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Whole blood viscosity issues VI: Association with blood salicylate level and gastrointestinal bleeding

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Abstract

Background: This series on whole blood viscosity issues has been trying to elucidate the sensitivity, specificity and usefulness of the laboratory parameter in clinical practice. The postulation has been that since antiplatelet is used in the management of stasis, of which blood viscosity is an index, the latter would be useful laboratory indication and/or contraindication. **Aim**: The aim of this study was to observe whether blood level of acetylsalicylic acid differs with the level of whole blood viscosity. **Patients and Methods**: Out of the ten years database, 538 cases that were concomitantly tested for haematocrit, total proteins and blood level of salicylate were selected for this study. A separate nine cases of positive faecal occult blood tests were audited for blood viscosity and reviewed. **Results**: A statistically significant difference is observed with lower blood viscosity being associated with higher salicylate level in comparison of the former between the highest vs. lowest quartiles ($p < 0.002$). This observation demonstrates the effect of aspirin in lowering blood stasis. Reviewing the positive faecal occult blood cases indicate that gastrointestinal bleeding is characterized by relative hypoviscosity and that hyperviscosity is not present during bleeding complications. **Conclusion**: The findings affirm that whole blood viscosity is a valid clinical laboratory parameter for evidence-based contraindication, indication and monitoring of antiplatelet medication. It calls for better appreciation and clinical utility of whole blood viscosity, which (in the absence of viscometer) can now be extrapolated from haematocrit and total proteins.

Keywords: Antiplatelet, aspirin, bleeding complications, blood stasis, clinical laboratory, evidence-based practice, faecal occult blood, whole blood viscosity.

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Introduction

This series on whole blood viscosity issues has been geared towards elucidating the sensitivity, specificity and usefulness of the laboratory parameter in clinical practice. The postulation has been premised on the following succinct points:

- Antiplatelet is used in the management of cardiovascular disease predisposition and stasis in particular [1-3];
- Whole blood viscosity (WBV) as a laboratory parameter is an index of blood stasis [4-7];
- Clinical guidelines express concern over bleeding complications [8-10]. Therefore, laboratory assessment performed to provide such evidence would be evidence-based and good clinical practice.

Salicylate drugs constitute a subset of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), and are either acetylated or non-acetylated. Aspirin belongs to the group of acetylated salicylates. In clinical pathology, aspirin level in blood is assessed as therapeutic monitoring of salicylic acid by Biochemistry Specialists. It is imaginable that a drug that requires therapeutic monitoring using laboratory methods would also employ

the laboratory to determine indication or contraindication. However, this is not the case; as our preliminary evaluation indicated [11].

Bleeding or haemorrhages as a health issue of vascular complication is not unrelated to thrombotic events. However, haemorrhage is equally related to increased haematocrit and its concomitant increase in WBV. It is acknowledged that correction of haematocrit and WBV levels to normal values reduces the risk of thrombotic events [12]. This acknowledgement draws attention to the possible effect of correction of WBV level and clinical pathology index of haemorrhage, as well as potential complementarity of both indices.

The main concern against antiplatelet therapy is the risk of gastrointestinal (GI) bleeding vis-à-vis hemorrhage. In clinical pathology, one of the frontline readily available indices of GI bleeding is faecal occult blood test. Given (i) the effect of antiplatelet on blood viscosity and (ii) the impact of antiplatelet on GI bleeding as a side effect; it is imaginable that a therapeutic monitoring of aspirin would benefit from laboratory assessment of faecal occult blood test complemented with blood viscosity status. Therefore, it is imperative to ascertain the need for WBV as complementary clinical evidence–base tool and thereafter rearticulate whether effective antiplatelet medication is inseparable from, but in tandem with correction of WBV level.

More importantly, essential pathology tests that have yet to be established are recommended for patients who have acute coronary syndromes. This is in consideration of the integrated approach to the 2006 Australian guidelines [13], which recognize hemorrhage as contraindication to antiplatelet [9]. Apparently, the recommendation is without WBV in perspective probably because the laboratory parameter has yet to be validated for use in monitoring antiplatelet efficacy.

