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In Confidence

PROPOSAL FOR A PROSPECTIVE STUDY OF BLOOD DONORS WITH ABNORMAL LIVER FUNCTION TESTS POSSIBLY INDICATING CARRIAGE OF NON-A, NON-B HEPATITIS

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INTRODUCTION

Since the advent of specific tests for Hepatitis A and B, non-A, non-B hepatitis (NANB) - so-called because of the lack of specific serological tests - has come to account for 80-90% of post-transfusion hepatitis (PTH) (Gitnick 1984). The remaining 10 - 20% of PTH is caused by other viruses (CMV, EBV and hepatitis B which still occurs occasionally despite donor unit testing).

Although NANB hepatitis is usually asymptomatic, being discovered only by routine testing of serum transaminases, chronic sequelae occur in approximately 50% of patients, ranging from mild persistent abnormalities of liver function tests, through various degrees of chronic persistent and chronic active hepatitis, to cirrhosis with portal hypertension. NANB hepatitis is a common complication of transfusion with blood and blood products (6.7 - 10% of patients receiving blood alone) (Alter et al 1981, Aach et al 1981, Steinbrecher et al 1983), and there is therefore a great need for a test system which would allow the identification of donors carrying the putative NANB hepatitis virus.

In 1981 two groups in the U.S.A. reported the results of large studies of PTH, using different methods (Alter et al 1981, Aach et al 1981). They showed that transmission of NANB hepatitis was associated with raised alanine aminotransferase (ALT) levels in donor blood. When corrected for volume of transfusion and other variables, both studies demonstrated that elimination of donor units with ALT levels $>$ 2.25 SD above the mean for their donor populations would prevent approximately 29% of NANB PTH.

The incidence of raised ALT in the NIH study (Alter et al 1981) was 1.6% and this therefore represents the number of donor units which would be lost if ALT screening was introduced.

The practicability of the introduction of ALT testing, and its economic implications, have been hotly debated (Hornbrook et al 1982; Lenes et al 1983; Khan 1983). So far only the Federal Republic of Germany has officially adopted this as a national policy although several U.S. centres are using ALT screening (NYBC, Irwin, San Francisco etc.). It is clear from other studies that the donor population from which the NIH and TTV data were drawn may have been different from those in other parts of the world. Thus Steinbrecher et al (1983) could not demonstrate a raised incidence of NANB PTH resulting from their donors in Montreal with raised ALT.

Taken with evidence that the incidence of sporadic NANB hepatitis in the population varies greatly from country to country (25% of all sporadic hepatitis in U.S.A., 9% in Greece, 4.3% in U.K. [Gitnick 1984]), it seems likely that the conclusions reached in the NIH and TTV studies are not universally applicable. Bayer (1984) has suggested that each transfusion centre should study its own donor population before reaching any decision about the instigation of ALT testing. Clearly, however, any testing programme will lead to the identification of substantial numbers of donors with raised ALT, at least 70% of whom will not be carriers of NANB hepatitis. So far little is known about those donors with raised ALT levels and no guidelines are available for counselling them and deciding on the need for further medical care. In the only study so far reported

(Alter 1984), 60% of ALT elevations were due to identifiable causes other than NANB hepatitis. 24% of raised ALT's were related to obesity, and 14% to alcohol consumption.

BACKGROUND TO THE PRESENT STUDY

ALT testing is a means of measuring hepatocyte damage, but it is not a specific test for liver disease as the enzyme is also present in other cells, notably red blood cells. The Department of Clinical Chemistry in the Royal Infirmary of Edinburgh has recently developed an immunoassay for an enzyme more specific to the liver, glutathione-S-transferase (GST). Initial studies suggest that measurement of GST levels in plasma may be a more sensitive and specific test for liver cell damage than current transaminase estimations (Beckett & Hayes 1984). A pilot study was performed in which over 200 blood donations taken at the South-East Scotland Regional Transfusion Centre were screened concurrently by both GST and ALT. Using cut-off values approximately 3 SD above the mean, as suggested by Alter et al (7ug/l for GST and 60u/l for ALT), 3.3% and 5% respectively of donors were found to be abnormal. There was good correlation between the two tests.

AIMS OF STUDY

We propose to repeat this screening exercise on a much larger number of donors in order to identify a cohort with raised ALT or GST, or both, and to follow these donors prospectively. The specific objective of this study is not to compare ALT and GST as possible screening tests for transmission of NANB hepatitis, but to study those

donors with apparently abnormal values in order to establish the presence or absence of disease. If it becomes necessary to introduce ALT or GST testing to screen for NANB hepatitis, the results of this study will be of great value in deciding which cut-off point may be appropriate for our local donor population, and will also be extremely helpful in the development of strategies for counselling and investigating donors identified as abnormal.

We propose to interview and examine these donors with their consent, performing the tests outlined below when donors agree to further testing. A control group of donors with normal ALT will also be selected, and their ALT levels followed prospectively, since it is known that patients with chronic NANB hepatitis show gross fluctuation in ALT level with time.

PROTOCOL

1. In order to identify approximately 100 donors with raised ALT or GST, 2000 donors from designated sessions within Edinburgh will be screened. At sessions to be screened, donors will be given an explanatory leaflet and opportunity to opt out (specimen attached).

