POTENTIAL TREATMENTS FOR CREUTZFELDT-JAKOB DISEASE

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Creutzfeldt-Jakob disease and other human prion diseases are invariably fatal and there is currently no proven treatment for the underlying process. There are however a number of potential treatments in development or under consideration. It must be stressed that, 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 and Flupirtine. There is an MRC-funded trial (PRION-1) that is currently studying the possible effects of Quinacrine.

An MRC-funded trial (PRION-1) studying the possible effects of Quinacrine stopped recruiting patients at the end of June 2006. The MRC funded an independent review of UK individuals who were treated with Pentosan Polysulphate (via the intracerebroventricular route) and the final report of this review is pending publication. A German study of Flupirtine was published in a scientific journal in 2004.

Further details are given in the specific sections.

The MRC set up the New Therapies Scrutiny Group for Prion Disease in April 2005 to provide an independent source of advice on research into treatment of prion diseases.
QUINACRINE

Dr Prusiner's group from San Francisco published an article in Proceedings of the National Academy of Sciences on 14/08/01 entitled 'Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease' (Korth et al.). This article provided evidence of inhibition of the formation of the disease associated form of prion protein in scrapie infected neuroblastoma cells by a number of compounds, with quinacrine and chlorpromazine exhibiting the greatest potency. The first paragraph of the article concludes "Because quinacrine and chlorpromazine have been used in humans for many years as anti-malarial and anti-psychotic drugs respectively, and are known to pass the blood brain barrier, we suggest that they are immediate candidates for the treatment of Creutzfeldt-Jakob disease and other prion diseases".

There was a report in The Mail on Sunday, on Sunday 12 August 2001, entitled "Briton 'cured' in CJD drug trial". The article described a 20-year-old female with variant CJD who was treated in a pioneer drug trial including Quinacrine in San Francisco and in whom the family reported neurological improvement. A subsequent study on experimental animals showed no benefit from Quinacrine (Collins et al.). Further laboratory work by another scientific group (published in 2003, Barret et al.) only partly confirmed the Prusiner results and failed to show any benefit in experimental animals.

Any finding that might lead to an effective treatment of CJD is to be welcomed. However, laboratory findings are simply indications of possible therapeutic value and the real test is whether a compound is actually effective (and safe) in human beings with disease. Further work is essential in order to establish whether these drugs can provide an effective treatment and proper assessment needs to be carried out in the context of a well designed clinical trial. A preliminary trial was undertaken by the National Prion Clinic/MRC in London and a more extensive MRC trial (PRION-1) started in 2004. New patient recruitment into the PRION-1 trial ceased at the end of June 2006; further information on the trial can be obtained from the National Prion Clinic and the MRC website.

Source: www.cjd.ed.ac.uk – last updated July 2006
A trial of quinacrine in CJD in the USA began recruitment of patients in April 2005. It is funded by the NIA (National Institute on Aging) and run by the UCSF (University of California, San Francisco) Memory and Aging Centre. Further details may be found here.

Quinacrine and chlorpromazine are available in the UK, but neither are licensed for use in the treatment of human prion diseases and would need to be prescribed in the context of a trial, or on a named patient basis.

A suggested treatment regimen for Quinacrine is 200mg 6 hourly for 5 doses followed by 100mg tds. The role and dosage regimen of chlorpromazine is uncertain and patients who have been treated to date have often received quinacrine alone.

References


PENTOSAN POLYSULPHATE

The present background rationale for treatment with PPS

Pentosan polysulphate (PPS) is derived from beechwood and has anti-thrombotic and anti-inflammatory properties. It has been used in routine clinical practice for some time in the treatment of thrombotic disorders and interstitial cystitis.

The present background rationale for any treatment with PPS rests essentially on experimental laboratory work: in vitro (laboratory work with chemicals or cells) and in vivo (animal) work.

