Institution: King's College London

Unit of Assessment: 3B - Pharmacy and Nutritional Sciences

Title of case study: Carbohydrate deficient transferrin as a diagnostic tool for the detection of continued drinking in high risk drink drivers

1. Summary of the impact (indicative maximum 100 words)

Research carried out at King's College London (KCL) showed that percentage carbohydrate deficient transferrin (%CDT) can be used as a means to monitor continuous drinking in high-risk offenders. The accurate screening of such drivers helps reduce the number of unsafe drivers on British roads. KCL work has resulted in a change to the Driver and Vehicle Licensing Agency's (DVLA) national policy for assessing drink drivers. Percentage CDT has been approved as the sole biomarker for the purpose of re-licensing high-risk drink drivers. This enables faster release of a licence to an abstinent high-risk offender; provides a better basis for the refusal of release in other cases and provides a more reliable control and therefore, a more practicable service, especially for periodic re-granting of licences for special (buses, heavy trucks) drivers.

2. Underpinning research (indicative maximum 500 words)

Chronic alcohol consumption is linked to particularly hazardous driving with significantly increased risk of involvement in road traffic collisions. Identification of continuous drinking in high-risk offenders (HROs) repeatedly arrested while drunk driving is considered to have important traffic-safety, health and social implications. As such, the UK's Driver and Vehicle Licensing Agency (DVLA) annually monitors approximately 40,000 individuals with repeated drink-driving offences. Research into a diagnostic tool for the detection of continued drinking in HROs is led at King's College London (KCL) by Dr Kim Wolff (1997-present, Reader in Addiction Science), Dr Elizabeth Marshall (1990-2008, Consultant Psychiatrist and Honorary Senior Lecturer) and Dr Francis Keaney (1999-2008, Consultant Psychiatrist and Honorary Senior Lecturer) and with Dr Roy Sherwood at Kings College Hospital.

Historically, liver damage biomarkers such as gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and mean cell volume (MCV) were used by the DVLA to provide evidence about alcohol consumption in HROs. Carbohydrate deficient transferrin (CDT) is a biomarker widely utilised in clinical drug-treatment settings. Transferrin is the principal ion-trapping glycoprotein in plasma and concentrations of the sialic acid residue-deficient asialo-, monosialo- and disialo-isoforms are elevated in dependent drinkers. To be able to test whether absolute values or values expressed relative to the total transferrin concentration provide the same diagnostic efficiency, a study by KCL researchers measured CDT in patients either with (n = 35) or without (n = 35) alcohol-related liver disease and 35 with chronic viral hepatitis using two commercial methods (the CDTect assay and the %CDTriTIA kit). Sensitivity and specificity were similar for both methods, however a linear relationship between CDTect measures and total transferrin was found that may produce misleading results in populations with a high prevalence of abnormal total transferrin concentrations and could cause difficulties in method comparisons unless taken into account. This suggested that the expression of CDT as a percentage of total transferrin with the %CDT method will produce more reliable results (Keating J, et al. 1998).

Following a successful bid to the Road Safety Division of the Department of Transport in 2005, KCL researchers examined CDT as an alternative to GGT as a biomarker of continuous drinking. In their study, 358 mainly white British (79%) subjects provided blood samples for measurement of AST, ALT, GGT and %CDT. Subjects were recruited from three different drinking populations: alcohol dependent inpatient (n = 165); community-based outpatient with harmful alcohol use (n = 165) and non-treatment social drinkers (n = 51). Nearly 32% were high risk drivers, having been breathalysed between one and five times; 20% had produced a positive breath test and, of these, all but seven (90%) have been convicted of drink-driving. A fourth group was recruited to control for confounders (obese, diabetic and those with liver disease) (n = 142). Analysis confirmed a significant link between harmful/dependent drinking and unsafe driving. The predictive value (a useful indicator of how a test will perform in a normal general population) of %CDT as a biomarker of continuous drinking within the whole sample was superior, exhibiting good diagnostic power (PPV = 0.85) compared to the more conventionally used GGT (PPV = 0.67). Good diagnostic

power was also found for %CDT when the alcohol treatment population was compared to subjects with medical diseases known to confound liver function tests. However GGT showed a distinct fall in specificity and positive predictive value. Overall the sensitivity and specificity of %CDT was superior to GGT as a biomarker of continuous alcohol consumption. A good diagnostic power was retained by %CDT when subjects with a formal alcohol use disorder were combined with subjects being treated for obesity, diabetes and non-alcoholic liver disease compared with GGT: positive predictive power for %CDT was 0.91 versus 0.63 for GGT, respectively (Road Safety Report: Wolff K, et al. 2010).