The aim of this study is to determine (i) whether blood level of acetylsalicylic acid differs with the level of whole blood viscosity, and (ii) if hyperviscosity is observable in conditions of gastrointestinal bleeding. The respective hypotheses investigated in this issue are that hyperviscosity would be (i) associated with low level of acetylsalicylate in blood and (ii) not observable in occasions of positive faecal occult blood. The findings that prove these hypotheses will corroborate with other reports to affirm that whole blood viscosity is not unspecific, but a valid laboratory parameter for evidence-based contraindication, indication and monitoring of antiplatelet therapies in clinical practice.

Patients and Methods

This work is part of Translational Biomedical Science Research initiative of Dr Uba Nwose. It is supported materially by the Albury South West Pathology – a unit of Western Pathology Cluster of NSW Health Australia. Ten years of de-identified archived clinical pathology data for the period of January 1999 to December 2008 constitute the research database, which was audited.

1,107 cases had results for serum salicylate, of which 538 were concomitantly tested from one phlebotomy collection point for haematocrit and total proteins to enable extrapolation of WBV values. Therefore, sample size for statistical analysis in this study constitute n=538 (female-male ratio = 331-207). Haematocrit results from the FBC were used in conjunction with total protein to extrapolate WBV values based on previously published algorithm [14].

Salicylate data for this study were determined according to the standard operational procedure (SOP) of the South West Pathology Service [15]. The SOP included quantitative measurement using the Dimensions® clinical chemistry systems (Dade Behring). Results of salicylate were reported with the following interpretative consideration:

- Analytical range 0.0 - 7.24mmol/L
- Reference range 1.1 -2.2mmol/L
- Toxic range >3.6mmol/L

In this study, numerical levels of Salicylate results have been used as reported. The data were ranked/sorted and categorized into quartiles by Salicylate concentration. Comparison of WBV levels using Student t-tests were performed between 1st vs. 4th quartiles. For proof of consistency in result, whether any statistical significance improve with increasing margin of ranked data, analysis was repeated between lowest [n=30] vs. topmost [n=30], and bottom vs. top halves.

For evaluation of WBV among people with evident gastrointestinal bleeding, nine cases (including six old cases and three consecutive recent (17th – 21st June 2010) cases of faecal occult blood, which had results for haematocrit and total protein to enable extrapolation of WBV were extracted for review. Two of the recent three cases included two cases of faecal cultures with red blood cells seen in stool microscopy.

Results

The summary statistics of data is presented in table 1. It shows that the study population includes persons with normal as well as abnormal levels of blood salicylate and viscosity (Table 1). From the very brief and simple statistical analysis, it is observed that the WBV level decreases with increasing salicylic acid concentration in blood (Table 2).

Table 1 Summary statistics of salicylate data

	Salicylate	WBV
Mean	0.22	16.61
Median	0.10	16.69
SD	0.37	1.72
Minimum	0.03	8.38
Maximum	4.20	21.17

Table 2 Summary of statistical comparison of whole blood viscosity level between ranks of salicylate concentration

Analysis	Mean WBV levels		Significance
	Higher	Lower	
Topmost vs. Lowest	16.11	18.19	$P < 0.0001$
4^{th} vs. 1^{st}	16.51	17.16	$P < 0.002$
Top vs. Bottom halves	16.40	16.82	$P < 0.01$

WBV: extrapolated whole blood viscosity at high shear rate (208 Sec^{-1}).

Faecal occult blood review is summarized in the following table (Table 3). Using the principal author's recommended reference range for WBV [14], cases 1 – 3, 5 and 9 presents with normoviscosity (15.01 – 19.01 ($208Sec^{-1}$)) while cases 4 and 6 – 8 presents with hypoviscosity (≤15.00 (208 Sec^{-1})). All patients are over 50 years old.

Table 3 Summary of fecal occult blood cases

Cases	Gender	WBV extrapolation			Faecal occult blood	
		HCT	TP	WBV	Chemical	Immuno'
1	M	42	81	18.46	Neg x3	Pos x3
2	M	45	74	17.63	Pos x2	Pos x3
3	F	41	72	16.64	Pos x1	Pos x1
4	F	29	69	14.86	Pos x2	Pos x2
5	F	39	63	15.04	Pos x1	Pos x1
6	F	35	63	14.56	Pos x1	Pos x1
7	M	25	56	12.17	Pos x1	Pos x1
8	M	32	60	13.69	**	
9	M	36	66	15.19		

HCT: haematocrit (%), Immuno': immunological method, TP: total proteins (g/L), WBV: extrapolated whole blood viscosity at high shear rate (208 Sec^{-1}). **Fecal occult blood not performed, but blood seen on stool microscopy.

