

EXTENDED REPORT

Minimising the risk of prion transmission by contact tonometry

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Aims: The unknown prevalence of variant Creutzfeldt-Jakob disease (vCJD) in the UK population has led to fears of horizontal transmission through routine medical procedures. The potential risk of transmission via contact tonometry was examined.

Methods: The total amount of protein carried over by tonometer tips after appplanation of patients was assessed.

Results: Tonometer tips had an inherent ability to carry proteinaceous material. There was a large variability in the load carried over between individual patients. Rinsing tonometer tips in water reduced protein carryover. Wiping the tonometer tips also reduced carriage, though less dramatically.

Conclusion: There is a small theoretical risk of transmission of vCJD by contact tonometry through reuse, but this should be reduced if the prisms are washed and wiped. In the light of these findings a protocol for the management of reusable tonometer prisms is recommended.

The transmissible spongiform encephalopathies are a group of neurodegenerative disorders, which include bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans. These diseases are associated with abnormal conformers of a normal glycoprotein, PrP. These abnormal conformations of PrP, known as prions, possess enhanced resistance to proteases and are termed PrP^{Sc} or PrP^{Res}.¹

Since 1985, the UK population has been at risk of exposure to the transmissible agent responsible for BSE in cattle following its entry into the human food chain. In humans, disease thought to arise from this route of transmission has been termed "variant CJD" (vCJD),² to distinguish it from classic CJD.³

It is conceivable that substantial numbers of the population may be incubating vCJD³ and the possibility of iatrogenic transmission via contaminated surgical or other invasive instruments remains a major concern, as prions resist normal cleaning and sterilisation procedures.⁴ This has been shown in CJD^{5–7} where neurosurgical techniques using contaminated instruments and materials have resulted in transmission of the disease.

In ophthalmology, the gold standard for intraocular pressure measurement remains the Goldmann tonometer. The routine examination of most patients, at most institutions including Moorfields Eye Hospital (MEH), involves assessment of intraocular pressure by contact tonometry, unless there is a contraindication. It is well known that some diseases—for example, adenovirus keratoconjunctivitis, can be unintentionally transmitted during this investigation. The possible risk of horizontal transmission of vCJD via contact tonometry has therefore given cause for concern.⁸ To partially address these concerns, the Spongiform Encephalopathy Advisory Committee (SEAC) issued a press release on 26 July 2001 declaring the importance of applying best decontamination procedures to the re-use of rigid trial set contact lenses and ophthalmic devices.⁹ These include the use of a solution of sodium hypochlorite containing 20 000 ppm of available chlorine. Ophthalmic devices include tonometer prisms, diagnostic contact lenses such as gonioscopes, and biometry probes. Most of these have not been shown to be capable of withstanding such treatment. Currently at MEH,

tonometer prisms are disinfected in 1000 ppm sodium hypochlorite for 5 minutes, a concentration and time that have not been shown to remove prion infectivity. Higher concentrations of sodium hypochlorite used for 1 hour¹⁰ may, however, cause cumulative corrosion of the prisms,¹¹ though the manufacturer Haag-Streit permits the use of such solutions on its Goldmann prisms for up to 100 times.¹² An alternative is the use of disposable tonometer tips, which may have significant cost implications in a busy clinical setting.

We set out to assess the potential risk for horizontal transmission by contact tonometry^{13–17} using reusable tonometer prisms, by measuring the amount of proteinaceous material accumulating on the contact surfaces of disposable tonometer tips. Our study aims to address the question as to whether stringent decontamination of re-usable prisms or the use of disposable tips or shields is preferable.

MATERIALS AND METHODS

We used disposable tonometer tips (Tonosafe, Clement Clarke International) made from clear acrylic plastic, using the same material and tip diameter as the standard Goldmann tonometer prism.¹⁸ Patients were enrolled in the study (Moorfields Eye Hospital institutional research and ethics approval, Project 655). Patients were routinely applanated, where appropriate, in the outpatient clinic. Either one or both eyes were applanated after instillation of a drop of 0.3%/0.125% benoxinate + fluorescein mixture, using the same disposable tonometer tip. If both eyes were applanated, no decontamination procedure was carried out between eyes.

The method of decontaminating the disposable tonometer tips after appplanation was varied. We used either no rinse, or soaked the tips in 1 ml of MilliQ ultra high purity water (uHPH₂O) for 5 minutes, or washed them in 50 ml of uHPH₂O for 5 minutes. Sodium hypochlorite was not used, as it interferes with protein quantitation (unpublished data). We also assessed the wiping of tonometer tips using an isopropyl alcohol swab (Steriswab, Seton Group).

The amount of protein remaining on the tonometer tips was assessed using two methods, the CBQCA protein quantitation kit (Molecular Probes), and the BCA protein quantitation kit (Pierce), in each case in accordance with the manufacturer's instructions following protein solubilisation

with 0.1 M sodium borate, pH 9.3, and 3 M guanidine HCl respectively. Each procedure was assessed on four used tonometer tips.

RESULTS

Observations

The tonometer tips had an inherent ability to carry a meniscus of fluid despite vigorous shaking (Fig 1).

There was large patient to patient variability in the tolerance of applanation. The more trauma involved in taking the reading, the more material (for example, cellular debris, mucus, tear fluid) appeared to be carried over into the protein analysis. After protein quantification, silver staining of the tonometer heads confirmed that no residual protein remained on the tonometer head.

