

Dear Fellow Clotter

Welcome to the first newsletter for 2005. This is a very big year with the ISTH in Sydney fast approaching. I encourage everyone to visit the website www.isth2005.com for all the details. In particular I would like to remind everyone that early bird registration is before 31st May 2005. Further I have received information from a very reliable source that 2900 abstracts from 2200 authors were received and are currently being reviewed. Emmanuel Falavero has included details of two 'Back to Basic Science' symposium sessions to be held on the Monday of the ISTH congress.

Please take time to peruse the latest on the HAA to be held in Sydney in October.

Also in this issue of the newsletter is a clinical trials group report, message from the President, the winning AstraZeneca Medal abstracts from 2004 and conference reports from the recent International Symposium on Women's Health Issues in Thrombosis and Haemostasis and from the Congress of the World Federation of Haemophilia held last October.

Thanks to all the contributors, I am very grateful for your efforts. A special thank you to Paul Coughlin who wrote the warfarin reversal guidelines summary for the last newsletter issue.

Emma Perrin

FROM THE PRESIDENT

Dear Colleagues,

There are many things that go in ones' mind in day to day life. As a person with an interest in thrombosis and hemostasis the most challenging concern continues to be the use of warfarin. While the drug has been around for a long time, we are still not very comfortable prescribing it to everyone who has a definite need. This may seem strange particularly that the drug is safe except for the potential for bleeding and teratogenicity. The narrow therapeutic window afforded by this drug continues to be a major source of concern and makes us all very reserved when initiating treatment. The wheels of new therapeutics in the thrombosis field continue to move forward albeit at a slower pace than any of us would like. It seems to me that we are stuck with warfarin for a little longer. We were all expecting that Ximelagatran was going to gain approval by the FDA but unfortunately this did not happen. The potential for hepatotoxicity caused the FDA to be concerned which is most appropriate. No one wants a new drug to be released before it is fully evaluated for safety and efficacy. The manufacturer has been asked to provide further evidence and conduct more clinical studies and we just have to wait for the final outcome. The good news is that several other large pharmaceutical companies have oral compounds (direct thrombin and X_a inhibitors) that are in reasonably advanced stages of clinical development.

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ASTH COUNCIL 2003-2005

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From page 1

Initial clinical experience with some of these compounds appears to be very promising, and certainly the oral anti- X_a manufactured by Bayer appears to be very promising and effective both as a therapeutic and prophylactic agent. It may be only another four to five years before we have a new "warfarin" on the market, but certainly the journey seems a long one. Another major challenge we have is the identification of individuals who have hyperactive platelets. Assessing this phenomenon in the laboratory has eluded us so far, and the same applies to a simple test that can reassure us that the patients' platelets have been subdued sufficiently without the risk of bleeding. The need for such tests is highlighted by the significant bleeding observed in patients receiving combination anti-platelet therapies. Take for example the Match study, where 2.6 % of patients receiving the combination of Aspirin and Clopidogrel developed a life threatening bleeding event. The definition of the latter was any fatal bleeding, symptomatic intracranial bleed, a drop in haemoglobin by more than 5gm/L or transfusion requirement of more than 4 units of packed cells. These are serious side effects not a simple bleed. The frequency of this type of bleeding in the Match Study is not very significantly different to what one observes with warfarin therapy highlighting the need for some laboratory tests to monitor the safety of these drugs when used in combination and again stressing the point that combination anti-platelet therapy can be quite dangerous and has to be handled carefully with due recognition of this significant side effect profile. I see so many patients that are taking Aspirin, Clopidogrel and Warfarin together, and I can't help feel alarmed. Most patients are not given adequate advice and education on the problem of bleeding from this combination. The only good news out of this is that there is still more work for all of us.

In this newsletter you will read how we are progressing in our final preparations for the ISTH and the ASTH meetings both of which will be in Sydney. Certainly Colin Chesterman and Chris Ward and their respective committees are doing a wonderful job and everyone I speak to is excited about the meetings.

At the Annual General Meeting in October of this year, we will farewell two of our senior councillors. Both have all served us extremely well, in an uninterrupted way and for the maximum duration that our constitution allows. Alex Gallus from South Australia and Tim Brighton from New South Wales will be both retiring from office. We are looking for nominations to replace them. Please consider nominating yourself or a colleague for this important role to help us make your society better.