Source: www.cjd.ed.ac.uk – last updated July 2006
The in vitro experimental results can be summarised as indicating that PPS has effects on prion protein production, replication and associated cell toxicity. However, there are certainly other chemical compounds which have shown in vitro promise that have then failed to show any clear cut clinical effect when used in the treatment of human disease. In addition, while the prion protein is central to diseases like CJD, the precise mechanism by which neurones become damaged and die is uncertain in prion diseases. Also, currently, there is no scientific rationale to suggest that drugs like PPS will cause or aid any recovery to previously damaged neurones.

The in vivo experimental results can be summarised as showing that PPS has a prophylactic effect in various animal models. In other words, if PPS is given to experimental animals at a time relatively close to the point of experimental infection, then there may be an increase in the incubation period of disease (i.e. a prolongation of the time between inoculation of infectivity and the appearance of clinical disease). In some instances, animals appear to be completely protected from the development of disease.

The clinical relevance of these findings is, of course, uncertain. Firstly, it is difficult to know how to extrapolate from laboratory animals (typically mice or hamsters) to humans, especially as there are no data concerning the experimental treatment of potentially more related animals, such as non-human primates. Certainly, the reported in vivo experimental effects of PPS, as with most drugs, are highly dependent on the dose and route of administration. Secondly, these experiments usually involve species adapted strains of prion disease (often rodent-adapted scrapie) and it is uncertain whether these results can be extrapolated to all prion strains in naturally occurring situations. Thirdly, the demonstration of a prophylactic value may not immediately relate to the usual human situation where patients present with established disease. While some have suggested that PPS has benefits in established disease, there is no specific experimental evidence of this. In the case of humans with variant CJD (and other forms of acquired CJD), by the time they become clinically ill, they have already gone through the incubation period. In sporadic CJD, the concept of ‘incubation
period’ does not simply apply, but there is likely to be some period of clinically silent disease development before the onset of actual symptoms. The duration of this incubation period for variant CJD is uncertain but the minimum incubation period may be 5 years and it would not be surprising if the average incubation period were around 10 years. It is important to realise that the current treatment of humans with CJD is a treatment being given after the actual onset of clinical disease. If a treatment is efficacious in progressive neurological disease, then it is very reasonable to believe that the sooner it is given, the better the positive results. Therefore, it is important that patients seeking treatment with PPS be given it as early as possible. However, the diagnosis must be as certain as possible when considering a treatment like intraventricular PPS administration and this may take a while, especially as current diagnosis necessarily involves observing the clinical progress over a period of time. Clinicians do see individuals who present in a manner similar to that of CJD and yet turn out to have other illnesses (sometimes with specific treatments of their own). The development of better, earlier diagnostic tests would be helpful in this respect, but, at present, clinicians must work with the available methods of diagnosis. The use of treatments like PPS in the incubation period of human CJD (prior to any symptoms) is not presently feasible; such an approach would require definitive demonstration of safety and efficacy in humans and a validated pre-symptomatic test (that does not, currently, exist).

Whatever evidence is available suggests that PPS may have some effects on the disease mechanisms of CJD, but there is no positive evidence that it reverses (or even halts) neuronal death and the associated neurological dysfunction.

A report from Doh-ura and colleagues from Japan concerns the intraventricular administration of PPS. PPS does not cross the blood brain barrier. Their preliminary results (in animal experiments) suggest that this is a possible means of delivering PPS to the central nervous system using standard neurosurgical techniques. This is a preliminary report, relating to experimental animal work, involving a hamster-adapted scrapie strain in experimental mice expressing hamster PrP and again essentially
studying incubation period. Therefore, although this work represents something new (in relation to mode of administration), it does not provide a firm scientific rationale for the routine clinical treatment of humans with established disease. Doh-ura’s work was published in the Journal of Virology 2004.

There is a UK DH-funded research being undertaken by Farquhar et al. into PPS in animal prion models. This includes studying BSE (301V) in mice, as well as mice and hamster scrapie models. However, there are only very limited data published at this point.

