

REGIONAL ANAESTHESIA

Determination of residual antiplatelet activity of clopidogrel before neuraxial injections[†]

H. T. Benzon^{1*}, R. J. McCarthy¹, H. A. Benzon⁴, M. C. Kendall¹, S. Robak¹, P. F. Lindholm², P. G. Kallas³ and J. A. Katz¹

¹ Department of Anesthesiology, ² Department of Pathology and ³ Department of Medicine, Northwestern University Feinberg School of Medicine, 251 E. Huron, Feinberg Pavilion, Suite 5-704, Chicago, IL 60611, USA

⁴ Department of Anesthesiology, Children's Hospital Boston, Boston, MA 02115, USA

* Corresponding author. E-mail: hbenzon@nmff.org

Editor's key points

- Management of antiplatelet therapy in patients undergoing neuraxial injections is controversial.
- The time course for recovery of platelet function was monitored in 13 patients undergoing epidural steroid injection.
- All subjects had <30% platelet inhibition after discontinuation of clopidogrel for 5 days.
- This small preliminary study suggests that 5 days might be sufficient for platelet recovery after clopidogrel before a neuraxial injection.

Background. Guidelines recommend discontinuation of clopidogrel for 7 days before a neuraxial injection, while other directives suggest that 5 days might be adequate. We examined the time course of antiplatelet activity after clopidogrel discontinuation in patients undergoing epidural injections.

Methods. Thirteen patients were studied at baseline, 3, 5, and 7 days after discontinuation of clopidogrel. P₂Y₁₂ determinations were performed using the VerifyNow[®] assay (Accumetrics, San Diego, CA, USA), and clot closure times with stimulation by collagen/epinephrine and collagen/adenosine diphosphate using the PFA-100[®] (Platelet Function Analyzer, Siemens Diagnostics, Deerfield, IL, USA). Repeated-measures ANOVA was used to evaluate P₂Y₁₂ platelet reaction units, PFA-100 closure times, and per cent P₂Y₁₂ inhibition values. Wilcoxon's signed-rank test was used to compare the frequencies of ≥30%, 11–29%, and ≤10% platelet inhibition between the baseline and subsequent sampling points after discontinuation of clopidogrel.

Results. On day 3 after clopidogrel discontinuation, two subjects had ≥30%, seven subjects had 11–29%, and four subjects had ≤10% platelet inhibition; the corresponding numbers were 0, 3, and 10 subjects on day 5 ($P=0.04$). There were no differences between the ≥30%, 11–29%, and <10% platelet inhibition groups between days 5 and 7 (0, 0, and 13 subjects, $P=1.0$). PFA-ADP closure times were normal throughout the study period except in one patient.

Conclusions. These findings support the recommendation that discontinuation of clopidogrel for 5 days allows >70% of platelet function and might be adequate before a neuraxial injection is performed.

Keywords: coagulation; complications; epidural

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Clopidogrel is P₂Y₁₂ ADP platelet receptor inhibitor that is used after coronary stent placement and for stroke prevention.^{1 2} Guidelines suggest that clopidogrel should be stopped 5 days before surgery to allow full platelet recovery.^{3 4} The consensus guidelines of the American Society of Regional Anesthesia (ASRA), Belgian Association for Regional Anesthesia Working Party on Anticoagulants and Central Nerve Blocks, and the German Society of Anaesthesiology and Intensive Care Medicine recommend discontinuation of clopidogrel for 7 days before a neuraxial injection.^{5–7} However, the 2010 guidelines of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine suggest that 5 days of

discontinuation of clopidogrel is adequate before a neuraxial block.⁸ There have been case reports of uneventful neuraxial injection or catheter removal within 5 days of stopping clopidogrel.^{9–11} This prospective observational study evaluated the time course of residual antiplatelet activity and the time required for clot formation after clopidogrel discontinuation in patients presenting for epidural steroid injections.

