Quantifying the Effect of Antiplatelet Therapy

A Comparison of the Platelet Function Analyzer (PFA-100®) and Modified Thromboelastography (mTEG®) with Light Transmission Platelet Aggregometry


Background: Antiplatelet therapy with aspirin and clopidogrel is known to confer protection against ischemic events. Increasing numbers of patients are presenting for surgery while taking these drugs. This may lead to an increase in perioperative blood loss, particularly in those who have a heightened response to the drugs, identifying these patients preoperatively would allow us to plan appropriate management.

Methods: The antiplatelet effect of aspirin and/or clopidogrel was measured using two point-of-care monitors: the platelet function analyzer (PFA-100®; Dade, Miami, FL) and the modified thromboelastograph (mTEG®; Haemoscope Corp., Niles, IL). This was compared with optical light transmission aggregometry.

Results: All people taking aspirin displayed a definitive aspirin effect on aggregometry (n = 20). Ninety percent of these were identified by modified thromboelastography (n = 18). Seventy percent were identified by the platelet function analyzer (n = 14). Fifty percent of people taking clopidogrel displayed a definitive response to the drug on aggregometry. Seventy percent of these were identified on modified thromboelastography (n = 7). None were identified by the platelet function analyzer. There was good agreement between the results of the aggregometry and modified thromboelastography in clopidogrel patients (κ = 0.81).

Conclusion: The search for a point-of-care monitor of platelet function has been the focus of much research. This study has shown that the modified thromboelastograph can be used for monitoring the effect of clopidogrel as well as aspirin. It potentially has a wide scope to be used for the monitoring of effectiveness of therapy as well as a possible predictor of perioperative bleeding.

ANTIPLATELET therapy with aspirin and/or clopidogrel is known to protect against vascular occlusive events including myocardial infarction, acute coronary syndrome, and stroke. In addition, some studies have shown an additional benefit when the drugs are taken together.2,5 Numerous patients presenting for surgery will be taking one or both of these drugs. It is common practice to stop them 7–10 days before surgery because of a perceived increase in perioperative bleeding. A number of studies (mainly in cardiac and vascular surgery) in patients taking aspirin or clopidogrel have demonstrated a trend toward increased blood loss and transfusion requirements.4–7 However, the evidence for this increase is not consistent or universal with further studies unable to demonstrate a significant effect.8–11

It is now becoming clearer that there is a spectrum of response to these drugs, with some patients having minimal change in platelet function (resistance) whereas others are “hyperresponders.”12–14 This variability in patient response may account for the fact that, although trends to increased blood loss are evident, not all patients seem to have the same bleeding risk when taking the same dose of antiplatelet drugs. There is also some concern that stopping antiplatelet therapy before surgery and allowing the recovery of platelet function may put the patient at an increased risk of ischemic events. In 2002, the French Society of Anesthesiology recommended that “the common practice of withdrawing antiplatelet agents [be] challenged because [of] an increased incidence of myocardial infarction in patients in whom treatment was interrupted.”15

The American College of Chest Physicians has also emphasized the need to continue preoperative medication including antiplatelet drugs in the perioperative period. In addition to this, there is a growing population with drug-eluting coronary stents who are at high risk for stent occlusion. They are usually recommended to continue taking both aspirin and clopidogrel in the year after stenting even when undergoing high-risk surgery.16

In light of this, it would be advantageous to have an effective method of monitoring the effects of antiplatelet drugs. Patients with profound inhibition of platelet function could be identified before surgery, and appropriate management could be planned in advance, including
QUANTIFYING THE EFFECT OF ANTIPLATELET THERAPY

Fig. 1. Diagram of action of the platelet function analyzer (PFA-100®). The PFA-100® simulates a vascular injury (left side). It measures the time taken for a platelet plug to occlude an aperture in a membrane that is impregnated with collagen and either epinephrine or adenosine diphosphate (right side). This is the closure time.

retesting platelet function after stopping therapy to ensure the return of platelet function.