Finally a couple of thank yous are required. Leonie Klomp left us in January this year to take up a new position with the Asthma Foundation. For many of you including myself Leonie was synonymous with the ASTH, and her departure left us with a big void. We are still trying to fill the position with the help of our executive director Ross Baker. Leonie worked tirelessly for the ASTH and has been responsible for many of our innovations and progress. Thank you Leonie, sorry that you are leaving us and good luck in your new position, we wish you all the best. I would also like to thank Emma Jones-Perrin, who continues to do a wonderful job with our newsletter. We know what our newsletter used to be like, and how wonderful it is now thanks to Emma's efforts. It is not an easy and simple task to extract all these articles and writings from people. Emma does it in a superb gentle way that makes it difficult for anyone to say no. We undoubtedly all benefit from the newsletter. I encourage you to write to Emma with your questions and comments on how to make this communication channel even better. Until next time, I wish you all a happy Easter and a great 2005.

Hatem Salem

DON'T FORGET THE SYDNEY HAA MEETING IN OCTOBER!

The ASTH is putting together a strong coagulation programme for this year's annual scientific HAA meeting, to be held at Darling Harbour between 16-19 October. International invited speakers include Drs Agnes Lee (clinical trials, cancer and thrombosis), Ken Clemetson (platelet receptors and signaling) and Jean-Marie Freysinnet (microparticle physiology and measurement). Symposia topics will include cancer and thrombosis, predicting cardiovascular risk, new assays for hypercoagulability and molecular technology in bleeding disorders. A joint session with ANZSBT will look at new strategies in massive haemorrhage including the role of rFVIIa. We will also feature updates from the recent ISTH meeting, focusing on new anticoagulants, antiplatelet agents and thrombophilia – both for anyone who couldn't attend ISTH and for all those who had to miss interesting sessions! We're sure the programme will continue the high standards of previous years and hope to see you there. Haematology trainees and junior scientists are particularly encouraged to present their work – the call for abstracts will be sent out in May and remember the ASTH travel grants!

Chris Ward

ISTH 2005

Dear Members,

Over the past year or so I have worked with the Local Organising Committee (LOC) of the 2005 ISTH Conference (Sydney), the purpose being to make the meeting both more relevant and more affordable to local Hospital Scientists. The response has been very positive and the LOC has asked me to distribute the invitation, which follows:

ISTH 2005 – Sydney, 6-12 August

A unique opportunity for Australian hospital scientists

The 2005 international meeting of the ISTH (International Society on Thrombosis and Haemostasis) represents a unique opportunity for Australian hospital scientists. These meetings are held every two years and, until now, held overseas. For the first time, the 2005 venue is Sydney, a situation unlikely to be repeated in the foreseeable future. These meetings represent the premier congress for scientists and clinicians with a special interest in Haemostasis and Thrombosis. The general meeting will run from Monday 8th to Friday 12th August, and this comprises plenary lectures, state-of-the-art lectures, symposia, as well as oral and poster presentations. Of particular interest to laboratory scientists are two 'Back to Basic Science' symposium sessions being held on Monday 8th, one covering bleeding disorders and the

other thrombophilia. Both sessions will include external quality assurance talks from the local RCPA QAP as well as other international programs (UK-based NEQAS and European-based ECAT). In addition, the bleeding disorders session will cover diagnostic issues in both von Willebrand disorder (VWD) and platelet function, and the thrombophilia session will cover testing, diagnosis and screening for thrombophilia and anti-phospholipid tests. International guest speakers include

Monica Galli and Marco Cattaneo. Registration is required to attend the ISTH meeting. Options include registration for the entire conference, or a special one-day registration is also available for scientists wishing to attend a single day's session. In addition, the ISTH meeting also includes separate sessions conducted by various SSCs (Scientific and Standardisation Committees) of the ISTH, and held Saturday 6th and Sunday 7th August. The SSC meetings are free of additional registration costs and are typically of extraordinary interest to scientists. Further information:

ISTH 2005 meeting, including SSC sessions: please check the website: <http://www.isth2005.com/>

'Back to Basic Science' symposium sessions:

Dr Emmanuel J Favalaro MAIMS, Senior Hospital Scientist, Haematology Westmead Hospital, NSW 2145. email: emmanuel@icpmr.wsaahs.nsw.gov.au.