It is important to understand that the precise pathogenesis of prion diseases (including variant CJD) is not completely understood. It is not necessarily the case that actions directly involving the prion protein are the specific or only reason for efficacy of drugs like PPS and other modes of drug action might be clinically useful. From a strictly clinical point of view, the mechanism of action of drugs is a rather secondary theoretical matter in relation to the important practical one of whether these drugs actually work. As indicated above, PPS does indeed have some kind of efficacy in experimental animal model settings. On present understanding, any process that slows or even halts the progress of CJD is extremely unlikely to lead to any recovery of previously injured or dead neurones. There is, therefore, limited scientific rationale for the use of PPS in prion diseases but no good scientific rationale for its being employed as a routine treatment in clinically established human prion disease. Of course, the absence of evidence is not the same as the evidence of absence. However, there have been specific individual circumstances in which clinicians, affected individuals and their families have wished to consider the treatment, particularly given the inevitable progression and fatal outcome of prion illnesses. Indeed, there are several UK individuals who have received the treatment via the intracerebroventricular route in these circumstances with published papers describing two such treated individuals, both diagnosed with variant CJD. The first publication describes the first individual to be treated in this manner, with suggestions of some associated improvement in his neurological condition (Todd et al, Journal of
Infection, 2005). However, the authors note the difficulties in judging the results in one individual and also report progressive cerebral atrophy on brain scans. The second publication describes treatment of another individual without any evidence of successful response (Whittle et al, Acta Neurochir, 2006).

A further publication described the background to cerebroventricular PPS treatment in prion disease and reported that a number of other individuals (including people with sporadic, variant or iatrogenic CJD and genetic prion disease) had received such treatment (Rainov et al).

The MRC commissioned an independent neurological review (by Professor Ian Bone) of the UK patients who had received intracerebroventricular PPS for prion diseases. Professor Bone's report was considered by the MRC New Therapies Scrutiny Group for Prion Disease in July 2006. The final report can be found here. Further research into PPS treatment is being considered.

Professor Bone is quoted as saying: "Pentosan Polysulphate itself does not seem to carry a high probability of side effects from prolonged usage. However, the surgical complications of intraventricular catheter and pump placement were significant. The drug does not appear to halt the progression of the disease. Loss of brain function continues after treatment has started and, where measured by imaging, loss of brain tissue also continued".

Additionally: "The patients treated with PPS appear to have survived for unusually long periods. However, we cannot conclude with certainty that the treatment has a beneficial effect, because it was impossible to make direct comparison with similar but untreated patients. Moreover, with such small numbers the results might be a matter of chance. The report recommends specific laboratory experiments to address the uncertainties."
References


Is there any other presently available treatment with proven therapeutic benefit?

There have been other compounds of recent interest eg Quinacrine (see above), Flupirtine (see below). Quinacrine is being assessed in the PRION-1 Trial at the National Prion Clinic in London and in a trial in the USA (details elsewhere in this section). Currently there is no proven therapy for CJD in clinically ill humans.

The blood brain barrier problem

Essentially, if one is to treat established clinical disease, the central nervous system, ie the brain, will be involved. Therefore, it is logical that any treatment that is to be effective must reach the brain. PPS does not readily cross the blood brain barrier.
Therefore, intraventricular administration has been proposed and, in fact, used in order to deliver the drug directly to the central nervous system, avoiding the blood brain barrier. This sort of approach has been taken in other clinical situations, with other drugs, in different diseases. PPS unfortunately does not cross the blood-brain barrier after oral administration and intraventricular administration delivers PPS to the brain. Spinal intrathecal administration has been considered (but it has not been tried, as far as is known).

The Possible Risks and Benefits of Intraventricular PPS

Risks

Risk of Neurosurgery

There are clearly risks involved in any neurosurgical operation and any anaesthesia. The surgery involves opening the skull by means of drilling a small hole and inserting an appropriate thin tube device into the ventricles of the brain. This must be associated with risk including cerebrovascular trauma and potential risks of infection. However, this kind of neurosurgical procedure is used (for a variety of reasons) on a regular and routine basis in all neurosurgical units. The risks are small and can be discussed with the appropriate neurosurgeon if such treatment is being considered. Long-term intraventricular access (as is required in this context) may be associated with some problems that again can be discussed with an experienced neurosurgeon prior to treatment.