Optical light transmission platelet aggregometry (LTA) is a well-established method that demonstrates the inhibitory effects of antiplatelet drugs.17,18 It is a well-recognized method demonstrating the effects of aspirin.19 A recent review discussing clopidogrel resistance quoted 10 studies where LTA had been used to demonstrate the effects of clopidogrel and described the method as the current “gold standard” for this purpose.20 Decreased platelet function demonstrated by LTA has been shown to be associated with an increase in perioperative blood loss.21 However, this method of monitoring is laboratory based and is too time-consuming to be routine.

There are two point-of-care techniques for assessing platelet function which may be more appropriate. These are the platelet function analyzer (PFA-100®; Dade, Miami, FL) and modified thromboelastography (mTEG®; Haemoscope Corp., Niles, IL).

The PFA-100® measures the time taken for a platelet plug to occlude an aperture in a membrane that is impregnated with collagen and either epinephrine or adenosine diphosphate (ADP). This is the closure time. Aspirin has been shown to increase the epinephrine closure time (C-EPI CT),22 while in some studies, clopidogrel has been shown to increase the ADP closure time (C-ADP CT).23–27 A recent review of the PFA-100® concluded that it “provides a rapid, simple and reliable measure of platelet function.”28

The thromboelastograph (TEG®) is a point-of-care coagulation monitor that readily demonstrates certain platelet aggregation defects including postcardiopulmonary bypass–induced platelet dysfunction related to GP IIb/IIIa receptors.29 However, conventional TEG®, because of the overwhelming presence of thrombin generation, is not able to detect the platelet adhesion and endothelial defects that occur with aspirin30–32 or demonstrate ADP receptor blockade. Patients using clopidogrel who had definitive platelet inhibition on aggregometry (and an 80% increase in the need for platelet transfusion after cardiac surgery) have been shown to have a normal maximum amplitude (MA) on conventional TEG®.32

A recent modification of the TEG® assay33 generates clot without thrombin generation using reptilase and factor XIIIa, therefore overcoming this limitation. The addition of platelet agonists (arachidonic acid or ADP) enables the measurement of the degree of platelet inhibition resulting from aspirin or clopidogrel, respectively. This is a novel technique that has only been described once in the literature. In this study of 43 patients, the mTEG® showed agreement with LTA.34

The primary aim of this observational study was to compare assessment of platelet function using LTA with both the PFA-100® and mTEG® in patients with known cardiovascular disease taking 75 mg/day aspirin and/or 75 mg/day clopidogrel. The secondary aim was to investigate whether the combination of atorvastatin and clopidogrel leads to decreased platelet inhibition, as has been previously suggested.34

Materials and Methods

After local ethics committee approval had been obtained (Royal Free Hospital Local Ethics Committee, London, United Kingdom), patients at routine cardiology or vascular surgery outpatient clinics were recruited. The study was explained, and written consent was obtained. Patients included were those with a history of ischemic heart disease or peripheral vascular disease, aged between 40 and 85 yr, who had been taking 75 mg/day aspirin and/or clopidogrel for more than 4 weeks. The following patients were excluded: those with a hemoglobin less than 10 g/dl, a platelet count less than 100 × 10⁹ or greater than 450 × 10⁹, clotting abnormalities (international normalized ratio > 1.1, family history of coagulation disorder), or renal impairment (creatinine > 100 μM); those receiving other drugs known to affect coagulation (e.g., warfarin, nonsteroidal antiinflammatory drugs); and those from whom consent was not obtained.

Blood Sampling

Before blood samples were obtained, demographic data were obtained, including diagnosis, current medication, and duration of time on antiplatelet therapy. Venous blood was sampled from the antecubital fossa via a 21-gauge needle into evacuated tubes (S-
Monovette, Starstedt, Germany) for full blood count, von Willebrand antigen levels, mTEG®, PFA-100®, and platelet aggregation. The tubes for the mTEG® analysis contained heparin, 10–30 U/ml blood; the sample for full blood count analysis was taken into a 0.134 M EDTA-containing bottle. All other samples were taken into tubes containing 0.106 M buffered sodium citrate solution.