Preliminary program ISTH 2005 MEETING 'Basic Science' Symposia

PLANNED DATE: MONDAY, 8TH AUGUST, 2005

SYMPOSIUM 1: Back to basics – Laboratory diagnosis of bleeding disorders

Chair persons: Eric Preston (UK NEQAS) and Katherine Marsden (RCPA QAP)

Talk 1: Diagnostic issues in haemophilia and von Willebrand disorder: The quality assurance perspective. Speakers: Steve Kitchen (UK NEQAS), Piet Meijer (ECAT), Sukesh Nair (ISHTM-CMC EQAS). Total 30 min (ie 3 x 10 min).

Talk 2: Diagnosis of von Willebrand disorder: Lessons from quality assurance and minimum requirements. Speaker: Emmanuel J Favalaro. 30 min.

Talk 3: Laboratory testing, diagnosis and management of platelet disorders. Speaker: Marco Cattaneo. 30 min.

SYMPOSIUM 2: Back to basics – Diagnostic issues in Thrombophilia

Chair persons: Eric Preston (UK NEQAS) and Katherine Marsden (RCPA QAP)

Talk 1: Testing for inherited thrombophilia – the quality assurance perspective. Speakers: Ian Jennings (UK NEQAS), Piet Meijer (ECAT), Roslyn Bonar (RCPA QAP). Total 30 min (ie 3 x 10 min).

Talk 2: Testing for thrombophilia: benefits and hazards; uses and abuses; knowns and unknowns. Speakers: Alex Gallus (12 min), Ross Baker (12 min), Emmanuel J Favalaro (5 min). Total 30 min.

Talk 3: Testing for antiphospholipid antibodies: lupus anticoagulant, anticardiolipin antibodies and anti-beta-2-glycoprotein-1. Which tests should we use and why? Speaker: Monica Galli. 30 min.

CLINICAL TRIALS GROUP REPORT

The ASTH Clinical Trials Group (CTG) met twice in Melbourne during the October HAA 2004 meeting. Unfortunately two small enthusiastic groups had independent discussions but failed to unite as planned on the day due to misunderstandings of the arrangements. Such is Murphy's Law of Trial Group Meetings!!!

The ASPIRE study has now moved out of the pilot phase into the fully-fledged study. This study examines the benefits of low-dose aspirin as prophylaxis against recurrent venous thrombosis after initial warfarin therapy in patients with unprovoked DVT or pulmonary embolism. There are 89 patients enrolled on ASPIRE and 20 or so enrolled in the Italian WARFASA study. There are now 20 active sites in Australia and New Zealand and the list of sites is being expanded to 50 sites over the next few months. The ASPIRE Executive continue to meet every 2 weeks and the International Trial Committee (current executive plus Prof G Agnelli, Prof A Gallus, Dr Paul Ockelford) has met twice and is being expanded. Progress toward opening the ASPIRE study in North America and some European countries is ongoing. We hope for a favourable response from the New Zealand HRC over the next month or so. The ASPIRE Investigators

meeting will be held on the Gold Coast QLD on 20-21st May 2005.

Investigators in the CTG are also busy with numerous industry-sponsored proposals. Many of these studies now involve novel anticoagulant drugs including fondaparinux sodium (the Van Gogh DVT PE and Extension studies, Organon & Sanofi-Synthelabo) and dabigatran etexilate (Revolution arthroplasty studies, Boehringer Ingelheim) to name only two. Other studies include PRODIGE (Extended prophylaxis with dalteparin in glioma patients) and the EXCLAIM study (Extended prophylaxis with enoxaparin in medical patients). These studies help contribute valuable resources for ASTH CTG investigators to explore and develop novel projects such as the ASPIRE study.

Lastly the ASTH CTG is always keen to receive new members and new ideas. Interested people or any enquiries may be directed to Tim Brighton (t.brighton@unsw.edu.au). The next ASTH CTG meeting is yet to be arranged but hopefully will occur during April-May 2005.

Tim Brighton

CONFERENCE REPORTS

A REPORT FROM THE INTERNATIONAL SYMPOSIUM ON WOMEN'S HEALTH ISSUES IN THROMBOSIS AND HAEMOSTASIS, BUDAPEST, FEBRUARY 2005

Hungary in early February is **cold**; cold enough to prompt second thoughts, as our small plane needed de-icing prior to take off. Cold enough to keep the snow lying on the ground and hordes of school children skating happily on a frozen lake. Cold enough to need a brisk pace on foot – and to really appreciate a spicy bowl of *gulyas* soup or a soak in one of Budapest's famous thermal baths. Hungary seems to have suffered more at the hands of its "allies" than its enemies and this turbulent history is a feature of the ancient capital. The inaugural two-day symposium on women's coagulation issues was held in a modern hotel on the banks of the Danube, beside the restored Chain Bridge, a casualty of the second World War. The 440 delegates exceeded the organiser's expectations, with 42 countries represented. Most were from Europe and Israel, with only 4 Antipodeans attending. Concurrent sessions were held throughout, on a wide range of haematology, obstetric and gynaecological problems.

