase I human trial.

How will you study drugs for prolonged use in epilepsy?

We have a colony of eight dogs – donated by their owners – who suffer from frequent seizures. Each dog has been implanted with a device developed for the prediction and detection of epilepsy. The dogs are housed in canine epilepsy monitoring units at the University of Minnesota and University of Pennsylvania Veterinary Colleges. A researcher from the Mayo Clinic who is an expert in electroencephalography (EEG) is helping to analyse the data. This device allows us to very accurately evaluate the effect of experimental drugs on the pattern of electrical activity, as well as precisely detect seizures. This is an important advantage because one of the limiting factors in human studies is the error rate in patients reporting seizures.
**Translating knowledge**

Scientists at the University of Minnesota, USA, are hoping to establish a translational platform for human therapeutic trials that may enable the development of effective pharmaceuticals to treat status epilepticus.

**HUMAN STATUS EPILEPTICUS** (HSE) is a serious and often life-threatening prolonged form of seizure, affecting approximately 152,000 people annually in the US. Existing guidelines and treatments for HSE were developed in the 1970s, comprising the use of pharmaceuticals phenytoin (PHT) and benzodiazepines, which are still administered to patients today. Due to the lack of progress and innovation in the field, there remains a substantial gap in knowledge between basic research discoveries and their applications in clinical settings to treat the disease; with internationally adopted therapeutics for HSE only proving effective for patient care in around 50 per cent of cases.

To address this challenge, Dr Ilo Leppik, Professor of Experimental and Clinical Pharmacology and Professor of Neurology at the University of Minnesota, conducted innovative National Institutes of Health (NIH)-funded research, which demonstrated that naturally occurring canine status epilepticus (CSE) is a workable platform to screen drugs for human therapeutic trials for HSE. The next objective for this team of seven veterinary centres in the US is to test the efficacy, safety and tolerability of three novel drugs for HSE.

As HSE requires single loading doses of pharmaceuticals rather than chronic treatment over a number of years, the commercial value of developing drugs for the disease may be limited. Moreover, training staff at a number of different facilities and gaining informed consent from patients for trials is both costly and time-consuming. To overcome such barriers the NIH created the Neurological Emergency Treatment Trials (NETT) programme, designed to bring together a number of different centres to conduct large, simple clinical trials. The Established Status Epilepticus Treatment Trials (ESETT) will use NETT to conduct an HSE study using standard anti-epileptic drugs (AEDs). Results from Leppik’s investigation of novel pharmaceuticals in dogs will then be analysed to help inform drug choice for future HSE trials.

**CANINE STATUS EPILEPTICUS**

CSE is an illness commonly encountered by veterinarians. Leppik chose to use CSE as an experimental model because dogs with naturally occurring CSE present very similar symptoms to patients with HSE. Studies have shown that dogs and humans experience comparable simple partial, complex partial and tonic-clonic seizures. In addition, canine interictal and ictal patterns, which are notably different from one another and indicate whether the subject is having a partial or generalised seizure, are very similar to those observed in humans. Canine subdural electrode recordings, used to map and localise the source of seizures, have also been comparable to human readings.

Leppik will initially test novel drugs used to treat CSE with the help of a pioneering medical device that can be implanted into a dog’s brain to monitor and predict oncoming seizures. This device has a key benefit, as Leppik explains: “The device is innovative because it allows for the study of the effect of drugs directly on the electrical activity of the epileptic brain”. Following testing in the dogs with the implant, the next step is to test the novel drugs in dogs with CSE presenting to seven veterinary neurology centres.

There are several advantages of using dogs as testing models. Firstly, the effects of PHT and benzodiazepines on canines are comparable to those in humans, and secondly, drugs for...
INTELLIGENCE
CANINE STATUS EPILEPTICUS: A TRANSLATIONAL PLATFORM FOR HUMAN THERAPEUTIC TRIALS

OBJECTIVES
To establish a translational platform for human therapeutic trials for the development of effective pharmaceuticals to treat status epilepticus.

KEY COLLABORATORS
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ILO LEPPIK is Professor of Pharmacy and Neurology and Director of Epilepsy Research and Education Program at the University of Minnesota, USA. His current research endeavours are centred on the development of a translational canine status epilepticus platform to develop effective drugs for the treatment of human status epilepticus, a prolonged and life-threatening form of seizure.

CSE treatment do not have to be FDA regulated. Leppik’s group will therefore be able to test treatment alternatives that may never have been available to HSE patients.

FOSPHENYTOIN
One of the preliminary aims of Leppik’s study was to demonstrate that fosphenytoin (FOS), a phenytoin prodrug designed to overcome the toxic effects associated with PHT, would provide a similar response rate in canines as in humans. The researchers conducted phase I trials on dogs with established cases of CSE using FOS doses designed to attain PHT concentrations similar to those observed in humans following 18 mg/kg doses.

In collaboration with James C Cloyd, Pharm D, and Ned Patterson DVM, PhD, the group identified that the most accurate loading dose for canines, to match human blood levels, is 15 mg/kg. This dose was used in double blind, placebo-controlled, randomised CSE trials in four veterinary acute care centres in the US – Minnesota, Chicago, Philadelphia and Washington DC. Their findings showed that the canine response rate was 59 per cent, which is the same as humans; thus preliminarily establishing that canines are valid models on which to base the translation of pharmaceutical-based knowledge for HSE treatment.

THREE NOVEL DRUGS
The researchers have now submitted a grant proposal to the NIH for funding to evaluate three novel drugs – currently unnamed by the researchers – that have proven superior to FOS in models of CSE. In the first stage of this project, Cloyd will determine the loading dose for each of the pharmaceuticals, so that they are comparable with human blood levels and response rates to ensure minimal toxicity. Leppik and colleagues will then use a loading dose representing the maximal tolerated dose in an efficacy trial. The second phase will see all three drugs evaluated at seven veterinary emergency care centres: “We will use an adaptive design to eliminate the need for a placebo, and the outcome measured will need to be superior to FOS,” explains Leppik. “Drugs found to be similar to FOS will not be recommended for human clinical trials.” If any of the pharmaceuticals are found to be superior to FOS, they will be included in the NETT system for use in future HSE trials.

TREATING HSE
Leppik’s study is pioneering, comprising a multidisciplinary team of experts and a translational platform, as he elaborates: “We are the first group to assemble a multidisciplinary group involving physicians treating epilepsy and SE, a pharmacist expert in pharmacokinetics, and a consortium of veterinarians to successfully complete a trial of drug treatment of canine SE”. The expansive scope of this project will substantially decrease the time it takes to evaluate drugs for use in human clinical settings, by providing far more evidence of efficacy and safety as observed in small animal models such as rodents.

Finally, Leppik’s canine-based research will pinpoint drugs that have little to no potential for use in HSE patients as well as those which could revolutionise HSE patient care, streamlining trials and speeding up discovery and the potential for developing fruitful therapeutics. If successful, this project will provide evidence-based knowledge that CSE research is an effective, inexpensive and rapid platform for translating agents for HSE treatment. In addition, as effective treatments for CSE do not currently exist, the new drugs will also benefit both dogs and humans; a true ‘dog helps man, man helps dog’ story.