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To determine the prevalence of aspirin resistance and/or platelet hypersensitivity as determined by platelet aggregometry in Caucasian patients who have suffered one or more atherothrombotic cerebro-vascular accidents (CVAS) and/or transient ischaemic attacks (TIAS) as compared with control subjects

Bernstein, Penelope Lizetta

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TO DETERMINE THE PREVALENCE OF ASPIRIN RESISTANCE AND/OR PLATELET HYPERSENSITIVITY AS DETERMINED BY PLATELET AGGREGOMETRY IN CAUCASIAN PATIENTS WHO HAVE SUFFERED ONE OR MORE ATHEROTHROMBOTIC CEREBRO-VASCULAR ACCIDENTS (CVAS) AND/OR TRANSIENT ISCHAEMIC ATTACKS (TIAS) AS COMPARED WITH CONTROL SUBJECTS.

Dr Penelope Lizetta Bernstein

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine

in

the branch of Molecular Medicine and Haematology

Johannesburg, 2009

DECLARATION

I, Penelope Lizetta Bernstein declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Molecular Medicine and Haematology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….

…….. day of ……, 2009

DEDICATION

To my husband, Jeremy and my mother, Irene for their interest, support and encouragement.

To my grandparents, Professor Ralph and Dr Mary Bernstein, for instilling in me a love for medicine and academia.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Bernstein PL, Jacobson BF, Connor MD, Becker PJ. Aspirin resistance in South African Caucasian patients with thrombotic cerebrovascular events. *J Neuro Sci* 2009; 277: 80-82.

Poster presentation at the South African Society of Thrombosis and Haemostasis Annual Conference, November 2006.

ABSTRACT

Objective*:* Stroke is the second most common cause of death in most countries.[1] In South Africa, which has a population undergoing demographic and epidemiological transition, stroke is the third most common cause of death.[2] Platelet response to therapeutic doses is not uniform, although aspirin remains an essential part of treatment. Some patients exhibit aspirin resistance and develop secondary thrombotic events. It was decided to determine the prevalence of aspirin resistance and/or platelet hypersensitivity, as determined by platelet aggregometry, in sixty Caucasian patients who have suffered one or more strokes and/or Transient Ischaemic Attacks (TIAs) as compared with sixty control subjects.

Methods: Aspirin resistance was determined by platelet aggregation (>20%) to one or more of the four agonists, namely arachidonic acid (1.5mM), adrenaline (0.05μg/ml), collagen (0.2μg/ml) or ADP ($0.1x10^{-5}$M).

Results: Two patients demonstrated 'complete aspirin resistance' (non-responder to aspirin) with resistance to arachidonic acid (high concentration) noted. Three patients demonstrated 'partial aspirin resistance' (semi-responder to aspirin). One control subject showed 'complete aspirin resistance'. There is a 1.67% chance of a control subject being resistant to aspirin in a general South African Caucasian population. A history of prior stroke or transient ischaemic attack was associated with a statistically significant increase in risk of aspirin resistance with an odds ratio of 5.36.

Conclusion: These results essentially concur with those of the studied literature in showing an 8.3% prevalence (statistically significant) of aspirin resistance (complete and partial) in South

African Caucasian patients with previous atherothrombotic cerebrovascular events i.e.CVAs and/or TIAs. The current study shows an increased prevalence of aspirin resistance in people who have had prior strokes / TIAs and raises the question whether people who have had these events are somehow predisposed to vascular events or indeed recurrent vascular events. 'Aspirin resistant' patients or 'poor responders' to aspirin must be considered at heightened risk of atherothrombotic events and laboratory monitoring of antiplatelet therapy may become clinically useful.

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ABBREVIATIONS

AA	Arachidonic Acid
ADP	Adenosine Diphosphate
AMP	Adenosine Monophosphate
APACT2	Automated Platelet Aggregation
ATP	Adenosine Triphosphate
Ca^{2+}	Calcium
cAMP	cyclic Adenosine Monophosphate
CI	Confidence Interval
COX	Cyclooxygenase
CT	Computed Tomography
CVA	Cerebro-Vascular Accident
FBC	Full Blood Count
GP	Glycoprotein
HIV	Human Immunodeficiency Virus
LTA	Light Transmission Aggregometry
MI	Myocardial Infarct
MRI	Magnetic Resonance Imaging
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NSAID	Non-Steroidal Anti-Inflammatory Drug
PGI_2	Prostaglandin Inhibitor
PPI	Proton Pump Inhibitors
PPP	Platelet Poor Plasma

PRP	Platelet Rich Plasma
SOP	Standard Operating Procedure
TIA	Transient Ischaemic Attack
tPA	tissue Plasminogen Activator
TTP	Thrombotic Thrombocytopenic Purpura
TxA_2	Thromboxane A_2
TxB_2	Thromboxane B_2
VWF	Von Willebrand Factor