JAMES PAGET HEALTHCARE NHS TRUST

CLINICAL GUIDELINE FOR PERI-OPERATIVE MANAGEMENT OF PATIENT RECEIVING ANTIPLATELET THERAPY

1. INTRODUCTION

Antiplatelet therapy is widely prescribed for the treatment and/or prevention of vascular events (Transient ischaemic attacks, stroke, myocardial infarction, acute limb ischaemia). Therefore anaesthetists and surgeons are often required to operate on patients receiving this kind of medication. Some of these drugs need to be stopped prior to surgery (because of the risk of bleeding) or if regional anaesthesia is envisaged (e.g. risk of spinal haematoma and neuroaxial block). However there is evidence that pre-operative withdrawal of antiplatelet drugs increases the risk of thrombotic events; e.g. aspirin cessation increases the risk of peri-operative myocardial infarction.

The risk/benefit ratio of discontinuation of antiplatelet drugs has to be defined for each patient before decision of withdrawal is taken.

2. SCOPE

This guideline is simply there to assist clinicians, anaesthetists, surgeons and pre-assessment nurses in the management of antiplatelet drugs during the peri-operative period.

3. GUIDELINE

Mode of action of antiplatelet drugs

The antiplatelet drugs commonly used are:

- Aspirin
- NSAID's
- Clopidogrel
- Dipyridamole
- Glycoprotein IIb/IIIa receptor antagonists (Abciximab, Tirofiban, Eptifibatide).

Similarities amongst these drugs: they are all potent antiplatelet drugs (inhibition of activation and aggregation of platelets).
Differences between these drugs: - reversibility (or not) of action
- duration of platelet function inhibition

Both **NSAID's** and **aspirin** inhibit platelets cyclooxygenase (COX).
COX inhibition by aspirin is irreversible. Therefore the antiplatelet effect of aspirin persists throughout platelet lifetime (7-10 days).

On the other hand, the action of NSAID's on platelet's COX inhibition is reversible. Subsequently duration of inhibition is correlated to the presence of the molecule in the plasma. Once NSAID's are stopped, the platelet function returns to normal within a period depending on their half-life. For example: Elimination half-life of Flurbiprofen is 5h (unchanged in elderly or renal impairment).

Clopidogrel is a thienopyridine. It impairs platelet function by inhibiting the binding of ADP to its platelet receptor. As for aspirin, its effect upon platelet function is irreversible and persists throughout platelet lifetime.

This fundamental difference in the mode of action explains the greater controllability of NSAID's in comparison to Aspirin and Clopidogrel.

Glycoprotein IIb/IIIa receptor antagonists (Abciximab, Tirofiban, Eptifibatide) prevent platelets aggregation by blocking the binding of fibrinogen to receptors on platelets (specialist use only). All have short half-lives: the return to normal platelet function after injection is up to 48h for Abciximab and 8h for Tirofiban and Eptifibatide. They may increase patient bleeding if the surgery is done close to administration.

Dipyridamole induces anti-aggregability in vitro (inhibition of the phosphodiesterase, elevation of AMPc platelets level) but does not increase the bleeding time in vivo. It has a short half-life (around 3hours). Based on labelling Dipyridamole should be discontinued 24h before surgery and treatment restarted in the immediate post-operative period.

Anaesthetic and surgical implications for patients under antiplatelet therapy

Patients under antiplatelet drugs and undergoing surgery often cause a dilemma for the practitioners looking after them - especially surgeons and anaesthetists - for the following reasons:

- Continuing some antiplatelet drugs in the pre-operative period might increase the risk of bleeding and sometimes the need for blood transfusion. Achieving spinal or epidural anaesthesia under certain antiplatelet therapy might also be at risk of spinal haematoma.

- Biological tests, including bleeding time, have a poor predictive value of the risk of bleeding.

- Last but not least, there is evidence that withdrawal of antiplatelet therapy increase the risk of thrombotic events in the peri-operative period e.g. myocardial infarction, ischaemic stroke or acute lower limb ischaemia after aspirin cessation in cardiovascular patients (1, 2, 3, and 4)

How can we deal with this?

Antiplatelet therapy and regional anaesthesia

- Regional block or general anaesthesia?

Are there potential benefits in terms of morbidity or mortality of regional anaesthesia compared to general anaesthesia?

Some recent meta-analysis/randomised trials show better outcome with regional anaesthesia. Mortality and/or morbidity decreases with epidural or spinal anaesthesia (5, 6) e.g. substantial benefits from epidural analgesia used in the per- and post-operative periods in high-risk patients undergoing major abdominal surgery (7, 8).

- Antiplatelet drug and regional anaesthesia:

Several studies show that **Aspirin** taken preoperatively does not increase the risk of spinal haematoma in patients who undergo spinal or epidural anaesthesia (9, 10, and 11). Even if regional block is planned, aspirin does not need to be stopped before surgery.

There is little data available to draw conclusions about the risk of spinal haematoma under thienopyridines (**Clopidogrel**). Therefore consensus from both the American and French anaesthetic societies suggests time interval between discontinuation of Clopidogrel therapy and neuroaxial blockade is 7 days (12, 19).

For **Glycoprotein IIb/IIIa receptor antagonist** the American Society of Regional Anaesthesia and Pain Medicine's (ASRA) recommends:
"Neuroaxial techniques should be avoided until platelet function has recovered":
24-48h for Abciximab and 8h for Tirofiban, Eptifibatide.

Antiplatelet therapy and surgery

The benefits of pre-operative antiplatelet therapy have to be balanced with the risk of excessive bleeding per- and post-operative, transfusion requirement and need for re-exploration to control haemostasis.