Professor Bone's review is likely to provide the best current data. His initial statement was: "Pentosan Polysulphate itself does not seem to carry a high probability of side effects from prolonged usage. However, the surgical complications of intraventricular catheter and pump placement were significant." Details will become available when his final report is published.
**Risks of PPS**

PPS does have anticoagulant properties and there is therefore some potential for haemorrhage in the brain either related to the drug administration itself or to the drug administration associated with the surgical trauma. There is also experimental evidence to suggest other toxicity. Any side effects of PPS (perhaps particularly any associated haemorrhage) will be partly dependent on the dose administered and on the route of administration. The relevant route for consideration here is the intraventricular one.

In Doh-ura's experimental work with intraventricular PPS, there were significant side effects. However, these were dose and species dependent. With lower doses of PPS (110-230 µg/kg/day), there were no adverse effects. With higher doses (eg 345 and 460 µg/kg/day), there were adverse effects in dogs but not in mice. In some dogs, at these higher doses, there were seizures and some of the affected dogs died. Some deaths were associated with intracerebral haematoma, but not all. Again, it is important to note that this work is not yet published and so detailed data are not available. However, the three basic facts are:

1. Adverse effects are dose-dependent.
2. Adverse effects appear to be species-dependent.
3. Fatality is not always related to haemorrhage.

In the DH-funded work of Farquhar and colleagues, there are preliminary data concerning toxicity. In some mice scrapie experiments, deaths resulted from intraperitoneal and intravenous PPS administration, some related to haemorrhage but others apparently not. Simultaneous intra-cerebral (not intraventricular) inoculation of scrapie and PPS resulted in fits and death, by unspecified mechanism. The PPS dosages used were reportedly much higher than those used in the Doh-ura rodent experiments and there has been no experimentation using the intraventricular route. There are relatively few data in the public domain from this group at present.
It is reasonable to postulate that these toxic effects relate to high doses of PPS being administered either directly to the central nervous system or gaining access to the central nervous system because of a breached blood brain barrier at the time of intracerebral inoculation of scrapie.

It is difficult to provide a definitive assessment of these results. However, the simplest interpretation is that there is dose-related toxicity in relation to PPS and the central nervous system. In the relatively lower doses used by Doh-ura and colleagues, there was no evidence of such toxicity.

It is difficult to know whether such toxicity is species specific in any way. However, the adverse effects associated with higher dosages in Doh-ura's work were observed only in dogs and not in mice and rats. This certainly could argue for species variability and therefore one would have to have additional caution in extrapolating any indications of safe and toxic doses to human beings.

Intraventricular PPS treatment has been undertaken in several individuals with prion illnesses (it is not possible to state the number treated with certainty). There are 3 publications reporting treatment (details given elsewhere in this section) and the best current data are likely to come from the MRC-commissioned review undertaken by Professor Ian Bone. In an initial statement, Professor Bone said: "Pentosan Polysulphate itself does not seem to carry a high probability of side effects from prolonged usage. In at least some cases, the dosage used has corresponded to the lowest dose used in the Doh-ura studies (with suitable corrections from animal to man), and, in others, higher doses are reported to have been used. The dosage range as reported in the publications to date has been 11-110 µg/kg/day.

**Benefits**

1. It is possible that this treatment will slow (or even halt) progression of disease but there is no guarantee and no present means of objectively quantifying the degree of possibility. Any such effect, IF it were to occur would probably be temporary. It is not possible to give any indication of any time limit on such
an effect. The possibility that any such effect could continue throughout the duration of treatment cannot be absolutely excluded but it seems unlikely. Clearly, the later in the disease process that such a treatment were to be undertaken, the less likely any benefit would be seen. Also, in late stages of disease, slowing of progression might be difficult to objectively assess. There are, currently, no validated laboratory or imaging assessments that could be used to give unequivocal evidence of efficacy; one would have to rely on more subjective assessments including everyday functional ability and serial neurological impairment examinations, perhaps with the adjunct of neuropsychological assessments. However, research is being undertaken to see if certain tests could be useful in monitoring disease progression.

