Pentosan Polysulphate Monitoring Study.

Ian Bone.
Size of treatment trials.

- Blood Pressure/Cholesterol lowering 10-20,000.
- Stroke 5-10,000.
- Cancer < 1,000.
- Multiple Sclerosis 2-400.
- Motor Neurone Disease 1-200.
- TSE / Human Prion Disease 100(+)
- PPS Monitoring 7.

Difficulties with small numbers could be overcome if there was a test - Surrogate marker - that could showed improvement.
Assessing the value of a test

- Establish a “normal” range.
- How sensitive is it?
- How specific is it?
- Is it reproducible?
- Is it person (operator) dependent?
- What proportion of those with an illness are +ve. (Positive predictive value)
- What proportion of those without the illness are –ve (Negative predictive value)

ONCE THESE ARE ANSWERED YOU MAY HAVE A VALUABLE TEST WHICH CAN DIAGNOSE AND PROGRESS.
Intraventricular therapies

1. PAIN (morphine)

2. MENINGEAL MALIGNANCY (methotrexate, cytarabine)

3. INTRAVENTRICULAR HAEMORRHAGE (urokinase, rTPA)

Leukoencephalopathy – methotrexate
Barriers to drug penetration in CNS disease

A) The blood-brain barrier (BBB).

- Endothelial cells (BCEC)
- Tight junctions (TJ)

The brain capillary endothelial cells and pericytes (P) are surrounded by a basement membrane (BM). Astrocyte foot processes (AFP) almost completely surround the brain capillary. CL, Capillary lumen; BECF, brain extracellular fluid.

B) The blood—cerebrospinal fluid (CSF) barrier.

- Choroid plexus endothelial cells (CPEC)
- Fenestrated capillaries
- Basement membrane (BM)

The choroid plexus endothelial cells (CPEC) form fenestrated capillaries. They are surrounded by a basement membrane (BM). The capillaries are covered by a single layer of choroid epithelial cells (CEC). These choroid epithelial cells are sealed together by tight junctions (TJ). One side of the choroid epithelial cell is in contact with the blood filtrate within the extracellular space of the choroid plexus (ECS). The opposite side is in contact with the CSF in the ventricles.

C) The CSF-brain barrier.

- CSF
- Ventricular ependymal cells (VEC)

The CSF is separated from the brain extracellular fluid (BECF) by the loosely linked ventricular ependymal cells (VEC). These cells do not form an anatomic barrier. Diffusion of compounds may occur in both directions. The brain extracellular fluid surrounds the astrocytes (A; with astrocyte foot processes (AFP)) and neurons (N). Neurons have dendrites (D) and an axon (Ax). One capillary is shown surrounded by astrocyte foot processes.
1. Medtronic Programmable Infusion pump

- 10-18 mls capacity
- Epigastric pouch

2. Rickham reservoir

- N-Vision programmer
Structure of pentosan polysulfate (PPS). PPS (MW, 4,000-6,000) is a sulphated semisynthetic polysaccharide consisting of a [beta] chain of D-xylose with an a-lateral fixation of 4-O-methyl-D-glucuronic acids in a ratio of 1 uronic to 9 xylose units. Obtained from beech tree bark.

*From:* Tanhehco: J Cardiovascular Pharmacology, Volume 34(1). July 1999. 153-161

Inhibits smooth muscle proliferation / anti-fibrinolytic / anticoagulant.

