Lay summary of a report by Professor Ian Bone: Intraventricular Pentosan Polysulphate in Human prion disease - A study of experience in the United Kingdom

Pentosan polysulphate (PPS) as a possible treatment for vCJD and related prion disorders.

Introduction

Currently there is no proven treatment for Creutzfeldt-Jakob disease and other human prion diseases. There are however a number of potential treatments being considered or under assessment. To date, no treatment has been shown conclusively to slow or halt the disease process in humans with any form of CJD. There has been media coverage of some potential treatments, in particular: Quinacrine, Pentosan Polysulphate (PPS) and Flupirtine.

This information leaflet aims to summarise the current state of knowledge on the administration of Pentosan Polysulphate. It is based on observations on a small number of UK sufferers who have taken this treatment.

Background rationale for use of PPS

Pentosan polysulphate (PPS) is a molecule derived from beech wood which has many properties such as blood thinning and suppressing inflammation. Taken by mouth it has been used in clinical practice for some while and is licensed to treat bladder inflammation.

The rationale for using Pentosan Polysulphate in humans with Creutzfeldt-Jakob disease and other human prion disorders rests essentially on experimental laboratory research. However it is often difficult to know whether laboratory findings will translate into real benefits in treating disease.

How is the drug given and what is is a safe dose?

The chemical nature of PPS means that it is unable to enter the brain when administered orally (by mouth, in tablet form) or intravenously (injection into the bloodstream).

A study in animals by Japanese researchers delivered PPS directly into the brain by passing a tube into the cavities (ventricles) deep within the brain. For the treatment to be effective it would need to circulate around the brain and spread deeply into the brain tissues. It is not known whether PPS does actually penetrate or how far it spreads through the brain and this requires further research to determine.

Work by the same Japanese group showed that the drug caused serious complications (bleeding in the brain and “fits”) when given in high doses to some animals. From this work, a safer dose for humans has been estimated.

The drug requires a complex delivery system. A pump is placed under the skin, either in the tummy or under the arm, and a tube from this leads up under the skin to the scalp. A small hole is then made in the skull and the end of this tube placed in the cavity (ventricle)

deep in the brain. This is a recognised method that has been used to deliver other drugs to the brain in other diseases.
This procedure is carried out under anaesthetic by a specialist surgeon (Neurosurgeon) who would outline any risks associated with the procedure beforehand.
The pump is then refilled with Pentosan every 4-8 weeks depending on the size of the pump used.
There is a risk of infection within the system and regular reviews by the specialists involved are necessary.

What is the background to its use in some UK sufferers?

On a number of occasions since 1999, the Department of Health has sought advice from the Committee for Safety of Medicines (CSM) and the CJD Therapy Advisory Group (CJD-TAG) as to the potential use of PPS as a preventative or therapeutic treatment for CJD[1].
However, neither Committee recommended its use because of the limited data available to support its use and concerns about the potential for serious side effects.

A number of persons (or families on their behalf) wishing to be treated with pentosan polysulphate subsequently sought a court order to allow this to happen.
This judgement ruled that individuals concerned should be allowed to receive this experimental treatment on compassionate grounds but included an injunction on passing knowledge relating to their condition and treatment to third parties.

It is thought that 9 patients have now received this treatment in the UK. In late 2004, the Department of Health asked the Medical Research Council (MRC) to take forward clinical monitoring of these patients and gather information that might help inform future treatment decisions.

Following a meeting in March 2005 with patient's families and their legal representatives, the MRC commissioned an independent neurological review led by Professor Ian Bone from the University of Glasgow, to monitor UK patients who had received PPS directly into the brain for their conditions.

Professor Bone's report was considered by the MRC New Therapies Scrutiny Group for Prion Disease in July 2006[2] and the findings are presented below.

[1] http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/CJD/CJDgeneralinformation/DH_4031039

[2] http://www.mrc.ac.uk/PolicyGuidance/PolicyDevelopment/NewTherapiesScrutinyGroupforPrionDisease/index.htm#P97_3578

Intraventricular Pentosan Polysulphate in Human Prion Disease – A study of experience in the United Kingdom.

The study was based on an analysis of seven patients' treatment over a six month period. The report is a summary of the responses that people with prion diseases have shown to PPS and should not be taken as conclusive owing to the small number of patients involved. Patients had different forms of prion disease, which can be very variable in their duration, and were treated in different ways and it was not possible to make like-with-like comparisons with similarly affected persons who have not taken the drug. However the study would have been able to show common severe side-effects or if there was a clear benefit of PPS treatment in halting progression of disease.

The key findings were:

- Pentosan Polysulphate (PPS) does not stop the progression of vCJD and other prion diseases. Loss of brain function continues after treatment has started and, where measured by a series of brain scans, loss of brain tissue also continued.
- The drug itself does not seem to carry a risk of serious side effects from prolonged usage at the modest doses given and provides qualified reassurance on the safety concerns that have been raised previously.
- Surgical complications of intraventricular catheter and pump placement occurred and will need to be discussed in detail with anyone considering this method of treatment.
- There remains uncertainty as to what precise dose should be administered to individuals.
- Some of the patients treated with PPS appear to have survived for long periods. However, it cannot be concluded that the treatment has had a beneficial effect, because it was impossible to make direct comparison with similar but untreated patients. It is also very difficult to determine exactly when the disease starts and this obviously affects the estimation of survival time.

When considering treatment options, patients and families should take into account all available current knowledge. The PPS report provides valuable information from a small group of individuals who, with their families hope that others might learn and be helped through their own experiences.

These "key findings" summarise a detailed report. It is strongly recommended that anyone considering treatment with PPS should review the report in full at http:// www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003453