The PFA-100® and mTEG® tests were performed after training in the Department of Haemophilia by the main author. The von Willebrand factor antigen and LTA were performed by the Department of Haemophilia laboratory manager, who has run the laboratory and performed these tests for many years.

**PFA-100® Assays**

Blood specimens for PFA-100® assays were tested according to manufacturer’s instructions after 30 min and within 4 h of the blood being drawn. For quality control, the PFA-100® self-test procedure was run when samples were analyzed to ensure adequate performance. Testing was performed using citrated whole blood with collagen–epinephrine and collagen–ADP cartridges.

Whole blood is aspirated under conditions of high shear stress through a 150-μM aperture covered with a membrane impregnated with collagen and one of two agonists: epinephrine or ADP. The time taken to occlude the aperture by a platelet plug is reported as closure time (CT). Maximum CT is 300 s; any value greater than this is reported as nonclosure.

Many factors may affect the results given by the PFA-100®, including the von Willebrand factor antigen levels. Previous studies have shown that people with higher levels of von Willebrand factor antigen have lower closure times.35,36

The results for the PFA-100® were divided into three groups: We defined a definitive response as those with a maximum CT of 300 s, a partial response as those with a CT greater than normal but less than 300 s, and a lack of response as a normal CT.

**Modified TEG® Assays**

Blood specimens for the mTEG® were tested after 30 min and within 2 h of the blood being drawn to obtain consistent results.37 Testing was performed using heparinized whole blood. The sample for the native TEG® was added to heparinase to neutralize the effects of the heparin as per the manufacturer’s instructions. This was then added to kaolin and run as a standard sample to measure total platelet function (fig. 2, outer trace).

The mTEG® assay uses reptilase and factor XIIIa to form a clot without thrombin generation in heparinized whole blood. Two traces are run concurrently: One is of heparinized whole blood treated with activator F (reptilase and factor XIIIa) 10 μl, which measures the contribution of fibrin to the MA (fig. 2, inner trace), and the second is of heparinized whole blood with 10 μl activator F and 10 μl agonist (fig. 2, middle trace). The results for the PFA-100® were divided into three groups: We defined a definitive response as those with a maximum CT of 300 s, a partial response as those with a CT greater than normal but less than 300 s, and a lack of response as a normal CT.

**Platelet Aggregation Assays**

Platelet-rich plasma was prepared by centrifugation of citrated whole blood for 15 min at 900 rpm. Platelet-poor plasma was prepared by the centrifugation of the platelet-rich plasma–deficient blood at 3,000 rpm for 12 min. After a 30-min rest period, aggregation was performed using a Payton Platelet Aggregometer (Buffalo, NY). The 100% line was set using platelet-poor plasma, and the 0% baseline established with platelet-rich plasma. Agonists were then added to stimulate aggregation: 1 mg/ml arachidonic acid and 2, 2.5, 3, and 5 μM ADP (final concentration). For the analysis, 5 μM ADP was used, as has been used in previous studies.

Regular aspirin ingestion is known to lead to no response to stimulation by arachidonic acid and a first-phase-only response to ADP. Recent studies have shown clopidogrel to cause little or no response to physiologic ADP and first phase only to high-dose ADP (5 μM or above), with a normal response to arachidonic acid.7

---

AGARWAL ET AL.