# Patient Characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Study number 01</th>
<th>Study number 02</th>
<th>Study number 03</th>
<th>Study number 04</th>
<th>Study Number 05</th>
<th>Study number 06</th>
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<tbody>
<tr>
<td><strong>Date Recruited</strong></td>
<td>Sep 05</td>
<td>Oct 05</td>
<td>Oct 05</td>
<td>Oct 05</td>
<td>Oct 05</td>
<td>Oct 05</td>
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<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Genotype/Mutation</strong></td>
<td>Not documented</td>
<td>129:M/M</td>
<td>P102L mutation</td>
<td>P102L mutation</td>
<td>129:M/M</td>
<td>129: M/M</td>
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<td><strong>Date of Birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Type of disease</strong></td>
<td>Iatrogenic (HGH)</td>
<td>Variant</td>
<td>Inherited</td>
<td>Inherited</td>
<td>Variant</td>
<td>Iatrogenic (HGH)</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
<td>Bed-bound</td>
<td>Chair-bound</td>
<td>Bed-bound</td>
<td>Mobile</td>
<td>Chair-bound</td>
<td>Bed-bound</td>
</tr>
<tr>
<td><strong>Symptom Onset</strong></td>
<td>Dec 03</td>
<td>Jun 03</td>
<td>Jun 01</td>
<td>Feb 01</td>
<td>Nov 02</td>
<td>Apr 03</td>
</tr>
<tr>
<td><strong>PPS Initiation</strong></td>
<td>Jul 04 (7)</td>
<td>Oct 03 (4)</td>
<td>Nov 03 (29)</td>
<td>Sep 04 (43)</td>
<td>Dec 03 (13)</td>
<td>Mar 04 (11)</td>
</tr>
</tbody>
</table>
Milestones

Milestones were developed from the Barthel Activities of Daily Living and the Disability Rating Scales.

(Mahoney & Barthel.1965, Wright 2000).

Stages of function were defined for 11 activities.

- feeding,
- grooming,
- swallow,
- bladder,
- bowel,
- mobility,
- balance ,
- cognition,
- hearing,
- seeing,
- communicating
Milestones

Participant 1

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language (5)</td>
<td></td>
</tr>
<tr>
<td>Seeing (3)</td>
<td></td>
</tr>
<tr>
<td>Hearing (3)</td>
<td></td>
</tr>
<tr>
<td>Cognitive (7)</td>
<td></td>
</tr>
<tr>
<td>Balance (7)</td>
<td></td>
</tr>
<tr>
<td>Mobility (5)</td>
<td></td>
</tr>
<tr>
<td>Bowel (3)</td>
<td></td>
</tr>
<tr>
<td>Bladder (3)</td>
<td></td>
</tr>
<tr>
<td>Grooming (4)</td>
<td></td>
</tr>
<tr>
<td>Swallow (5)</td>
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<tr>
<td>Feeding (3)</td>
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Time from disease onset to end April '06 (months)

Participant 2

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language (5)</td>
<td></td>
</tr>
<tr>
<td>Seeing (3)</td>
<td></td>
</tr>
<tr>
<td>Hearing (3)</td>
<td></td>
</tr>
<tr>
<td>Cognitive (7)</td>
<td></td>
</tr>
<tr>
<td>Balance (7)</td>
<td></td>
</tr>
<tr>
<td>Mobility (5)</td>
<td></td>
</tr>
<tr>
<td>Bowel (3)</td>
<td></td>
</tr>
<tr>
<td>Bladder (3)</td>
<td></td>
</tr>
<tr>
<td>Grooming (4)</td>
<td></td>
</tr>
<tr>
<td>Swallow (5)</td>
<td></td>
</tr>
<tr>
<td>Feeding (3)</td>
<td></td>
</tr>
</tbody>
</table>

Time from disease onset to end April '06 (months)
Milestones

Participant 3

- Language (5)
- Seeing (3)
- Hearing (3)
- Cognitive (7)
- Balance (7)
- Mobility (5)
- Bowel (3)
- Bladder (3)
- Grooming (4)
- Swallow (5)
- Feeding (3)

Time from disease onset to death (months)

PPS initiation
Visit 1

Participant 4

- Language (5)
- Seeing (3)
- Hearing (3)
- Cognitive (7)
- Balance (7)
- Mobility (5)
- Bowel (3)
- Bladder (3)
- Grooming (4)
- Swallow (5)
- Feeding (3)

Time from disease onset to end April '06 (months)

PPS initiation
Visit 1
Milestones

Participant 5

Time from disease onset to end April '06 (months)

Participant 6

Time from disease onset to death (months)
Post-operative imaging.

Bi-ventricular placement 25/10/03
Post-operative imaging.

Uni-ventricular (right) catheter placement without radiological complications
Symptomatic capsular infarction

Post-operative imaging.