Methods

After approval of the Institutional Review Board of Northwestern University, written informed consent was obtained from patients receiving chronic clopidogrel therapy and

[†]This article is accompanied by Editorial II.

undergoing epidural steroid injections without epidural catheter placement. Clopidogrel was discontinued after consultation with their cardiologist or neurologist. Blood was withdrawn into citrated tubes the day before (baseline) and at days 3, 5, and 7 after discontinuation of clopidogrel. A platelet count was performed on the baseline sample. Patients with platelet count $<100\,000\ \mu\text{L}^{-1}$, history of a coagulopathy, serum creatinine $>2.0\ \text{mg}\ \text{dL}^{-1}$, liver function test >2 times the upper normal limit, or the current use of anticoagulants including warfarin, direct factor Xa inhibitors, low-molecular-weight heparin, heparin, and drugs inhibiting platelet function other than aspirin and clopidogrel were excluded. Concomitant aspirin was continued or discontinued based on mutual agreement with the primary physician.

Inhibition of platelet function by clopidogrel was determined using the VerifyNow® (Accumetrics, San Diego, CA, USA) assay. The instrument measures platelet-induced aggregation as an increase in blood light transmittance induced by ADP/prostaglandin E1 as activated platelets bind to fibrin-coated microbeads. Using a proprietary algorithm, the system reports values as platelet reaction units (PRU). In a second channel, baseline platelet function (BASE) is simulated by evaluating light transmittance of blood stimulated with iso-TRAP (thrombin receptor-activating peptide), PAR4-AP (PAR4-activating peptide), and fibrin-coated microbeads. Based on these results, platelet inhibition (%) is calculated using the formula $(1 - \text{PRU}/\text{BASE}) \times 100$.¹² Similar to Muller and colleagues,¹³ we considered $<10\%$ platelet inhibition as no-response, between 11% and 29% inhibition a partial response, and $\geq 30\%$ inhibition responsive to clopidogrel platelet inhibition. Platelet inhibition of $<20\%$ has been considered as a sign of platelet recovery.¹⁴ Consideration of platelet inhibition of $\leq 20\%$ as acceptable for neuraxial injection leaves a small degree of residual anticoagulation as a compromise between the risk of haemorrhagic complications and the risk of thrombosis.¹⁵

The decay of antiplatelet effect of clopidogrel was also evaluated with the PFA-100® (Platelet Function Analyzer, Siemens Diagnostics, Deerfield, IL, USA) assay. The PFA-100® system measures the time required for occlusion of an aperture by citrated blood aspirated at high shear rates through a membrane coated with platelet activators. Tests were performed with both collagen/epinephrine (PFA-EPI) and collagen/adenosine-5-diphosphate (PFA-ADP) membranes. Closure times for PFA-EPI [increased by aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)] and PFA-ADP (variably affected by ADP receptor disorders and clopidogrel) were determined.¹² Reported normal reference ranges of the PFA-EPI assay are 93–223 and 64–117 s for PFA-ADP.¹⁶ The cut-off value for residual cyclooxygenase-1 antiplatelet activity was defined as ≥ 166 s for PFA-EPI.¹⁷

Sample size calculations were performed using Power Analysis and Sample Size (PASS) 2008 (Version 8.0.15 release date September 8, 2010, NCSS LLC, Kaysville, UT, USA). A sample of 13 in a design with four repeated measurements having a compound symmetry covariance structure achieves an 83% power to detect a difference of

10% in platelet inhibition when the standard deviation (sd) is 10% and the correlation between observations on the same subject is 0.7 at an α of 0.05. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the hypothesis of normal distribution. Repeated-measures ANOVA was used to evaluate PRU, PFA-100 closure times, and per cent inhibition values at the baseline and at the third, fifth, and seventh day of discontinuation of clopidogrel. Pair-wise comparisons of estimated marginal means were made using the Bonferroni corrected paired *t*-tests. The Wilcoxon signed-rank test was used to compare the number of samples with $\geq 30\%$, 11 – 29% , and $\leq 10\%$ inhibition between the baseline and subsequent time points. *P*-values for paired comparisons were corrected using the Bonferroni method. Data are presented as mean (sd) or median (inter-quartile range, IQR). Data were analysed using R version 2.13.0 (release date April 13, 2011, The R Foundation for Statistical Computing).