Normal haemostasis was reviewed in both the mother and fetus. Brenner (Israel) noted the marked changes in factor levels and function during pregnancy, including a late rise

in TAFI, and explored the profound differences between endothelium and trophoblast, with regard to tissue factor expression. Manco-Johnson (Denver, USA) provided an elegant review of fetal haemostatic factors, based on human and sheep studies. The latter sheep model confirmed that fetal clearance of clotting factors was much faster, with implications for therapy of bleeding disorders in the neonatal period. Fetal fibrinogen, which persists until 3



weeks postpartum, is also different from the adult version, due to changes in sialation, phosphorylation and negative charge. Lee (London, UK) discussed the impact of inherited bleeding disorders on menstruation, and pregnancy outcome, including the confusing range of antenatal testing now available. She noted that carriers of haemophilia A/B may require recombinant factors for procedures if their levels are below 50 IU/dL. Haemophiliac neonates have a low overall risk of intracranial haemorrhage (1-4%) but this increases after vacuum extraction or instrumental delivery.

Strategies for diagnosing and treating menorrhagia were outlined by Kouides (Rochester, USA), who admitted using “anecdotal-based medicine” rather than EBM; the only reasonable trial data supports the use of tranexamic acid and the levonorgestrel-releasing IUD (Mirena), although the latter has a high drop-out rate due to spotting.

Moving on to more dramatic obstetric disasters, our own Claire McLintock (Auckland) reviewed the risk factors and management of post-partum haemorrhage. She reported three local cases where recombinant Factor VII was used for uncontrolled bleeding, and also pre-emptively in a coagulopathic woman with acute fatty liver of pregnancy needing Caesarian delivery. Reports of rFVIIa for obstetric bleeding are increasing, but the cases described to date have used a wide dose range and often needed hysterectomy. Administration of rFVIIa was associated with cessation of bleeding and there is only one report of thrombosis (ovarian vein) so far. The interface between pregnancy and DIC or microangiopathies such as TTP, was also discussed by Levi (Amsterdam) and Scheppenheim (Hamburg), respectively. Although levels of ADAMTS13 drop during late pregnancy, they don't reach the levels associated with TTP (<5%).

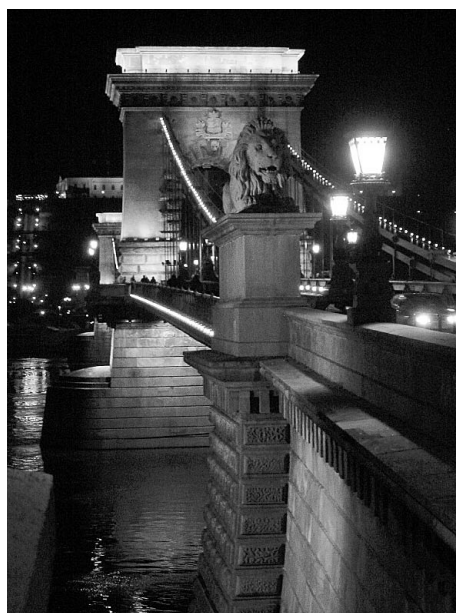
Thrombosis topics included the effects of hormonal contraception, IVF and hormone replacement therapy. LMWH have become the standard for therapy of VTE in pregnancy and Greer (Glasgow) presented reassuring data on safety from a meta-analysis of 64 reports (2777 patients). LMWH use in pregnancy (prophylactic and treatment doses) was associated with VTE rates of less than 1%, total bleeding rates of 1.8% with only 0.94% PPH, similar to untreated pregnancies. The most controversial aspect of the symposium was the link between thrombophilias and adverse fetal outcomes, where there remains far more supposition than science. More meta-analyses were presented, along with data suggesting that newer defects,

such as low Protein Z, may also contribute to risk. As the list becomes longer, global assays, such as the overall haemostasis potential (Antovic) or ProC Global (Sarig) are a more appealing way to predict individual risk. The results of intervention studies in women with recurrent pregnancy loss were presented: a French study of 174 women with RPL and documented thrombophilias observed a live birth rate of 85% in those randomised to enoxaparin (4000 IU/d), but only a 30% success rate in those on aspirin (Gris). However, these women were highly selected, from a cohort of almost 4,000 with unexplained pregnancy loss. While some delegates argued for dose adjusted LMWH in women with combined thrombophilic defects, there is insufficient evidence to support this. Brenner's Livenox study of 180 women with heterogenous defects and RPL found similar rates of live birth on 40mg (84%) versus