Anesthesiology, V 105, No 4, Oct 2006
In this study, we defined a response to aspirin as less than 10% aggregation to arachidonic acid stimulation by LTA, as has been defined in other studies.38 There is a lack of consensus regarding the definition of clopidogrel response on LTA. In this study, all those with less than 20% aggregation to all concentrations of ADP were regarded as showing definitive clopidogrel effect. Those with greater than 50% aggregation to 5 μM ADP were classed as showing clopidogrel resistance. For those that fell between the two definitions, the aggregation traces were examined. Those with between 20% and 50% aggregation to 5 μM ADP but showing only a first-phase response were categorized as having a moderate clopidogrel response; those that demonstrated a second-phase response were categorized as clopidogrel resistant.

Statistical Analysis
All statistical analysis was performed using SPSS version 11.0. (Chicago, IL) Agreement between tests was determined by κ analysis. This provides a measure of the degree of agreement of tests when the results are sorted into categories. A κ value of less than 0.20 indicates poor agreement, between 0.2 and 0.4 indicates fair agreement, between 0.41 and 0.6 indicates moderate agreement, and greater than 0.61 indicates good agreement.39

Results
Ten normal volunteers were analyzed. All of these people had greater than 80% aggregation on LTA to both arachidonic acid and ADP (5 μM). All had less than 20% inhibition demonstrated on mTEG® (arachidonic acid and ADP) and PFA-100® CTs within our laboratory’s normal range for both collagen–epinephrine and collagen–ADP.

Aspirin
Twenty-seven patients who were taking aspirin were recruited, all of whom had PFA-100® and mTEG® tests conducted and 20 of whom had LTA performed. Table 1 shows the range of the values of the results of these tests.

For the 20 patients with complete sets of tests, the results were categorized by response to aspirin as described in the Materials and Methods section. Table 2 shows the results by category. Twenty of those who had LTA performed showed a definitive response to aspirin (less than 10% aggregation to 1 mg/ml arachidonic acid). Ninety percent (n = 18) of these were shown to have a definitive response to aspirin on mTEG® (as defined above) and therefore agreed with the LTA. Two people who demonstrated platelet inhibition on LTA showed no inhibition on mTEG®. Kappa analysis was unsuitable for use because of the number of zero values.

Seventy percent of these patients (n = 14) demonstrated a maximal prolongation of C-EPI CT on PFA-100® (indicative of platelet inhibition) in agreement with LTA. Of the remaining six patients, one demonstrated a partial response to aspirin on PFA-100®, and five (25%) showed no response (C-EPI CT within the normal range). Again, κ analysis was unsuitable for use. However, all of those found to have maximal prolongation of C-EPI CT were shown to have greater than 50% inhibition on mTEG®. Kappa analysis showed a moderate agreement between the PFA-100® and mTEG® in these patients (unweighted κ = 0.42; quadratically weighted κ = 0.47; additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org).

There was no correlation between either C-EPI CT or C-ADP CT and the von Willebrand factor antigen levels in these patients (for C-EPI CT, r = 0.04; for C-ADP CT, r = 0.05; n = 27).

Clopidogrel
Twenty-eight patients who were taking clopidogrel were recruited, all of whom had PFA-100® and mTEG® tests conducted and 20 of whom had LTA performed. Table 3 shows the range of the values of the results of these tests.

Table 1. Results of PFA-100®, mTEG®, and LTA in People Taking 75 mg Aspirin

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Reference Range</th>
<th>Median</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-EPI CT, s</td>
<td>27</td>
<td>77–163</td>
<td>300</td>
<td>147.5–300</td>
</tr>
<tr>
<td>% Platelet inhibition on mTEG®</td>
<td>27</td>
<td>&lt; 20</td>
<td>92.6</td>
<td>74.6–100</td>
</tr>
<tr>
<td>% Platelet aggregation on LTA arachidonic acid</td>
<td>20</td>
<td>&gt; 80</td>
<td>5.0</td>
<td>3–6.5</td>
</tr>
</tbody>
</table>

C-EPI CT = collagen–epinephrine closure time; LTA = light transmission aggregometry.