2. On the basis of current understanding, there is no realistic possibility of actual improvement in the sense of reversal of previously established neurological deficit. Again, this cannot be absolutely excluded but it seems highly improbable, especially in relatively late stages of disease.

To date, at least several human individuals with prion disease have been treated with intraventricular PPS. There are also families who have considered the treatment and decided that they do not wish for it. There are no hard data currently in the public domain. However, one individual (with vCJD) has apparently not undergone any significant clinical deterioration and furthermore is reported to have shown some possible minor improvement in their neurological status (Todd et al, 2005, as detailed elsewhere in this section). This person was at a late stage of illness at the time of treatment, with very significant neurological impairment and it could be difficult to evaluate any signs of deterioration or minor improvement in this sort of situation. This period of apparent clinical stability could be taken as evidence that this treatment has indeed had a beneficial effect in this one individual. However, some individuals with prion diseases go through 'plateau' periods and, to some extent, survival in the later stages of illness depends on the level and quality of general nursing care provided.
The present duration of apparent clinical stability, with suggestions of minor clinical improvement, must at least suggest the possibility of some treatment efficacy. However, at present, it cannot be stated that this one treated individual provides definite evidence of efficacy of intraventricular PPS. Another treated individual appeared to show no response (Whittle et al 2006, as detailed elsewhere in this section). No detailed information is currently available on the other treated individuals, but Professor Bone's report should provide further information. At present, his summary is that:

"The drug does not appear to halt the progression of the disease. Loss of brain function continues after treatment has started and, where measured by imaging, loss of brain tissue also continued. The patients treated with PPS appear to have survived for unusually long periods. However, we cannot conclude with certainty that the treatment has a beneficial effect, because it was impossible to make direct comparison with similar but untreated patients. Moreover, with such small numbers the results might be a matter of chance. The report recommends specific laboratory experiments to address the uncertainties."

**The best possible outcome from intraventricular PPS**

On the basis of the available evidence, the best possible outcome that could be expected after treatment with intraventricular PPS is that there may be some temporary slowing of the disease progression. However, there is little likelihood of significant clinical improvement. Nor is there a likelihood of permanent halting of disease progression. Of course, to some extent, this might depend on the duration of intraventricular PPS administration. It is not clear on what basis one would decide on the duration of treatment.

Naturally, a treatment which stabilises an individual's condition could conceivably lead to an individual being in a state of potential suffering for a longer period of time. It might be proposed that any slowing of progression or halting of progression might
allow an individual to survive longer and therefore receive future more beneficial
treatment if it were to become available. However, this would be a speculative view
and, while treatments for CJD are being researched, there is no realistic expectation of
a complete cure in the immediate future.

Additional Comments

Any conclusion concerning these above considerations, in the context of an
individual person, would necessarily involve a number of very difficult or personal
judgements about quality of life and the degree of suffering experienced by an
individual in a disease like CJD. Any such judgements are bound to be subjective and
reflect both general belief systems and personal evaluations of the individual patient.
There are clearly important issues of consent and also issues as to the full
understanding of those involved as to the potential benefits and risks. Clearly, there
are few hard data on which to make clear decisions. At this point, the human
treatment data do not allow for any specific comments which can be made concerning
problems or benefits, aside from the facts that there are no reported major serious
complications and that there has been no obvious clinical deterioration over some
months of treatment in at least one case.

Any decision about a given patient would have to be taken in an entirely individual
way, based on a detailed assessment of both the patient and the concerned relatives.
The overriding principle should be: What is in the best interests of the individual
patient? bearing in mind that CJD is inevitably and invariably a progressive and fatal
disease.

There is, of course, an argument that such treatment should be evaluated in the
context of a properly organised clinical trial. There are no current plans to set up such
a trial and, in relation to this specific issue, the comments of two relevant professional
bodies (given in the section below) should be noted.
Advice from relevant professional bodies

The Department of Health have statements on intraventricular PPS on their website: www.doh.gov.uk/cjd/pentosan_revised.htm

This includes the 2003 statements of advice from the CJD Therapy Advisory Group and the CSM.

