

Information for parents

Research project: Safety and efficacy of pentoxifylline in the treatment of necrotising enterocolitis in preterm neonates– A randomised, placebo controlled pilot trial

Principle investigators: Dr Sanjay Patole, Professor Karen Simmer

Dear

We sincerely appreciate your efforts during this stressful time in reading the information about our research project. Your baby is eligible for participation in the project because he/she has been diagnosed to have “necrotising enterocolitis” (NEC), a condition where the gut is significantly inflamed.

Is there a specific treatment for NEC?

Currently there is no specific cure for NEC because despite decades of research we still do not know exactly what causes it. Once the condition is diagnosed the management currently is symptomatic in providing support including antibiotics, breathing assistance, transfusion of blood products, and if needed, guidance from the pediatric surgeon. Whether the illness will progress to an advanced stage where the need for surgery and risk of complications is high or whether it will settle down, is mostly out of our control.

What does this research project involve?

Pentoxifylline is an anti-inflammatory drug with additional unique actions (eg. improving the intestinal circulation, reducing toxic oxygen molecules) that may be beneficial in preventing progression of the intestinal inflammation in NEC. Our research is designed to study the safety and potential short-term benefits (eg. preventing progression of the illness to advanced stages, reducing the death rates) of pentoxifylline in NEC. The drug is not officially approved for use in babies. Researchers have used it earlier in critically ill premature babies (similar to the ones who are eligible for participation in our study) with severe infection. The results have been encouraging in that the death rates were reduced significantly and no significant side effects were noted. Our animal experiments, involving premature rat pups with NEC, have shown that pentoxifylline significantly reduced the frequency as well as the severity (by 70%) of the illness. Given these promising results we think that pentoxifylline may be beneficial as a specific treatment for NEC in premature babies.

How would the research study be conducted?

We are conducting a preliminary (pilot) “*randomised, placebo-controlled trial*” in premature babies with NEC to study the potential benefits of pentoxifylline in preventing progression of the illness to advanced stages. The trial has been registered with appropriate national authorities including the Therapeutic Goods Administration (TGA) office in Canberra.

What is randomisation? What is a placebo? What are the chances that our baby gets pentoxifylline and not the placebo?

Randomisation is a process where a computer-generated sequence of random numbers decides whether a baby will receive *either* pentoxifylline *or* a dummy (placebo) solution. For any baby in the trial, the chances of receiving either pentoxifylline or the placebo solution will be equal (50-50). The appearance of the placebo (normal saline) and the pentoxifylline solution is identical. The medical as well as the research team members thus would not be able to identify the actual research treatment (blinding) that the baby is receiving. Randomisation, use of placebo, and blinding helps us to avoid bias and make the trial scientifically sound.

Is our baby eligible for participation in the trial?

Yes, being less than 32 weeks gestation at birth and having diagnosed with NEC, your baby would be eligible for participation once you have given an informed consent after reading, and understanding the information about the trial with help of the research investigator/s.

Are there any benefits of participating in the trial?

Yes, there are potential benefits. The risk of complications such as intestinal perforation, need for surgery, and the risk of death are significantly higher with progression of the intestinal inflammation in NEC. As proposed if the progression is indeed prevented by pentoxifylline, the frequency and severity of such complications *may* decrease in babies who receive the drug but we will not know this until the end of the study. It is important to appreciate that the design of our study, where a baby has an equal chance (50:50) of receiving *either* pentoxifylline *or* placebo and standard care, helps us in determining

both, the potential benefits as well as adverse effects of the drug without any bias using a scientifically sound method.

Are there any adverse effects?

Just as for any other drug there is a possibility of side effects with pentoxifylline. A drop in the blood pressure, a tendency for bleeding, and aggravation of pre-existing bleeding inside the brain or occurrence of a new bleeding inside the brain are the potential adverse effects that may be related to treatment with pentoxifylline. It is important to appreciate that the risk of these complications is high in premature babies with definite NEC. Babies participating in the trial will be monitored carefully for *all* possible side effects of the drug. Members of the specially appointed independent committee will decide whether any significant adverse effect is related to pentoxifylline. The trial will be stopped at any stage in case the frequency and / or severity of any of the significant side effects is noted to be higher in babies receiving pentoxifylline.

We wish to point out that no such adverse effects have been reported in any of the studies of pentoxifylline in critically ill premature babies with severe infection. The babies in these studies are comparable in terms of maturity, and possibly severity of illness to those participating in our trial. Additionally the dose, duration, and route of administration of pentoxifylline in our trial are based on these earlier studies.

Is there any pain, discomfort, and blood collection involved in the trial?

Babies with definite NEC are usually given morphine to ease the pain and discomfort due to the abdominal distension, and inflammation. The administration of pentoxifylline or normal saline (as a placebo) *per se* is not expected to cause any undue pain or discomfort. As part of the study we will be collecting 0.5 mls of blood before, halfway through, and at the end of the study to measure the levels of the chemicals that create and/or aggravate intestinal inflammation. No additional pain and discomfort is expected, as the timing of this collection will be synchronised with the daily routine blood sampling that is an essential part of baby's care. Babies with definite NEC commonly require blood transfusions for significant anemia. The total amount of blood loss (1.5 ml) over the 6-day trial period is thus not a significant concern.

What if we do not wish to have our baby participate in the research trial?

We wish to assure you that the standard of care given to your baby will not be compromised in any way if you do not wish to have your baby participate in the trial. It will also not be compromised if you wish to withdraw your baby from the trial at any stage having given the consent.

Whom shall we talk to if we need more information?

At least one of the research team member, including Dr Patole or Prof. Simmer will always be available (Tel: 9340 2003) to provide you with more information about the study if needed. If you have any concerns or complaints about the conduct of the study please contact the Executive Director Medical Services on 9340 8222.

We hope we have answered most of the questions that may come to your mind at this stage. Please do let us know if you need anymore information about the research trial.

.....
Dr Sanjay Patole, MD, FRACP Professor Karen Simmer, FRACP, PhD.

Department of Neonatal Paediatrics, King Edward Memorial Hospital for Women,
University of Western Australia, Perth
Western Australia 6008
Tel: 08-93401260
Date: 15th March 2005