Table 2. Results of Aspirin Patients by Category of Response to Aspirin (n = 20)

<table>
<thead>
<tr>
<th>Test</th>
<th>No Response to Aspirin, %</th>
<th>Partial Response to Aspirin, %</th>
<th>Definitive Response to Aspirin, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA to arachidonic acid</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>PFA-100® (C-EPI CT)</td>
<td>25</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>mTEG® (AA)</td>
<td>10</td>
<td>0</td>
<td>90</td>
</tr>
</tbody>
</table>

AA = arachidonic acid; C-EPI CT = collagen–epinephrine closure time; LTA = light transmission aggregometry.
For the 20 patients with complete sets of tests, the results were categorized by response to clopidogrel as described in the Materials and Methods section. Table 4 shows the results by category. Of 20 patients who had LTA performed, only 50% (n = 10) showed a definitive response to clopidogrel, 15% (n = 3) showed a partial response, and 35% (n = 7) showed resistance to clopidogrel. Of the 10 patients who had a definitive response to clopidogrel on LTA, 7 demonstrated a definitive response to clopidogrel on mTEG®, whereas 3 had a partial response. Six of the 7 people with no response to clopidogrel demonstrated on LTA were identified as having little or no response on mTEG®. In all, there were 14 agreements out of 20. Kappa analysis demonstrated good agreement between the results of the mTEG® and LTA with a quadratically weighted $\kappa$ of 0.81 (additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org).

The PFA-100® was abnormal in only two people taking clopidogrel. Both of these people had inhibited platelets as shown by LTA. However, there was no agreement between the results of the PFA-100® with either aggregation or mTEG®.

Five of the 28 patients taking clopidogrel were also taking atorvastatin. There was no significant difference between the platelet inhibition in these patients compared with those not taking atorvastatin. There was no correlation between the C-EPI CT or the C-ADP CT and the von Willebrand factor antigen levels in these patients. (for C-EPI CT, $r = 0.01$; for C-ADP CT, $r = 0.14$; n = 28).

**Combination Therapy**

Eleven patients who were taking both aspirin and clopidogrel were studied. Table 5 shows the range of the values of these results.

Table 6 shows the results of the 10 patients with complete sets of results when categorized by degree of response. LTA showed all the patients on both drugs to have profoundly inhibited platelets to stimulation with both arachidonic acid and ADP (all concentrations). This profound inhibition was seen on mTEG® using arachidonic acid stimulation in all patients and in 5 subjects using ADP stimulation (table 6). The PFA-100® demonstrated inhibition when using the epinephrine cartridge—as shown with the aspirin patients—but not with the ADP cartridge.

There was no correlation between the closure times and the von Willebrand factor antigen levels in these patients (for C-ADP CT, $r = 0.561$; for C-ADP CT, $r = -0.269$, n = 11).

**Discussion**

The primary aim of this study was to compare assays of platelet function using LTA with both the PFA-100® and mTEG® in patients with known cardiovascular disease taking 75 mg/day aspirin and 75 mg/day clopidogrel.

Aspirin is a nonsteroidal antiinflammatory drug that leads to irreversible acetylation of platelet prostaglandin synthetase. This leads to irreversible inhibition of the production of thromboxane A2—a vasoconstrictor and proaggregant. Aspirin has been shown to increase perioperative blood loss and transfusion requirement, although not in all patients.5,7,9,10 This is possibly because there is a spectrum of response to aspirin, with some having no response at all, whereas others become hypocoagulable.11-42

Clopidogrel, a prodrug, is a thienopyridine derivative that, when active, acts via irreversible ADP antagonism at the P2Y12 receptor on the platelet surface, thus preventing platelet aggregation. Metabolic steps that involve cytochrome P450-dependent pathways are required to generate the active metabolite responsible for in vivo activity. Hence, differences in the action of P450, including genetic differences and drug-induced ones, as well as genetic differences in receptor activity, lead to a variety of responses to a standard 75-mg dose. In partic-