Results

Thirteen patients completed the study (Table 1). Subjects had been taking clopidogrel for an average of 2.7 (1.6) yr with a median of 2 (1–5) yr before discontinuation. Seven of the 13 patients were also taking aspirin; two patients continued aspirin therapy during the study. Mean baseline platelet counts were $176\ (57) \times 10^9\ \text{litre}^{-1}$ with a median of $167\ (146\text{--}188) \times 10^9\ \text{litre}^{-1}$. P_2Y_{12} PRU and inhibition values at baseline and after discontinuation are shown in Figure 1 and Table 2. At discontinuation of clopidogrel, seven patients were responders with platelet inhibition $>30\%$, four were partial responders with platelet inhibition of 11 – 29% , and two patients were non-responders with platelet inhibition $\leq 10\%$.¹³ Three days after clopidogrel discontinuation, two, seven, and four subjects demonstrated $\geq 30\%$, 11 – 29% , and $\leq 10\%$ platelet inhibition, respectively, which was not different from the baseline ($P=0.18$). By day 5, 0, 3, and 10 subjects demonstrated $\geq 30\%$, 11 – 29% , and $\leq 10\%$ platelet inhibition, respectively, which was different from day 3 ($P=0.04$). On day 5, platelet inhibitions in the three patients who were partial responders were 16% , 13% , and 20% . On day 7, all subjects had inhibition values $\leq 10\%$, which was not different from day 5 ($P=1.0$). There were no statistical differences between the P_2Y_{12} PRU inhibition values on days 5 and 7 after clopidogrel discontinuation.

PFA-100 assay values are shown in Table 2. There were no differences from baseline values in mean closure times for either the PFA-EPI or PFA-ADP assay at any time after discontinuation of clopidogrel. The mean baseline PFA-EPI value of ~ 200 s was probably due to seven patients who were on concomitant aspirin therapy. Only two patients continued aspirin during the study explaining the decrease in the values on subsequent testing. PFA-EPI closure times >166 s were seen in two subjects at both 5 and 7 days after discontinuation of clopidogrel. One of these subjects had continued and the other had discontinued aspirin.

Two of the 13 subjects had prolonged baseline PFA-ADP values (Table 2). One of the patients, whose aspirin was

Table 1 Patient characteristics and concomitant medications. ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BB, β -receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CEB, calcium entry blocker; CVA, cerebrovascular accident; GERD, gastroesophageal reflux disease; HMG-CoA RI, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor; HTN, hypertension; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischaemic event

Age	Gender	Indication for clopidogrel	Duration of therapy (yr)	Concomitant medical conditions	Concomitant medications
53	M	Kidney stent	3	HTN, diabetes, s/p renal transplant	ACE-I/ARB, BB
76	M	CABG	5	HTN, CAD, s/p CABG	ACE-I/ARB, HMG-CoA RI
67	M	Coronary stent	3	HTN, CAD, hyperlipidaemia	BB, HMG-CoA RI
64	F	Coronary stent	2	CAD, MI, PVD, CRI	Nitrate
81	F	TIA	1	HTN, PVD, TIA, hyperlipidaemia	CEB HMG-CoA RI
54	M	Acute coronary syndrome	3	HTN, CAD, diabetes	BB, ACE-I/ARB
61	M	Coronary stent	5	CAD, MI, HTN	α_2 -agonist
61	F	Coronary stent	1	HTN, CAD, MI, GERD	ACE-I/ARB, BB
68	M	Coronary stent	2	HTN, CAD, MI	BB
63	F	CVA	1	HTN, hyperlipidaemia	CEB
63	M	Coronary stent	2	HTN, CAD, hyperlipidaemia	ACE-I/ARB, HMG-CoA RI
59	M	Coronary stent	1	HTN, CAD, hyperlipidaemia	BB, ACE-I/ARB, HMG-CoA RI
68	F	Acute coronary syndrome	6	HTN, CAD	BB, ACE-I/ARB, HMG-CoA RI