Total protein carriage after applanation

Analysis of the protein levels carried over on tonometer tips showed that there was a great deal of variability in the load of proteinaceous material carried over between individual patients. The lowest amount of protein detected directly from an eye was 4.3 µg, whereas the highest carryover, from a red and inflamed eye, was in excess of our measured upper limit of 20 µg (Table 1). Rinsing the tonometer tip in uhpH₂O for 5 minutes reduced protein carryover, with the greater volume producing the greater reduction (using ANOVA, $p = 0.259$). Wiping the tonometer tip with an isopropyl alcohol swab tended to further reduce carryover but likewise this did not reach significance, probably because of the interpatient variation (data not shown) and the small numbers assessed.

DISCUSSION

Our data show that tonometer tips are capable of carrying proteinaceous material that could potentially be transferred from one eye to another. The amount of protein contaminating a second eye could conceivably be in the tens of micrograms (µg) in the case of a first inflamed eye that tolerates applanation poorly, suggesting that this constitutes a potential route for the horizontal transmission of vCJD. A recent study, however, demonstrated that no PrP^{Sc} could be detected in the anterior segment (lens, aqueous humour, iris, and cornea) of the eyes of vCJD or sporadic CJD patients.¹⁹ The levels of PrP^{Sc} cannot be directly correlated with units of human infectivity, but this absence of PrP^{Sc} suggests that levels of infectivity in the anterior segment are at least 400× lower than in brain tissue. If we assume this level of

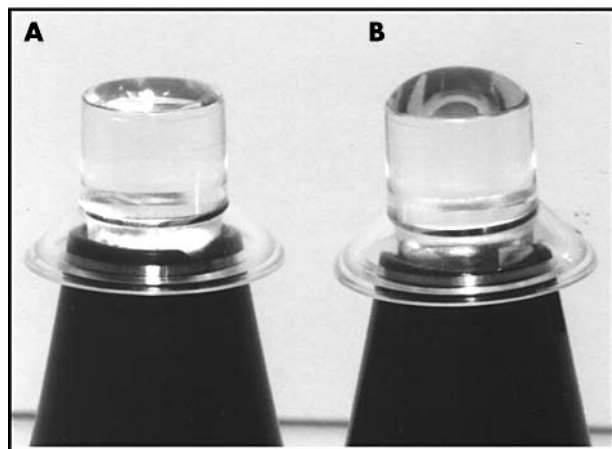


Figure 1 Disposable tonometer heads mounted on reusable holders showing variations in the volume of the fluid meniscus. (A) shows the meniscus after shaking and (B) shows the meniscus without shaking.

Table 1 Effect of rinsing tonometer tips

Volume of rinse	No	Mean (SD)	Range
No rinse	4	7.6 (8.4)*	4.3–20>*
1 ml	4	3.7 (2.2)	1.3–5.9
50 ml	4	1.9 (1.7)	0.8–4.4

Mean = mean amount of protein present on tonometer tips (µg); n = number of patients analysed; range = minimum/maximum values from the group of patients

*A reading in excess of our upper limit for measurement (that is, above 20 µg); for the mean reading, a value of 20 was used.

infectivity in the anterior segment, then by a worst case scenario calculation there would be less than one infectious unit (intracerebral LD₅₀) per µg of total protein on the ocular surface. Therefore, there exists a small theoretical risk of transmission of prion disease by contact tonometry if tonometer prisms are reused, but this risk can be substantially reduced if the prisms are washed and disinfected.

The risk of transmission could be further reduced by using larger volumes of washes for longer periods, and adding wiping between washes.²⁰ Regular replenishment of the wash should also be encouraged, as substantial amounts of patient derived protein could accumulate with repeated use (an estimate of up to 1 mg after 50 successive applanations).

CONCLUSION

To completely eradicate the risk of horizontal transmission of prion protein, disposable tonometer prism tips should be used. However, if disposable tips are not used, reusable tonometer prisms should be soaked in the largest volume (at least 50 ml) of aqueous solution for at least 5 minutes. Consideration should also be given to the use of sodium hypochlorite at a concentration of 20 000 ppm, as recommended in the guidance published by the College of Optometrists and the Association of British Dispensing Opticians.²¹ The soaking container should be changed frequently, ideally between patients. In addition, the prisms should be mechanically wiped. These actions may be equally useful in the reduction of protein carryover.

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ECHO

Gamma-D crystallin gene mutation causes autosomal dominant congenital cerulean cataracts

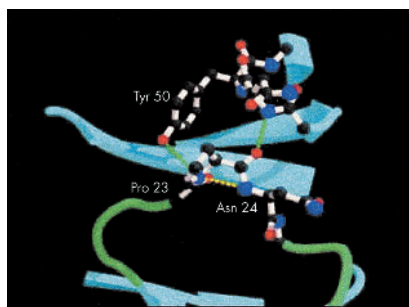


Figure 1 Schematic view of the protein fold determined by x ray crystallography centred on residue P23 and looking along β -sheet 2 of the normal CRYGD protein.

Researchers from Morocco and Paris (France) have mapped the gene responsible for autosomal dominant congenital cerulean cataract (ADCCC) by studying a family of 19 affected and 24 unaffected subjects spanning four generations.

The gene was localised to a region of chromosome 2q33-q35, spanning the γ -crystallin gene (*CRYG*) cluster. This is the third locus identified in ADCCC, and characterises a phenotype with early onset (diagnosable at birth) and rapid progression.

All affected members of this kindred had a C>A transversion in exon 2 of the *CRYGD* gene. This class of genes encodes a superfamily of major soluble structural lens proteins. The particular transversion found results in a proline to threonine substitution at amino acid 23 in the first of the four Greek key motifs that characterise the protein. This may alter the protein folding or decrease the protein's thermodynamic stability or solubility.

▲ *Journal of Medical Genetics* 2003;**40**:262-267.

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