



e-Network Forum

CALIFORNIA BLOOD BANK SOCIETY

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How long should you wait after administering a dose of the platelet inhibitor Plavix (clopidogrel) before a patient may be transfused with platelets?

As you recall, an anesthesiologist asked one of the e-network members, "How long should you wait after administering a dose of the platelet inhibitor Plavix (clopidogrel)?"

The anesthesiologist was concerned over transfusing platelets too soon after a dose of Plavix, since he **thought the drug might inactivate transfused platelets**, prohibiting them from functioning adequately. To complicate matters, it takes several days before the bleeding time returns to normal, after a patient has received several doses of the drug. In addition, the **manufacturer of Plavix recommends that elective surgery should be put off for seven days** after cessation of Plavix therapy, but this is of no help in deciding how to treat patients that need **emergency** surgery. Finally, if a patient who received Plavix develops TTP, how dangerous are platelet transfusions, if the transfusions are given to control bleeding?

Several interesting replies were received in response to the above questions. **The responses can be grouped into four categories:**

- a. The **mechanism** by which Plavix causes platelet dysfunction;
- b. Evidence that you should take the drug manufacturer's advice and **put off surgery for seven days** after cessation of Plavix therapy;
- c. The risk of platelet transfusion in the event a patient on Plavix develops **TTP**;
- d. **Deferral from blood donation** of individuals who are taking Plavix:

a. The mechanism by which Plavix causes platelet dysfunction:

1. A blood banker in **Texas** commented that in his personal experience Plavix takes 5-7 days to show its full effect which is characterized by about a 50% inhibition of platelet aggregation by ADP in Platelet rich plasma and almost 100% inhibition in Whole Blood Aggregation. Plavix acts most likely by inhibiting an ADP receptor (P2TAC) ([Geiger et al., Arterioscler Thromb Vasc Biol 1999](#)). Since it takes so long for Plavix to show a therapeutic effect, it could be that the drug or an active metabolite (not identified yet) is acting at the level of the megakaryocyte. Hence only platelets that have been freshly released from the bone marrow may be affected. In either scenario, **transfused platelets should NOT be affected, and platelet transfusion therapy should be effective**, since Plavix or its known metabolite (carboxylic acid derivative) does not affect platelet aggregation in-vitro ([Quinn MJ et al., Circulation, 1999](#) and [Bennett JS et al., Thromb Haemost, 2001](#)). The effect of the drug lasts for up to 7-10 days. Therefore, if an urgent surgery is required, a single dose of platelets (one plateletpheresis unit or a pool of multidonor platelets) just before surgery should provide hemostasis, depending upon the underlying condition(s). If microvascular bleeding is expected, then another dose of platelets may be given during surgery.

b. Evidence that you should take the drug manufacturer's advice and postpone surgery for seven days after cessation of Plavix therapy:

2. A blood banker in **California** reported that a small study was recently completed at her institution that looked at, among other things, the use of Plavix for patients undergoing emergency CABG procedures. The study was undertaken due to excessive post-operative bleeding in some patients who had received Plavix. The reporting blood banker hopes the data from the study will be published. (**Editor's NOTE:** Until the reporting blood banker's data are scrutinized by a peer review process, the e-network membership is cautioned to regard the following data as anecdotal). The blood banker reported that a group of **31 patients received Plavix and aspirin prior to undergoing a CABG**; a **control group of 31 patients received aspirin (but NO Plavix)** prior to a CABG. Some patients in both groups required emergency surgery. The patients who received Plavix plus aspirin received their last dose of Plavix within 72

hours of surgery (remember that the drug manufacturer recommends waiting for 7 days before surgery) and these patients used 650 units of blood and blood products (average of 21 units/patient). The reporting blood banker made no mention of pre-surgical platelet transfusions (as suggested in response #1), to reverse the hemostatic effects of Plavix. The patients in the control group (who received aspirin but NO Plavix) used only 141 units of blood and blood products (average of 5 units/patient). Individuals who received Plavix plus aspirin had to return to surgery for re-operation due to excessive bleeding; findings upon return to surgery included clots, microvascular bleeding, hemothorax, arterial pumper circling the graft, periosteal bleeding, RCA graft bleeder, coagulopathy, bleeding at a suture site. No patients who received aspirin without Plavix had to return to surgery. The reporting blood banker believes that her institution's findings suggest that **surgeons and anesthesiologists should proceed with caution when treating a patient in an emergency situation**, if the patient has Plavix on board. The reporting blood banker commented that at her institution Plavix is truly "the hot topic", and she wanted to thank the e-Network Forum for sharing this input.

(**Editor's NOTE:** While the recommendation in response #2 is very encouraging, I strongly recommend that the [prescribing information](#) for this drug should be taken very seriously.)