---

**Table 3. Results of PFA-100®, mTEG®, and LTA in People Taking 75 mg Clopidogrel**

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Reference Range</th>
<th>Median</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-ADP CT, s</td>
<td>28</td>
<td>64–114</td>
<td>92</td>
<td>77.5–113</td>
</tr>
<tr>
<td>% Platelet inhibition on mTEG®</td>
<td>28</td>
<td>&lt; 20</td>
<td>33.3</td>
<td>20.7–58.2</td>
</tr>
<tr>
<td>% Platelet aggregation on LTA to 5 $\mu$m ADP</td>
<td>20</td>
<td>&gt; 80</td>
<td>48.0</td>
<td>24.5–73</td>
</tr>
</tbody>
</table>

ADP = adenosine diphosphate; C-ADP CT = collagen–ADP closure time; LTA = light transmission aggregometry.

**Table 4. Results of Clopidogrel Patients by Category of Response to Clopidogrel (n = 20)**

<table>
<thead>
<tr>
<th>Test</th>
<th>No Response to Clopidogrel, %</th>
<th>Partial Response to Clopidogrel, %</th>
<th>Definitive Response to Clopidogrel, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA to 5 $\mu$m ADP</td>
<td>35</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>PFA-100® (C-ADP)</td>
<td>90</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>mTEG® (ADP)</td>
<td>40</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

ADP = adenosine diphosphate; C-ADP CT = collagen–ADP closure time; LTA = light transmission aggregometry.
ular, atorvastatin is thought to inhibit its action.\textsuperscript{54} In contrast to previous work in this study, atorvastatin did not seem to interfere with the action of clopidogrel, although the numbers here were small (n = 5).

Clopidogrel has been shown to increase perioperative bleeding, particularly in cardiac surgery.\textsuperscript{4,5,32} A recent study in cardiac patients demonstrated a significant increase in bleeding and transfusion requirement in patients undergoing coronary artery grafting on bypass.\textsuperscript{43}

There is no ideal method of assessing platelet function. LTA is one of the standard methods used in hemostasis laboratories. However, it is poorly standardized across laboratories, particularly in terms of the use of various types and concentrations of agonists to demonstrate drug effect, and therefore, it is difficult to compare the results from different hospitals. It also requires a specialist laboratory and is unlikely to be able to be used in widespread clinical practice. However, previous studies have demonstrated an association between marked platelet inhibition shown on LTA and increased perioperative blood loss.\textsuperscript{20,21}

Previous work has demonstrated the spectrum of response to aspirin by using the PFA-100\textsuperscript{\textregistered},\textsuperscript{22,30} Some studies have shown that up to 40% of people taking a standard 75-mg dose of aspirin may have a normal closure time, whereas up to 20% may have a maximal C-EPI CT. However, the PFA-100\textsuperscript{\textregistered} has not been successful in showing differences in response with clopidogrel.\textsuperscript{6,28} No data as yet have been published showing the mTEG\textsuperscript{\textregistered} to be of benefit in assessing the platelet function of these patients.

In contrast to previous studies,\textsuperscript{7,12,18} we did not demonstrate large variability in the response to a single daily 75-mg dose of aspirin; all patients had significant platelet inhibition shown on LTA. Ninety percent of these showed greater than 50% platelet inhibition of the MA on mTEG\textsuperscript{\textregistered}. This is a novel method of monitoring platelet function that stimulates the platelets in a blood sample to aggregate with the addition of an agonist—in this case, arachidonic acid. It should therefore produce similar results to LTA, and this study has demonstrated good agreement. The PFA-100\textsuperscript{\textregistered} also showed good agreement with LTA in aspirin takers—70% of patients also demonstrated a definitive response to aspirin.

The existence of a “hyperresponse” to aspirin is of concern to surgeons and anesthetists alike because of the increase in perioperative blood loss in patients who are profoundly hypocoagulable.\textsuperscript{5,7,10,20} Previous work has attempted to define the hyperresponse in terms of the C-EPI CT on PFA-100\textsuperscript{\textregistered} with the usual definition being a C-EPI CT of greater than 300 s.\textsuperscript{44–46} Our study demonstrated that 70% of subjects (14 of 20) had a CT of greater than 300 s.