Sub cortical infarction with haemorrhagic transformation 11/10/03.

Follow up Scan 12/12/03 (post PPS initiation).
<table>
<thead>
<tr>
<th>(01)</th>
<th>Maintenance Dose</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>110mg/kg/day = 6.5 mg</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>(02)</td>
<td>11mg/kg/day = 0.55mg</td>
<td>none</td>
</tr>
<tr>
<td>(03)</td>
<td>11mg/kg/day = 0.55mg</td>
<td>none</td>
</tr>
<tr>
<td>(04)</td>
<td>11mg/kg/day = 0.55mg</td>
<td>none</td>
</tr>
<tr>
<td>(05)</td>
<td>32mg/kg/day = 1.8mg</td>
<td>none</td>
</tr>
<tr>
<td>(06)</td>
<td>110mg/kg/day = 5mg</td>
<td>none</td>
</tr>
<tr>
<td>(07)</td>
<td>110mg/kg/day = 7.5 mg</td>
<td>? – tonic clonic seizure*</td>
</tr>
</tbody>
</table>

*Evidence of associated sepsis

- Note daily dose range 7.5 – 0.55 mg / day
<table>
<thead>
<tr>
<th>Surgery</th>
<th>Early complications</th>
<th>Delayed complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>(01) (R) ventricle epigastric</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>(02) S. (R) &amp; (L) vents epigastic</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>(03) (R) ventricle subcostal</td>
<td>Catheter placement (3) Inter-operative stroke</td>
<td>Pump alarm (1)</td>
</tr>
<tr>
<td>(04) (R) ventricle subcostal</td>
<td>none</td>
<td>Catheter disconnection</td>
</tr>
<tr>
<td>(05) S (R) ventricle epigastric</td>
<td>Catheter placement (2) Post op pyrexia</td>
<td>Pump pouch re-fashioning</td>
</tr>
<tr>
<td>(06) (R) &amp; (L) vents attempted Subclavicular</td>
<td>(R) Catheter unsuccessful. Post op pyrexia</td>
<td>none</td>
</tr>
<tr>
<td>(07) (R) &amp; (L) vents epigastric</td>
<td>Catheter placement (R) 2</td>
<td>none</td>
</tr>
</tbody>
</table>
Follow up imaging

1/11/03, 19/04/04, 6/01/05, 9/5/05
## Human Prion Disease: Natural history.

<table>
<thead>
<tr>
<th>Type</th>
<th>Median Age of onset</th>
<th>range</th>
<th>N</th>
<th>studies</th>
<th>Median Duration of illness</th>
<th>range</th>
<th>N</th>
<th>studies</th>
<th>PPS Patients. Duration of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSS P102L</td>
<td>44yrs</td>
<td>22-71yrs</td>
<td>38</td>
<td>7</td>
<td>48m</td>
<td>2-84m</td>
<td>21</td>
<td>6</td>
<td>52m(d) 60m(a)</td>
</tr>
<tr>
<td>iCJD (HGH)</td>
<td>26yrs</td>
<td>10-37yrs</td>
<td>121</td>
<td>3</td>
<td>16m</td>
<td>3-30m</td>
<td>111</td>
<td>3</td>
<td>30m(a) 29m(d)</td>
</tr>
<tr>
<td>vCJD</td>
<td>28yrs</td>
<td>12-74yrs</td>
<td>145</td>
<td>2</td>
<td>14m</td>
<td>6-40m</td>
<td>145</td>
<td>2</td>
<td>36m(a) 42m(a) 61m(a) 16m(d)</td>
</tr>
</tbody>
</table>

From Lesley Stewart et al. 2006.
PPS Survival.

- Chance?

- Date of diagnosis Vs Date of onset?

- Self selection?

- Interventions and Quality of care?

- PPS treatment effective?
Conclusions.1

- The Judgement of the High Court of Justice (Family Division) November 2002 was made in the absence of any studies evaluating the short and long term safety, dosage, tolerability and efficacy of continuous intraventricular infusion of PPS in human prion disease.

- There are currently no such prospective open dose-finding and efficacy (phase I/II) follow-up studies planned.