80mg (78%) enoxaparin. Clearly, we need prospective studies to avoid the severe selection bias in the literature; Lindqvist (Malmö, Sweden) expanded on his landmark prospective study on Factor V Leiden (FVL) women, with the finding that non-FVL APC resistance (but not FVL carriage!) increased the risk of second trimester fetal loss. There was an impassioned plea for placebo-controlled studies of RPL, before LMWH becomes the *de facto* “therapy” – at least two such studies are underway.

Finally, the scientific highlight of the meeting came from Weiler (Milwaukee, USA), whose group has shown the critical importance of

thrombomodulin (TM) and the Protein C pathway in fetal development. Trophoblast tissue can clearly regulate haemostasis, and its proliferation is controlled by thrombin. In previous transgenic mice work, a TM knockout proved to be embryonic lethal, whereas FVL mice showed normal fertility. A modified TM (TM-Pro) with reduced functional activity was then “knocked-in” and these mice crossed with the FVL strain. If the mother had FVL and the fetus carried TM-Pro, then fetal loss was 100%. Treating the mice with enoxaparin completely “rescued” these fetuses, but could not rescue those with a complete TM knockout. This animal study provides support for our emerging belief that heparins can improve fetal outcomes – most importantly, it confirms that both the fetal and maternal genotypes contribute to morbidity. Weiler's work dovetails nicely with the recent report (Girardi, Nature Med 10:1222) that heparins rescue fetal loss in antiphospholipid antibody model through inhibiting complement, rather than any anticoagulant effect. If so, then once again we have stumbled on the right therapy for the wrong reasons...



Chain Bridge, Budapest.

CONFERENCE REPORTS

A REPORT FROM THE INTERNATIONAL SYMPOSIUM ON WOMEN'S HEALTH ISSUES IN THROMBOSIS AND HAEMOSTASIS, BUDAPEST, FEBRUARY 2005 *Continued*

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This symposium provided a focus on a rapidly evolving area of coagulation (or inflammation) – one where appropriate intervention holds great promise for women and their offspring-to-be. We hope it will be the first of many such meetings; for now, the symposium proceedings

(*Thrombosis Research* 2005, 115, Suppl 1) and the JTH compilation issue on women's health make essential reading for all clottologists.

Chris Ward

26TH NATIONAL CONGRESS OF THE WORLD FEDERATION OF HAEMOPHILIA

The 26th National Congress of the World Federation of Haemophilia (WFH) was held in Bangkok from October 17th to 21st 2004.

The meeting was attended by 3800 participants and is a blend of Scientific and Medical content with consumer forums and organisational sessions for the WFH. Having heard of terrible traffic problems in Bangkok and the venue being a distance from the centre of Bangkok – I was concerned the meeting would be difficult, but was pleasantly surprised by the organisation and content.

The meeting was held in BITEC, a purpose built Convention Centre approx 15 km from the centre of Bangkok – if you can say there is a centre. Participants were ferried by bus to the Convention Centre – the morning trip took 30-45 minutes depending on the location of the hotel, but the return trip at 5.30pm took longer – with one stop at a set of traffic lights for 15 minutes!! And then caught in dense traffic 200 metres from the hotel and not able to get out as the door was blocked by other traffic.

Overall the Medical/Scientific sessions were well attended and informative. There were many highlights.

Ian Peake gave a preliminary report on the EU study in Type 1 VWD. This study has recruited 153 index cases with Type 1 VWD and undergone extensive phenotypic and genotypic assessment. The diagnosis of Type 1 was based on determination by individual centres in Europe. 67% of index cases have mutations in the VWF gene. A variety of mutations are found mostly missense with small numbers of deletions, splice site, and nonsense mutations. Mutations were identified across the gene with 9 common mutations and 22 other mutations. The Tyr 1584 Cys mutation, initially reported by the Canadians, was found in 8.3% of EU cases (23% of UK cases). The penetrance of the Y1584C mutation is estimated to be 85%. Sensitive multimer analysis demonstrated abnormal profiles in 33% of these Type 1 cases. Abnormal profiles were more likely to have lower VWF: Ag levels and a genetic mutation. Further information from this study and a similar Canadian study are awaited.