A large variability in response to clopidogrel was demonstrated in this study, as was expected from other work.\textsuperscript{42,47} Gurbel et al.\textsuperscript{47} found a wide variability in platelet inhibition using aggregation and platelet receptor expression and concluded that “the response to clopidogrel therapy is heterogeneous and that resistance occurs.” There are no standard definitions of the response to clopidogrel shown on LTA in the literature. Many studies have used a supraphysiologic strength of ADP ranging from 5 to 20 $\mu$M.\textsuperscript{35} For this work, we assessed the response to four standard concentrations of ADP, ranging from 2 to 5 $\mu$M. For the analysis, we chose 5 $\mu$M—a supraphysiologic strength used in some of the previous work.\textsuperscript{35}

Assessing the response shown on LTA using 5 $\mu$M ADP,
we found that only 50% of patients (10 of 20) had platelet inhibition with clopidogrel. Importantly, 35% (n = 7) had virtually no response to the drug at all. The mTEG® was effective at identifying these patients with good agreement demonstrated between the two tests. The PFA-100®, as has been shown in previous studies, was ineffective at showing this variability in response.6 It has been speculated that this could be because the PFA-100® cartridge has a high concentration of ADP—equivalent to 50 μM.

This work confirms the findings of other studies that have shown wide variability in response to antiplatelet medication when taken alone with a more profound effect when aspirin and clopidogrel are combined.48,49 The effect of this combination is usually additive, although, unpredictably, it may be synergistic.49

All 10 patients taking both drugs had profoundly inhibited platelets shown on LTA. Both the mTEG® and the PFA-100® were effective in showing this when using arachidonic acid/C-EPI CT; the ADP-based tests were less successful. Compared with when the drugs were taken alone, the percentage inhibition shown on mTEG® increased when the drugs were taken together.

These results confirm that in high-risk patients such as those with drug-eluting coronary stents, combination therapy may provide increased platelet inhibition and hence better protection.

The search for a point-of-care monitor of platelet function has been the focus of much research. The PFA-100® has been proposed as such a monitor, particularly in cardiac surgery.22,25–27 Certainly, it may be useful in monitoring aspirin, although the definitions of hypore- sponse and hyperresponse may need some revision; however, this study has confirmed that it is not sensitive enough to detect platelet dysfunction due to clopidogrel therapy.

This preliminary study has shown that the modified TEG® can be used for monitoring the effect of clopidogrel as well as aspirin. It shows good agreement with light transmission aggregometry. As an easy-to-use point-of-care monitor that gives results within an hour, it potentially has a wide scope to be used for the monitoring of effectiveness of therapy as well as a possible predictor of perioperative bleeding. Although further studies are required before categorical guidelines can be given, it is possible that the test could be used to help determine the time of surgery after a return of platelet function has been demonstrated.

As yet, there are no data that predict at what level of platelet inhibition bleeding is likely to occur or when it is safe to perform invasive procedures. It seems likely that patients with an excessive level of platelet inhibition are at most risk of increased perioperative bleeding, and those with little demonstrable inhibition are at least risk. This hypothesis requires validation in clinical trials.

References


PTCA during and after infusion of c7E3 Fab in the presence of other antiplatelet agents. Thromb Haemost 2000; 83:540–4
32. Tanaka KA, Szlam F, Kelly AB, Vega JD, Levy JH: Clopidogrel (Plavix) and cardiac surgical patients: Implications for platelet function monitoring and post-operative bleeding. Platelets 2004; 15:325–32
34. Clarke TA, Waskell LA: The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. Drug Metab Dispos 2003; 31:53–9

Anesthesiology, V 105, No 4, Oct 2006