- Basic scientific data on intraventricular PPS pharmokinetics and parenchymal brain penetration is lacking.
The size and differing disorders within the group have dictated an observational rather than statistically based approach to PPS evaluation.

A case control approach to evaluation has proved problematic with respect to numbers, comparability, consent/assent and retrieval of records.

The clinical assessment scales for prospectively evaluating the patient group were imprecise at the level of disability being assessed. However in four participants visited on three separate occasions over the six month period, one remained stable, two showed minimal worsening and one progressed significantly.

Both early and recent scientific data makes PPS a promising potential therapy for human prion disease.
Conclusions.3

- The study group is small and comprises specific human prion disorders with differing presentations and natural histories.

- There is the suggestion of increased procedural risk associated with ventricular catheterisation. This observation supports other published observational reports. However, numbers are too small to assume significance.

- PPS infusion is well tolerated at all doses with only one possible serious adverse reaction at 110 micrograms/kg/day within the study group.

- Long term tolerability has been demonstrated to 32 months (10 micrograms/kg/day) and 23 months (110 micrograms/kg/day) within and to 41 months (11 micrograms/kg/day) out with the study.
PPS recipients have survived longer than the reported mean survival time for their specific condition but not out with the reported range. A further recipient (not participating in this monitoring programme) has survived 61 months (out with the reported range for his particular prion disorder).

Duration of survival within the group and including the non participating recipient of PPS suggests the possibility of potential efficacy whilst demonstrating no harm.

Interrogation of case records showed no alternative explanation for observed duration of survival (such as aggressive and early management of infection).
A range of surgical approaches were used (stereotactic uni-ventricular or bi-ventricular cannulation).

There was variability in PPS dosage (10, 32 and 110 micrograms/kg/day), timing of initiation after surgery and rate of dose escalation thereafter. Actual daily dose range was 7.5 – 0.55 mg/day.

Pump management was carried out by a range of medical specialties (Anaesthesics/Neurology/Neurosurgery).

Frequency and nature of clinical follow up varied in each centre.

There was no single approach to the conduct or timing of follow up investigations (imaging, neuropsychology or neurophysiology).
Conclusions.6

- Serial cranial CT scans, available in three participants, showed progressing brain atrophy over the period of PPS therapy.

- Whilst co-operation was obtained from all participating centres retrieval of Hospital records and scan was often a protracted process and some data still outstanding.

- The identification of controls was difficult given the nature of illness and the complexity in gaining assent and locating records in relation to deceased persons.

- A case controlled component to the assessment seems, both logistically and statistically, unfeasible but sampling further control data (with respect to vCJD and Genetic CJD) necessary before any final discussion reached.
Recommendations.1

1. Should a similar circumstance arise in the future, early instigation of a structured follow up is essential and should be a requirement of the Judicial Ruling.

2. Further experimental work to confirm and elaborate upon the findings of Doh-ura et al. This should include studies of PPS distribution and binding following intraventricular administration.

3. If the results of this experimental work are encouraging it should lead to a prospective, longitudinal standardised follow-up study.
4. Future newly diagnosed patients are informed, verbally and in writing, about PPS when all treatment options are discussed.

5. Informed persons opting for intraventricular PPS should undergo catheter and pump placement in single centre neurosurgical centre following an approved protocol of surgical procedure, dose and dose escalation.

6. Future PPS treated persons are follow up through an approved protocol including clinical assessment, imaging (MR), neurophysiology.
7. The complexity in establishing and evaluating RCTs, rarity of human prion disease and variables possibly influencing survival emphases the pressing need to establish a surrogate marker of disease progression. This should be an urgent priority. Such a protocol should consider including exploratory investigations such as HRV / PET etc.

8. New therapies that extend survival require assessment measures that capture progress in those with advanced disability. The lessons learnt from this current evaluation should inform the Clinical Outcomes Group.

Acknowledgements

The Persons and Families suffering human prion disease who allowed me into their homes to carry out this study.

The Families of Control Cases for access to records and those who did not participate in the prospective study but agreed to data being used.

Dr Sarah Walker and Laura Belton MRC Clinic Trials Unit for statistical advice and data handling.

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