3. References to the research (indicative maximum of six references)

Keating J, Cheung C, Peters TJ, Sherwood RA. Carbohydrate deficient transferrin in the assessment of alcohol misuse: absolute or relative measurements? A comparison of two methods with regard to total transferrin concentration. Clin Chim Acta 1998;272(2):159-69. Doi: http://dx.doi.org/10.1016/S0009-8981(98)00008-4 (23 Scopus citations. Clin Chim Acta is an Internationally-recognised, peer-reviewed journal)

Wolff K, Gross S, Walsham N, Marshall EJ, Keaney F, Sherwood R. The role of carbohydrate deficient transferrin as an alternative to gamma Glutamyl transferase as a marker of continuous drinking in high-risk drivers**.** Road Safety Research Report No 104. 13.Jan.2010. http://www.dft.gov.uk/publications/rsrr-theme6-report-104/

Grant

2005-2007. PIs: Wolff K**,** Marshall EJ, Keaney F, Sherwood R. Investigation to compare efficacy of GGT and CDT for identification of continuous drinking in high-risk drink drivers. Department for Transport, Home Office, £106,087

4. Details of the impact (indicative maximum 750 words)

KCL research helps the Department for Transport (DfT) establish a new biomarker for HROs

Alcohol is the most frequently detected psychoactive substance in the UK driving population as well as in seriously and fatally injured drivers. In the DVLA's high-risk offenders (HROs) scheme the licences of convicted drink-drivers are returned only if they can convince the court that they do not have an alcohol abuse problem. Biomarkers are used to aid assessment as part of the process leading to a decision to reinstate driving entitlement for HROs. Concerns raised about the specificity and sensitivity of traditional tests led the DfT to call for research to identify more specific alcohol consumption biomarkers and for them to subsequently fund such a project at King's College London (KCL). In 2010, the results of this research (discussed in the previous section and published by the DfT as a Road Safety Report) provided evidence that %CDT was a better test than current biomarkers. This was based on diagnostic efficiency (combined sensitivity and specificity) to identify continuous drinking in drivers. As well as being released as a downloadable online DfT report, these findings have been published as a paperback (1a) and the report was distributed to around 20 key stakeholders across the country, such as the DVLA and forensic lab providers. KCL also led on a 2010 review for the DfT discussing the advantages and disadvantages of a number of biomarkers. This concluded that "CDT is reliable enough on its own to support a diagnosis of alcohol dependence, harmful or hazardous use, and has the advantage that common medications seem to have no influence on the performance of this biomarker" (1b).

KCL researchers contribute to government policy

In 2008 KCL's Dr Kim Wolff presented the findings of the research and literature review (later published as the Road Safety Reports) to the Secretary of State for Transport's Honorary Medical Advisory Panel on Alcohol, Drugs and Substance Misuse and Driving (HMAP) (of which she is also a member). Presentations also took place at DVLA headquarters in Swansea and tendering was undertaken as part of a process to introduce %CDT testing into the HRO scheme (2a). Following on from this, in 2009, the HMAP "agreed that, given its sensitivity and specificity profile, the measurement of %CDT should be the marker of choice for the HRO population" and a pilot scheme was proposed (2b). In 2010, a 'potential supplier day' took place at the DVLA with UK laboratories accredited for CDT testing (2c) and in 2011, the HMAP Panel "agreed that CDT would become the sole test for assessing harmful use of alcohol in the HRO population, in conjunction

with a thorough medical history and examination." This changed previous policy that required Medical Advisors to consider a combination of four different liver function tests (GGT, AST, ALT and MCV) (2d). The Chair of HMAP confirms that "Dr Wolff's research on CDT was hugely significant in changing the direction of testing. On advice from the advisory committee, having reviewed Dr Wolff's research on CDT, the DVLA changed their entire procedures" (2e).

From policy to practice

The Drivers Medical Group at the DVLA promote road safety by establishing whether drivers who have medical conditions such as alcohol dependence are able to satisfy the medical standards required for safe driving. To undertake this task, the DVLA employs Medical Advisers who process in excess of 600,000 cases every year. In 2011, the DVLA's Senior Medical Advisor informed the HMAP Panel that the DVLA were proposing to use CDT testing "on cases where there was uncertainty in the interpretation of abnormally raised blood tests, which were currently used as markers of alcohol misuse, and where a licence recommendation could not otherwise be made" (3a, b). A letter of corroboration from the DVLA's Head of Medical Licensing Policy states that "the DVLA recognised the significant impact that research by Dr Wolff had had on the area of diagnosing alcohol misuse and/or dependency and, more specifically, on the introduction of CDT testing in DVLA as a more accurate way of determining this" (3c).