3. A blood banker at **Vienna University** was of the opinion that in case of an emergency, whether or not a patient has been taking an anti-platelet drug, "you need to do what you need to do! **If you have to treat or prevent bleeding, do it!**"

c. the risk of platelet transfusion in the event a patient on Plavix develops TTP:

4. The same individual who provided reply #1 also stated that "If the patient has evidence of **TTP in association with Plavix, platelets should not be transfused**. But if there is bleeding and no evidence of microangiopathy, platelets can be transfused safely."
5. A blood banker in the **San Diego**, California area stated that with regard to the transfusion of platelets to a patient with Plavix induced TTP, "**it is my belief that platelet transfusions are almost always inappropriate to stop bleeding in patients with TTP**. I find that intensive plasma exchange usually suffices. There are reports of platelet transfusions causing fatal platelet aggregation in patients with TTP. Some consider platelet transfusions contraindicated in this disease."
6. Another blood banker in **Texas** (not the same person as in responses #1 and #4) commented regarding Plavix that **a study is being planned** to address the efficacy of platelet transfusion versus hemostatic drug therapy for patients who are receiving the drug. This Texan goes on to say that "Some hope that cardiologists will heed the report of [Salliere et al.](#), (N Eng J Med, 2000) and seek alternate anti-platelet therapy due to the low but real risk of therapy-related TTP".

d. deferral from blood donation of individuals who are taking Plavix:

7. A blood banker who works in **a southern state** bordering on the Atlantic Ocean commented that she thinks individuals who are **taking Plavix should be deferred from blood donation, especially for platelet donation**. However, she is of the opinion that such deferrals are NOT occurring at many blood collection centers. She goes on to comment that when she used to work for the American Red Cross, aspirin, but not Plavix (or Ticlid, which is another anti-platelet drug) was defined as a cause for platelet donor deferral. This blood banker states that even today, some individuals who are taking Plavix are allowed to donate platelets, and this drug is being used more and more often in place of aspirin.

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8. **Another transfusion medicine specialist** wrote that the role of Plavix in contributing to bleeding is **complex**. The initial clinical trial (CAPRIE - Lancet 1996;348:1329-1339) found no difference between clopidogrel and ASA-treated groups when considering any report of bleeding (clopidogrel - 9.27%, ASA - 9.28%). However, when analyzing GI bleeding there was a significant reduction in the risk of GI bleeding for clopidogrel-treated patients: clopidogrel -1.94%, ASA - 2.6%(p<0.05). Based on these findings clopidogrel is considered to have a safety profile superior to ASA. A follow-up study (Bhatt, Am. Heart J 2000;140:67-73) from the CAPRIE trial reports a reduced rate of readmission for thrombotic and bleeding complications in clopidogrel-treated patients. The rate of readmission for GI hemorrhage was 0.52% for clopidogrel vs. 0.72% for ASA. The CURE trial presented at this year's American College of Cardiology meeting by Yusuf studied the effect of clopidogrel in unstable angina. There was a 19% relative risk reduction for endpoints of cardiovascular death, MI, and non-fatal stroke. There was 33% increase in major bleeding in clopidogrel treated patients. This study used a loading dose of clopidogrel (300 mg) in combination with ASA. In the CAPRIE trial; clopidogrel was

the sole anti-platelet agent. In patients with intact blood vessels clopidogrel does not appear to have great bleeding risk when used as a single agent. The CURE trial suggests that combination ASA+clopidogrel therapy changes the safety profile. Data on the effect of clopidogrel in patients requiring major surgery are limited. This transfusion medicine specialist's institution studied bleeding and transfusion rates for 53 patients treated with clopidogrel prior to surgery. A marked increase in transfusion incidence was noted: clopidogrel - 98% vs. ASA - 68%. CABG patients treated with clopidogrel use more blood components than routine CABG cases. However, when compared to emergent CABG cases, the difference in component use is significant only for the number of platelets transfused. These data will be reported at the 2001 ISTH meeting. The transfusion medicine specialist has preliminary data on sequential assay of platelet function (ADP-mediated platelet aggregation and PFA-100) in clopidogrel-treated patients. There is a fair amount of heterogeneity in the degree of platelet inhibition. This may be related to whether the patients are in the steady-state of clopidogrel inhibition. The data are too preliminary to comment on this. In the transfusion medicine specialist's experience, patients with a reasonable degree of preservation of ADP-mediated aggregation, e.g., > 50% ADP aggregation response have good outcomes. Platelet transfusions have not been required in 3/7 clopidogrel patients monitored with serial platelet function assays. **He recommends evaluation of platelet function in patients exposed to clopidogrel within 7 days** prior to elective CABG surgery. If the ADP-mediated platelet aggregation response is low, he recommends postponing surgery. In cases where the risk of delay is too great and platelet function is impaired, he transfuses platelets to achieve adequate platelet function using both PFA-100 and ADP-mediated platelet aggregation as guides.

Please submit comments to the [e-Network Forum](#).



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