As the meeting was held in Bangkok, there was an emphasis on Haemophilia Care in developing countries where costs of factor concentrate can severely limit care. Dr Velandar summarised progress with transgenic livestock as a possible solution. Pigs appear to be the best producers of protein in milk, with appropriate posttranslational processing required to produce active protein. He suggested that a colony of 60 pigs could produce enough factor to supply the USA. With such abundant and possibly cheaper source of factor concentrate, oral use may be possible to allow prophylaxis.

Georges Rivard discussed delaying exposure to Factor VIII concentrates in infants to reduce the incidence of inhibitors. Some studies have demonstrated an increase in Factor VIII inhibitors if infants are exposed to Factor VIII early in infancy. Rivard proposed treating haemorrhagic episodes with Recombinant VIIa in the first 2 years compared to controls. The approach was minimally effective in delaying Factor VIII usage. Recombinant VIIa was less effective for mouth bleeds and haemarthrosis. There was no difference in inhibitor development between delayed exposure and routine treatment – but numbers in the study were low.

Lavery summarised Preimplantation Genetic Diagnosis (PGD) – at Hammersmith, London. He presented many difficulties with PGD – noting overall pregnancy rate of 20% in his cohort. At present PGD for Haemophilia is by sex selection, but there were two abstracts outlining PGD with direct mutation detection of point mutations – allowing normal male births.

Overall the meeting was very successful. It provides an interesting blend of science and consumer (patient) issues demonstrating the WFH approach to improving Haemophilia Care around the world – with development of Haemophilia Associations in each country and support for them in their discussions with government. The next meeting is in 2006 in Vancouver and will undoubtedly preview further advances in Haemophilia Care.

John Rowell

TIROFIBAN INDUCED THROMBOCYTOPENIA IS ASSOCIATED WITH DRUG DEPENDENT ANTIBODIES THAT CAUSE PLATELET ACTIVATION AND INCREASED ISCHAEMIC EVENTS

Scott Dunkley; Sue Evans; Leonie Gaudry; Nigel Jepson
Departments of Haematology and Cardiology, Prince of Wales Hospital

Background

Tirofiban induced thrombocytopenia is due to drug dependent antibodies (DDAb's). The frequency of thrombocytopenia has been reported less frequently than with other IIb/IIIa inhibitors. In such cases there is a higher incidence of myocardial infarction and mortality raising the possibility of platelet activation. We followed consecutive cases to determine the incidence of thrombocytopenia and confirmed that this was due to Tirofiban dependent antibodies. We then tested if these antibodies could cause platelet activation *in vitro* and correlated this with clinical outcome.

Methods and Results

In 871 treated patients, severe thrombocytopenia was

observed in 11 cases, an incidence of 1.26%. Tirofiban dependent antibodies were confirmed in all cases, using a flow cytometric assay. The effects of the patient serum (DDAb's) on platelet activation was analysed by measuring P-selectin (CD62p) and annexin V, in the presence or absence of Tirofiban, by flow cytometry. In addition, platelet activation was sought using the Serotonin release assay. In 5 cases there was evidence of platelet activation and this was significantly associated with further coronary ischaemic events.

Conclusion

Tirofiban induced thrombocytopenia due to DDAb's is a common occurrence and can lead to platelet activation and increased thrombotic events.

IDENTIFYING HYPERCOAGULABLE STATES WITH A SIMPLE GLOBAL COAGULATION ASSAY: OVERALL HAEMOSTATIC POTENTIAL (OHP)

Jenny Curnow, Marie-Christine Morel-Kopp, Margaret Aboud, Chris Ward
Haematology Dept, Royal North Shore Hospital

Hypercoagulable states typically result in arterial and/or venous thromboembolism. Affected patients are not identified by routine coagulation tests and thrombophilia testing detects, at best, 50% of patients at risk. We hypothesise that the OHP can differentiate patients with various hypercoagulable states from a control group. The OHP is a global coagulation assay of fibrin generation and lysis in citrated plasma. We established reference ranges with plasmas from 100 normal donors, then assayed plasmas from 90 clinically hypercoagulable patients being tested for a lupus anticoagulant. A further 81 patients with demonstrable antiphospholipid antibodies (APLAs) were then assayed. Statistical analysis involved calculation of means, medians, standard deviations and Mann-Whitney testing. All parameters tested were significantly different in the clinically hypercoagulable group ($p < 0.001$), demonstrating accelerated fibrin generation and markedly reduced fibrinolysis. On subgroup analysis patients with arterial (8) or venous

thromboembolism (30), antiphospholipid antibodies (9), normal or complicated pregnancy (22) and autoimmune diseases (12) all showed significantly increased fibrin generation and lysis compared with controls.