In 2011 KCL initiated a DVLA-funded pilot project (£50,000) to establish the logistics of using CDT prior to full adoption of the policy for HRO's in the UK in 2014. The pilot included the use of CDT tests in difficult DVLA cases across the UK, such as those for whom the Medical Advisor was unable to diagnose either abstinence or continuation of drinking because of confounding factors. As such, since 2011, 1223 HROs have been tested using the new biomarker instead of conventional biomarkers. CDT was found to help improve re-licensing decisions in this traditionally difficult population to manage. The use of %CDT prevented 131 current dependent drinkers (10.7%) from returning to driving; a further 52 (5.3%) were identified as non-abstinent but not dependent drinkers and were refused a licence pending a second test and the remaining 1040 (85%) HROs were re-licensed and deemed fit to drive. In early 2013 a further summary on the results of the CDT pilot noted that "use of CDT in the licensing process had, in addition to the benefits of using an up-to-date medical marker in line with Panel advice, brought advantages in terms of the time and cost of processing alcohol-related cases" (4a, b). The Chair of HMAP confirms that "this more accurate test has resulted in quicker decisions, fewer appeals against licensing decisions, a greater ethos of evaluation and more research" (2e).

As well as providing information regarding the use of %CDT, Dr Wolff also provided guidance notes for DVLA Medical Advisors on %CDT cut-off concentrations linked to licensing. In early 2012 these percentages were discussed and approved by HMAP with current commercial laboratory assays. Here, in a traffic light system, CDT values up to and equal to 2.5% are compatible for licensing (Green), while values equal or greater than 3% should be considered an indication of harmful use of alcohol (Red) and lead to licence refusal or revocation. CDT levels between 2.6 and 2.9% (Amber) would trigger further enquiries with the HRO's General Practitioner or Hospital Specialist. Within the DVLA, the Policy and Operational Support Departments are currently investigating how this is to be taken forward (5a). This was publicised as an E-brochure by the DVLA Medical Drivers Group (5b). The DVLA's Head of Medical Licensing Policy confirms that Dr Wolff " had considerable input into the determination of suitable cut off points for licensing decisions and in running of a pilot" (3c).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Road Safety Reports
   a. Road Safety Research Report S. 104 (Paperback). Publisher: Department for Transport. Published 1.Jan.2010. ISBN: 9781848640016: http://www.waterstones.com/waterstonesweb/products/7474164/
   b. Wolff K, Walsham N, Gross S, Marshall EJ, Keaney F, Sherwood R. Road Safety Research Report No 103. The role of carbohydrate deficient transferrin as an alternative to gamma Glutamyl transferase as a biomarker of continuous drinking: A literature review. Published 13.Jan.2010: http://www.dft.gov.uk/publications/rsrr-theme6-report-103/

2. Secretary of State for Transport's Honorary Medical Advisory Panel on Alcohol, Drugs and Substance Misuse and Driving
    a. March 2008. Presentation of a preliminary report on the role of CDT as an alternative to GGT as a marker of continuous drinking: http://webarchive.nationalarchives.gov.uk/20110726015847/https://www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/minutes/~/media/pdf/medical/min_120308.ashx
    b. September 2009. Declaration on the use of %CDT as the sole test for HROs: http://webarchive.nationalarchives.gov.uk/20110726015847/https://www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/minutes/~/media/pdf/medical/mins_30092009.ashx
    c. March 2010. 'Potential supplier day' at DVLA: http://webarchive.nationalarchives.gov.uk/20110726015847/https://www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/minutes/~/media/pdf/medical/mins_17032010.ashx
    d. January 2011. Affirmation of use of %CDT as sole test: http://webarchive.nationalarchives.gov.uk/20110726015847/https://www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/~/media/pdf/medical/mins_12012011.ashx
    e. Letter of corroboration (on request) from The Chair of the Secretary of State for Transport's Honorary Medical Advisory Panel on Alcohol, Drugs and Substance Misuse and Driving, Consultant Psychiatrist in Addictions (Newcastle University)**.**

3. Drivers Medical Group at the DVLA
    a. October 2011: http://webarchive.nationalarchives.gov.uk/20130411225420/http://dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/minutes/~/media/pdf/medical/mins_19102011.ashx
    b. October 2012: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/205258/10th_October_2012_minutes.pdf
    c. Letter of professional support from The DVLA, Acting Head of Medical Licensing Policy

4. Updates on HRO %CDT pilot scheme:
    a. October 2012: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/205258/10th_October_2012_minutes.pdf
    b. February 2013: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/205256/27th_February_2013_minutes.pdf

5. Commercial use of %CDT
    a. March 2012: http://webarchive.nationalarchives.gov.uk/20130411225420/http://dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/~/media/pdf/medical/mins_07032012.ashx
    b. E-Brochure: http://www.nhspurchasing.com/brochome.asp?OrgCode=1730