2. Those identified as having abnormal levels (ALT or GST $>$ 2 SD above mean) will be informed that a new screening test has identified a minor abnormality of doubtful significance, and will be asked to attend for interview. The reason for the study will be explained in detail and the donors will be asked to consent to further questioning, examination and blood tests (specimen consent form attached).

3. A cohort of age and sex-matched controls, from the same sessions, will be identified, and ALT/GST measurements performed at each subsequent donation during the study period.

4. History and examination will be carried out by a qualified physician (JG).

5. Blood will be taken for:-

   (a) repeat ALT and GST, and other liver function tests viz bilirubin, alkaline phosphatase, AST and γ GT (+ γ GT electrophoresis).

   (b) HBsAg, HBcAb, HA IgM, EBV and CMV serology.

   (c) Caeruloplasmin and α-1 antitrypsin.

   (d) Blood alcohol.

   (e) Autoantibodies (ANF, smooth muscle, mitochondrial).

   (f) Serological tests of possible relevance to the detection of NANB hepatitis (see above).

6. The above studies will be repeated at 6 monthly intervals for up to 2 years.

EVALUATION

After the initial assessment of those donors consenting to take part in the study it should be possible to reach preliminary conclusions about the prevalence of overt disease within the group and identify

possible causes (eg. alcohol abuse, recent subclinical viral infection, etc.). The importance of the sequential studies is in the group with no apparent liver disease, to ascertain whether enzyme levels fluctuate or progress, and whether any evidence of disease becomes manifest. Appropriate statistical comparisons of ALT values will be made within groups at different time points, and between groups at each 6 monthly assessment. It is expected that sub-group analysis and exclusion of donors with identifiable causes of raised ALT/GST levels may lead to a more precise definition of normality in blood donors.

Should a specific test for NANB hepatitis become available a further study of this selected group with their controls would be of great interest.

Note:- 1. Donors showing evidence of clinically significant disease will be offered further investigation with the permission of their G.P.

2. Donors found to have moderately elevated ALT/GST but no evidence of significant disease will not be asked to discontinue donation during the study.

3. Donors with detectable levels of alcohol in the blood will be advised that the test results suggest they may be drinking more than is advisable. The donor's G.P. will be advised of the result.

4. Full follow-up of recipients is not a part of the present protocol. The requirement for recipient follow-up will be reviewed after data on the initial 2000 donors

is available for analysis or if evidence becomes available relating to apparently specific markers for NANB hepatitis infectivity.

5. The S.N.B.T.S. Ethics Committee will be requested to approve the study.

FINANCIAL SUPPORT REQUIRED

Financial support will be sought for the cost of reagents for ALT screening (£1,100). The cost of GST screening will be met by the Department of Clinical Chemistry.

Specimen Consent Form

STUDY OF LIVER FUNCTION TESTS IN BLOOD DONORS

I understand that as part of a research study investigating minor blood abnormalities in blood donors, I am being asked to consent to an interview and medical examination by a qualified physician, and to a range of further blood tests designed to uncover any evidence of liver disease or of previous hepatitis.

The significance of the minor blood abnormalities is not known at this time. If they are confirmed, or if other abnormalities are discovered, I will be informed of the results and offered further testing to clarify their meaning.

I understand that the results of these tests will be treated with complete confidentiality. In the event of further tests being required to clarify the significance of the study results, I agree that my General Practitioner should be informed and his agreement obtained.

My entrance to this study is completely voluntary, and I understand that I am free to withdraw at any time.

Any questions I may have about this study may be addressed to Dr. J. Gillon, who is fully acquainted with all of the details of this study.

Signature of donor _____ Signature of doctor _____

Date _____ Date _____

Name and address of G.P. _____

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STUDY OF ALT AND GST LEVELS IN BLOOD DONORS

Information for donors:

We would like to screen all the blood collected at this session using additional tests which may help to prevent the transmission of hepatitis to patients receiving transfusions. When the results are available we may wish to see you again to obtain further samples. This would help us to interpret the usefulness of the test.

This is purely a research project at this stage and we can assure you that your blood donation will be used in the normal way regardless of the results of the test.

If you do NOT wish us to test your blood in this way, please sign below and hand this slip back to the receptionist.

The Director and Staff of the Edinburgh & South-East Scotland Blood Transfusion Service thank you for your co-operation.

JG/OS

STUDY OF ALT AND GST IN BLOOD DONORS

Information for session staff:

The commonest cause of post-transfusion hepatitis is non-A, non-B hepatitis (NANB). Epidemiological evidence suggests that at least 2 different viruses may be involved, but these have not been isolated or cultured and no specific serological test is available. NANB is a common complication of transfusion (5-10% of all transfusions), but is usually asymptomatic. Jaundice occasionally occurs, and some recipients develop a chronic low grade hepatitis.

Two large studies in the USA have shown that screening of blood for raised levels of alanine aminotransferase (ALT) can reduce the indicence of NANB post-transfusion hepatitis. However, this test is not specific for liver disease, and it has been emphasised that each Centre should study its own donor population before deciding whether to introduce screening.

This study is designed to provide information on ALT levels in our own donors. We are also comparing these results with a new liver-specific enzyme estimation, glutathione S-transferase (GST). We propose to invite donors found to have "abnormal" values to attend for further testing. In so doing we hope to be able to shed some light on the reasons for abnormal liver function tests in apparently healthy people.

A pilot study revealed raised ALT/GST levels in around 3% of donors; so only a small number will be asked to undergo further testing.

If more information is required please contact Dr. J. Gillon.