The subsequently tested 81 patients with APLAs also showed a significantly hypercoagulable OHP compared with controls ($p < 0.01$). APLA positive patients with thromboembolism showed a non-significant trend to accelerated fibrin generation and delayed fibrinolysis when compared to those without thromboembolism. APLA positive patients taking warfarin showed significant hypercoagulability when compared with APLA negative patients on long term warfarin therapy ($p < 0.01$). The OHP clearly identifies patients with clinically hypercoagulable states, even in the presence of warfarin. Fibrin generation is increased and fibrinolysis delayed. We postulate that the OHP may identify patients at high risk of thromboembolism.

OESTROGEN REGULATION OF THE ANTI-COAGULANT PROTEIN S

Hughes, Q., Staton, J., Watson, M. and Baker, R.
Royal Perth Hospital, University of Western Australia.

Aims

The anticoagulant Protein S (PS) is coded for by the PROS1 gene and serves as a co-factor to APC inactivation of FVa and FVIIIa. Previous Studies have shown a reduction in circulating PS levels with increasing oestrogen (E2) levels resulting in an increased thrombotic risk.

Methods

We have identified a potential oestrogen response element (ERE) spanning -350 → -367 within the 5'UTR of PROS1. Using an EGFP expression vector, clones containing this ERE, the entire 5'UTR (948bp) and the Sp1 binding site (-66 → -75) have been transfected into HepG2 cells and expression measured by flow cytometry.

Results

The ERE sequence alone was able to independently drive transcription. Surprisingly, the PROS1 5' UTR vector increased expression with increasing E2 levels.

Conclusions

These results suggest that the ERE is responsible for part, but not all, of the regulation of PS levels by E2. Further regulation is likely to be exerted by E2 regulated binding proteins. The discovery of an ERE in the PROS1 promoter and identification of previously undescribed (or novel) interacting proteins is a significant step forward in explaining the *in vivo* observation of E2s influence on circulating PS levels.

UPCOMING MEETINGS

MEETING	WHERE/DATES	CONTACT
10th International Myeloma Workshop	Sydney 10-14 April 2005	Myeloma 2005 Workshop Managers Tel: 61 2 9248 0800 www.myeloma2005.org
45th British Society of Haematology ASM	Manchester 11-13 April 2005	www.b-s-h.org.uk
XVIIIth International Symposium on Technological Innovations in Laboratory Haematology	San Francisco 11-14 May 2005	www.islh.org
Xth Congress of the European Hematology Association	Stockholm, Sweden 2-5 June 2005	www.ehaweb.org
Coagulation Testing Quality: Lessons and Issues from Quality Assessment, Standardization and Improvement Programs and Studies	Rochester, Minnesota, USA. 15-17 June 2005	Mayo Medical Laboratories' Education Department, toll free, at 800-533-1710, directly at 507-284-0286, or by fax at 507-284-8016.
AIMS National Scientific Meeting	Sydney 6-8 July 2005	www.aims.org.au
XXth Congress of the International Society of Thrombosis & Haemostasis (ISTH 2005)	Sydney 6-12 August 2005	www.isth2005.com
XXXth World Congress of The International Society of Hematology. ISH2005	Istanbul 28th Sept-2nd Oct 2005	www.ish2005istanbul.org
13th National Haemophilia Conference – Integrating Knowledge and Practice	Melbourne 30th Sept-2nd Oct 2005	www.haemophilia.org.au
3rd International Conference on Thrombosis and Hemostasis Issues in Cancer (ICTHIC)	Bergamo, Italy 14-16 October 2005	www.bergamoconference.com
HAA 2005 Annual Scientific Meeting	Sydney 16-19 October 2005	haa2005@fccventions.com.au
American Society of Hematology	New Orleans 3-6 December 2005	www.hematology.org