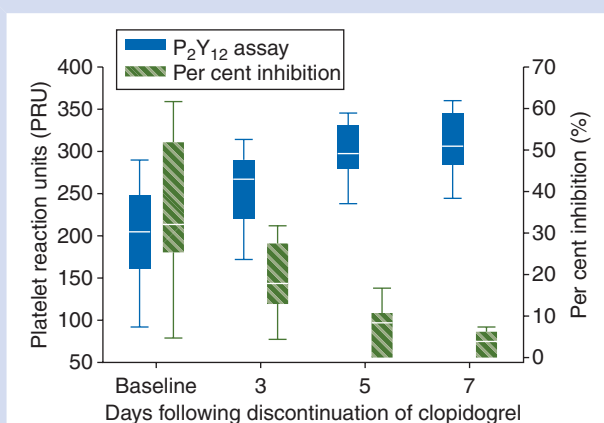


Fig 1 Changes in platelet aggregation measured in PRU and calculated per cent inhibition using a P₂Y₁₂ specific assay (VerifyNow®, Accumetrics) after discontinuation of clopidogrel therapy in patients awaiting neuraxial steroid injection.

also discontinued, had PFA-ADP normalized by the third day. This patient's platelet inhibition decreased from 58% baseline to 27% on the third day and 13% on the fifth day. The other patient who continued to have prolonged PFA-ADP throughout the study also discontinued aspirin. This patient's platelet inhibitions decreased from a baseline of 24–15% on the third day to 9% on the fifth day.

All patients had a series of epidural steroid injections. No increased bleeding was noted and there was no bruising on follow-up. There also were no cases of thrombotic events.

Discussion

The important finding of this study is the lack of statistical differences between the P₂Y₁₂ PRU values, per cent platelet

inhibition, and PFA-ADP closure times in patients undergoing epidural steroid injections at 5 days compared with the values at 7 days after discontinuation of clopidogrel. These data support the 2010 published guidelines of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine which suggest that 5 days of discontinuation of clopidogrel is adequate before a neuraxial block.⁸ The platelet inhibition as measured by the P₂Y₁₂ assay at day 5 after discontinuation showed inhibition of 29% or less, which is considered the level of a 'semi-responder'.¹³ If minimal inhibition of platelet function is accepted before a neuraxial injection,¹⁵ similar to the recommendations of the different guidelines wherein patients on aspirin or non-steroidal anti-inflammatory agents or those with slightly elevated international normalized ratio values (1.4 or less) are acceptable for neuraxial injection,^{5–8} then values of 20% or less inhibition by the P₂Y₁₂ assay is probably acceptable for neuraxial blocks.

Light transmission aggregometry (LTA) is considered the gold standard test in the determination of platelet function.¹⁸ The P₂Y₁₂ assay used in this study has been shown to correlate with light transmission aggregation induced by ADP.¹⁸ In contrast, the PFA-100 appears not to be suitable to detect residual antiplatelet activity of clopidogrel.¹⁹ This has also been shown in our results. While only one patient had an abnormal result in his PFA-ADP closure time on day 3, five patients still had >20% platelet inhibition by P₂Y₁₂ assay (Table 2). This patient continued to have prolonged PFA-ADP and PFA-EPI closure times throughout the study even when aspirin was discontinued with clopidogrel. In contrast, inhibition by P₂Y₁₂ assay progressively decreased and normalized on the fifth day. To improve the accuracy of the PFA-100 system, the company recently introduced a new test cartridge, the INNOVANCE PFA P2Y*, to measure ADP receptor inhibition more precisely. However, the sensitivity and clinical relevance of this test are now just being investigated.¹⁹