The advice from the CJD Therapy Advisory Group (2003) can be summarised as follows:

- There are insufficient clinical data to support the claim that PPS is effective during clinical disease.
- There are insufficient safety data on which to base a rational treatment regimen in humans.
- Further animal model experimental work is warranted.
- Nevertheless, at the dosage used in at least one individual, there have been no definite harmful effects attributable to the drug.
- All patients with prion disease should undergo appropriate monitoring during disease progression, in a way that allows collection of data on the natural history of disease and on any treatments that might be given.

The advice from the CSM is similar and states further that:

- "there is no evidence in support of its use as a treatment in late stage disease".
- "In the light of the limited information on PPS treatment of clinically established vCJD it is impossible to assess the risk/benefit relationship of PPS in these indications".
- There was insufficient information to reach any conclusions about the efficacy of treatment in [the single case known about at the time of the statement].
- They also recommended that further study of PPS should be undertaken in a clinical trial setting.
Following the presentation of the report of Professor Ian Bone's study to the MRC New Therapies Scrutiny Group for Prion Disease, in July 2006, the following statement was made:

- Further experimental work in animals will provide the most immediate source of evidence of whether or not PPS is likely to extend survival. We need better information on the extent to which PPS penetrates and spreads through the infected brain. The Medical Research Council will take this forward.

- Further clinical research could be undertaken. Ideally, a formal prospective longitudinal standardised follow-up study would be required but this must be dependent on the results of the experimental animal work being encouraging. In the meantime, newly diagnosed patients should be informed verbally and in writing about current knowledge of PPS, including the risks associated with intraventricular catheterisation, when treatment options are discussed. The Medical Research Council will take forward this recommendation with the Department of Health.

- Informed people opting for intraventricular PPS should undergo the procedure to fit the catheter and pump at a neurosurgical centre with appropriate experience of such surgery. However, dose initiation and escalation could be managed locally. People treated in this manner should be followed up through an approved protocol of clinical assessments and investigations.

- Current patients on PPS should continue to be monitored as part of a supportive, structured review, and should be given up to date information and advice.

Individual clinicians may decide to treat an individual patient; such decisions remain absolutely individual ones. However, clinicians would wish to consider any such decisions in the light of all the available information and advice and to note the above comments of the New Therapies Scrutiny Group.

The case of the first individual who received this treatment was referred to the High Court and there was a ruling in favour of this particular individual being allowed to
receive such treatment, as being in that individual's overall best interests. However, this was an individual ruling relating to a particular individual. It is understood that other cases have been referred to court, but again on an individual basis. There are important issues of consent regarding such 'experimental' treatment, both with regard to the age of some affected individuals and also with regard to competence (where disease affects the brain). The legal issues surrounding treatments in these circumstances are not the same in all parts of the UK.

The Department of Health sought to identify certain selected hospitals where IVPPS treatment might be instituted, if there was a strong desire for it by a family and agreement by their relevant clinician, so as to centralise any experience with this treatment. Such centres will develop protocols for the referral of patients and the process of arranging such treatment (including the various potential legal issues, such as consent) should thereby become simpler. However, there is no current formal scientific trial of intraventricular PPS in humans and the treatment is one that has been given essentially on a speculative basis. The present provision of IVPPS remains an individual decision between patient, family and their immediately responsible clinician, after full understanding and discussion of the facts as detailed above.

**FLUPIRTINE**

A study published in 2004 (Otto et al.) reported some beneficial effects on cognitive function in patients with CJD but there is no evidence for increased survival with the treatment.

**Reference**


Source: www.cjd.ed.ac.uk – last updated July 2006
**MRC PRION1**

As indicated above, the MRC has funded a formal [treatment trial of CJD](#). The trial commenced in 2004, initially aiming to study Quinacrine. Recruitment to this trial ceased in June 2006. Further details are available from the websites given elsewhere in this section.

Source: [www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk) – last updated July 2006