On critical evaluation of the WBV results of recent cases, Case #7 had haematocrit and total protein 18months to be 44% and 73g/L respectively. This transcribes to WBV level of 17.34 (208 Sec^{-1}), which is normal. Case #9 had also previously presented haematocrit of 45%. From the extrapolation chart [14], 1% change in haematocrit amounts to 0.12 change in WBV. This transcribes the recent WBV level in Case #9 is just normal but could much higher if the haematocrit were normal.

Discussion

The mean and median WBV in the study population is in consonance with previous reports from this series that average blood viscosity in generally normal (Table 1). The result indicates that salicylate medication vis-à-vis aspirin reduces WBV level. Conversely and by default, lower or no salicylate would mean relatively higher WBV level (Table 2). This observation proves the hypothesis that antiplatelet – prophylaxis or therapeutic – in the scheme of CVD risk management is meant to reduce stasis, of which WBV is a clinical laboratory parameter. While this may have been implied or known [4-7], the contribution here is a demonstration that a clinical pathology method is available for evidence-based practice with regards to compliance to clinical guidelines. The importance and further demonstration is that in the absence of viscometer, WBV is assessable by extrapolation from haematocrit and total proteins results.

The observation is in consonance with other reports on pharmacologic effects of aspirin on blood viscosity [16]. Mannini and his group had reported that in patients with coronary diseases, the level of blood viscosity and its associated factors are modulators of the effects of aspirin [17]. It has also been identified that insufficient antiplatelet effect is tantamount to increased cardiovascular risk in patients taking regular doses of aspirin. The need to assess aspirin responsiveness with a view to identify non-responders has also been suggested [18]. This present report affirms the validity of WBV as a laboratory parameter for contraindication, indication and monitoring of aspirin and other antiplatelet medication. A determination of WBV level that is unchanged in the course salicylate therapy would be good indication of non-responsiveness to the medication.

The review of positive faecal occult blood cases shows that hyperviscosity is not present in condition of gastrointestinal bleeding. Although, normoviscosity is observable, hypoviscosity is a characteristic. The implication is that while positive faecal occult blood test may be insufficient to rule out hypoviscosity that would be contraindication of antiplatelet medication, WBV test could complement to confirm contraindication in the presence of need of clinical management. It also brings to the fore the implication that the concept of individualized reference may need to be employed in interpreting WBV results (Table 3). Every individual's WBV should be interpreted by comparing the haematocrit and/or total proteins against healthy-state routine check-up values.

Especially in colorectal cancer patients, aspirin as a NSAID is used with concerns for the gastrointestinal side-effects [19]. While faecal occult blood test is a widely accepted diagnostic index for gastrointestinal bleeding and a cost effective one [20-23], there is still the need to explore important factors that influence cost-effectiveness, as well as helpful in judging the general merit of a given medical strategy [23].

The issue addressed in this report is that antiplatelet complications and effectiveness would benefit from both faecal occult blood and WBV analysis. In patients who have results for full blood count and total proteins, assessment of WBV is at no additional cost. Yet, a result of hypoviscosity or hyperviscosity provides information whether aspirin is contraindicated or indicated respectively. For individuals with normoviscosity, a positive faecal occult blood test would provide evidence-base to indicate the need to seek alternative medication. The review of faecal occult blood is limited by sample size and selection. More case review as well as follow-up studies will benefit to affirm this report.

Conclusion

This short paper utilizing a brief and simple analysis

demonstrates the effect of aspirin in lowering blood stasis as indicated by blood salicylate and WBV respectively. It postulates that gastrointestinal bleeding is characterised by relative hypoviscosity and that hyperviscosity is not present during bleeding complications. WBV is a valid clinical laboratory parameter that is useful for contraindication, indication and monitoring of aspirin and other antiplatelet medication. It calls for better appreciation and clinical utility of whole blood viscosity, which in the absence of viscometer can now be extrapolated from haematocrit and total proteins.

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