Table 2 Results of P₂Y₁₂ and PFA-100 assays after discontinuation of clopidogrel. Data presented as mean (SD) and median (range). †Different from the baseline value, *P* < 0.05. Normal range in our laboratory: PFA-EPI: 58–171 s; PFA-ADP: 41–134 s. *The one patient with persistently abnormal PFA-ADP had platelet inhibition of 24% at baseline, 15% on day 3, 9% on day 5, and 0% on day 7 of discontinuation of clopidogrel (see text)

Parameter	Baseline	3rd day	5th day	7th day
P ₂ Y ₁₂ (PRU)				
Mean (SD)	203 (76)	255 (50) [†]	294 (49) [†]	306 (46) [†]
Median (range)	205 (82–345)	268 (168–318)	297 (167–368)	306 (211–368)
Per cent inhibition				
Mean (SD)	35 (20)	19 (10) [†]	7 (6) [†]	3 (3) [†]
Median (range)	32 (0–65)	18 (2–35)	8 (0–20)	4 (0–8)
Number of patients with >20% platelet inhibition	11	5	0	0
PFA-EPI (s)				
Mean (SD)	198 (90)	149 (67)	129 (68)	136 (68)
Median (range)	206 (77–300)	124 (98–200)	106 (86–125)	109 (100–164)
Number of patients with prolonged closure times	7/7 patients on aspirin	4 (2 patients continued aspirin during the study)	2 (2 patients continued aspirin during the study)	2 (2 patients continued aspirin during the study)
PFA-ADP (s)				
Mean (SD)	106 (68)	93 (45)	101 (61)	97 (49)
Median (range)	81 (60–300)	77 (52–229)	85 (54–294)	85 (68–255)
Number of patients with prolonged closure times	2	1*	1*	1*

Clinicians use platelet inhibition to gauge the antiplatelet effect of clopidogrel.¹³ The maximum platelet inhibition at 4–5 h after a 300 mg loading dose of clopidogrel is 49% which is maintained for at least 24 h.^{20–21} Clopidogrel, at 75 mg daily, produces a maximum of 56% platelet inhibition.²⁰ If 10–15% of platelets are replaced each day²² and the new platelets are hyper-reactive to ADP,²³ then ADP-mediated platelet aggregation could be adequately restored by 5 days after discontinuation of clopidogrel.⁸

Aspirin and NSAIDs increase PFA-EPI but do not affect the PFA-ADP closure time.¹⁷ The effect of clopidogrel on closure times is variable for both PFA-EPI and PFA-ADP assays, probably due to the high rates of shear used in determination of the values. The lack of change in closure times seen after clopidogrel and aspirin termination suggests a lack of high residual reactivity during the period of discontinuation before the neuraxial procedure. We evaluated PFA-EPI because we were interested in the residual effect of aspirin, in view of the caution raised in patients who are taking two antiplatelet drugs.^{5–24} In patients whose aspirin was discontinued with clopidogrel, baseline values were elevated but were within normal limits by the third day, suggesting that any potentiating effect between aspirin is probably gone by the third or fifth day after discontinuation.

The results of our study show similar rates of decay of clopidogrel antiplatelet activity when compared with studies done in healthy volunteers. In a study using flow cytometry, a complete restoration of platelet function to 5 μM ADP activation did not occur for 7 days. However, a platelet subpopulation (30%) was fully activated by ADP at day 3 after

discontinuation of the drug and CD62P expression at 5 days was not different from the baseline.²³ Using the same P₂Y₁₂ assay as used in the current study, inhibition of <20% was achieved in most subjects by day 3 after discontinuation of daily clopidogrel and that the median (IQR) per cent inhibition at 5 days was only 12% (0–17.4).¹⁴

Our study showed that six patients, excluding the two patients with baseline platelet inhibition of 10% or less, attained platelet inhibition of 20% or less at day 3. By day 5, no patient had a platelet inhibition >20%. Studies in volunteers and our findings in subjects administered clopidogrel for cardiovascular problems lend further support to the recommendation that a 5-day discontinuation of clopidogrel might be adequate before a neuraxial injection.⁸ This contention is supported by case reports,^{9–11} and by a clinical trial that showed less perioperative bleeding at 5 or more days after clopidogrel was stopped.³ It should be noted that a report of 306 patients who underwent epidural catheter placements while receiving clopidogrel found no spinal haematoma,²⁵ although the small number of patients in this report does not assure safety in view of the low incidence of spinal haematoma.

One of our 13 patients had inhibition of 20% after 5 days of discontinuation of clopidogrel. This patient had diabetes mellitus and chronic kidney disease. The two case reports of spinal haematoma after a neuraxial injection after clopidogrel was stopped 7 days before the injection were in patients with renal impairment.^{8–26–27} Conversely, patients with chronic renal failure or diabetes mellitus have been shown to have decreased platelet responsiveness to clopidogrel.^{28–29} Nonetheless, we believe that for patients with

diabetes mellitus or renal insufficiency, a P₂Y₁₂ assay should probably be done before a neuraxial injection is performed.

As noted, there are rare occurrences of spinal haematoma 7 days after discontinuation of clopidogrel.^{26 27} We also noted a patient with platelet inhibition of 20% after 5 days of clopidogrel discontinuation. In addition, the clinician might be unfamiliar with all clopidogrel–drug interactions or the pharmacokinetics and metabolism of the drug.^{30 31} For these reasons, we recommend that residual antiplatelet activity of clopidogrel be determined 5 days after discontinuation of clopidogrel. It is probably not necessary to monitor the antiplatelet activity of clopidogrel after 7 days of stoppage since there is almost a complete turnover of the circulating platelet pool at this time.

Our study has several limitations, including the very small number of patients studied. We recruited just 13 patients over a 2.5 yr period. It was extremely hard to recruit patients who found it difficult to return to the clinic for a baseline determination and three more days before their epidural injection. We could not go to their residence to draw their blood since the sample cannot be frozen and the assay has to be performed within 4 h. A study of volunteers has been done by Price and colleagues.¹⁴ It should be noted that we have seen two patients, who were not part of this study, whose platelet inhibition was 8% 5 days after discontinuation of clopidogrel. One patient had spinal anaesthesia and the other patient had an epidural steroid injection. A final limitation of our study is that *in vitro* measures of platelet function do not correlate well with peri-surgical bleeding.

It is important to identify the earliest time when a neuraxial procedure can be safely performed in patients on antiplatelet medications. A clustering of death or acute myocardial infarction has been observed in the very first weeks after stopping treatment with clopidogrel.³² In fact, myocardial infarction has been observed in three of 24 patients during the 5 days when their clopidogrel was stopped before surgery.³³ Prasugrel, a new antiplatelet drug, produces a more rapid, potent, and consistent inhibition of platelets. Although its half-life is shorter than clopidogrel, it causes up to 90% inhibition.²⁰ While the manufacturer recommends at least a 7 day discontinuation before surgery, the Scandinavian guidelines considered a 5 day discontinuation of platelet inhibitors to be adequate based on an adequate turnover of the platelet pool at 5 days.⁸ Ticagrelor, another P₂Y₁₂ inhibitor, has been used in Europe since December 2010 and approved by the Food and Drug Administration in July 2011. Similar to prasugrel, it has a short half-life and causes up to 90% inhibition of platelets.³⁴ The appropriate number of days of discontinuation of prasugrel and ticagrelor before a neuraxial injection, based on the decay of its antiplatelet effects, has yet to be formally studied in patients with vascular problems.

In summary, our results add to the growing body of evidence that 5 days of discontinuation of clopidogrel is likely sufficient before a neuraxial injection. Ideally, a P₂Y₁₂ assay should be performed if a neuraxial injection is to be performed 5 days after discontinuation of clopidogrel.

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Conflict of interest

None declared.

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