For tonsillectomy and prostate surgeries, **Aspirin** taken pre- and post-operatively may induce peri-operative bleeding and increase the number of revision procedures for haemostasis (13, 14, 15). In these cases, Aspirin should be avoided and replaced by another antiplatelet drug (see replacement therapy below). The same precautions should be taken for neurosurgery, spinal cord surgery or for a surgery where the risk of excessive bleeding is common-

e.g. revision of hip replacement. In all other procedures there is no evidence in the literature that aspirin increases the risk of haemorrhage and exposure to transfusion per- and post- surgery. In these cases Aspirin should not be stopped (16).

The lack of data relating to **Clopidogrel** prevents any conclusions as regards the safety of this product; Clopidogrel should be avoided if surgery is decided and replaced by another antiplatelet drug (see replacement therapy below).

GP IIb/IIIa antagonists may increase patient bleeding if the surgery is done close to administration. They are also contraindicated within four weeks of surgery.

Withdrawal of antiplatelet therapy: How to avoid the risk of thrombotic events?

There are an increasing number of reports of dramatic consequences of withdrawal of antiplatelet therapy in cardiovascular or cerebrovascular patients (1, 2, 3 , 4).

As explained above, in some cases antiplatelet drugs have to be withdrawn before surgery, which might put the patient at arteriovascular risk.

Clopidogrel should be stopped before surgery or if regional anaesthesia is planned. Substitution for Aspirin has to take place 7 days before surgery.

In case of allergy/intolerance or contraindication of Aspirin, Clopidogrel should be replaced by another antiplatelet therapy. **Flurbiprofen** which has a reversible and short action has proven efficiency in the prevention and recurrence of myocardial infarction and reocclusion in patients treated by thrombolysis and/or transluminal angioplasty (17, 18).

Therefore, as it is stipulated in the “expert recommendations of French society of Anaesthesiology and Intensive Care 2001” Flurbiprofen can be used as replacement therapy for Aspirin or Clopidogrel in the pre-operative period (19). Prospective studies to compare the efficiency of these 3 medicines are still needed.
The recommended dosage is:
Flurbiprofen: 50mg twice daily, po. The last dose is given 24h prior to procedure.

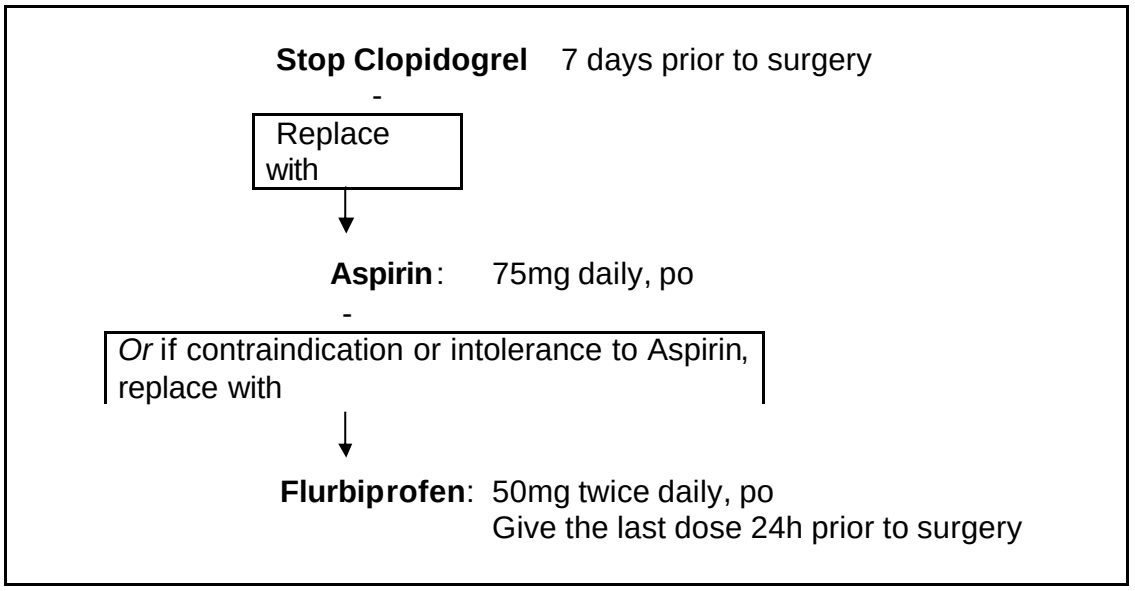
As explained above, in the majority of surgery **Aspirin** should not be stopped. Exceptions are: tonsillectomy, prostate surgery or in surgeries with major fear of bleeding (e.g. revision of hip replacement). For these cases Aspirin should be stopped 7 days before surgery and replaced by Flurbiprofen.

In summary

- Stopping antiplatelet drugs increases the risk of cardiovascular events.

- **Dipyridamole**
  Abstention on the day of surgery, restart in the immediate post-operative period

- **Clopidogrel**



- **Aspirin**
  In majority of cases: do not stop Aspirin before surgery. For tonsillectomy, prostate surgery or expected difficulties regarding surgical haemostasis Aspirin should be stopped 7 days before surgery and replaced by Flurbiprofen as above.

- **Clopidogrel and Aspirin**
  Patients under Clopidogrel and Aspirin need to stop Clopidogrel and continue Aspirin until surgery.

- **GP IIb/IIIa antagonists**
  They have to be stopped before surgery. The time between the last injection dose and surgery should be 24-48h for Abciximab and 8h for Tirofiban, Eptifibatide.

- **Responsibilities**
  Replacement therapy will be organized during pre-assessment clinic (an explanatory letter will be sent to the patient's GP).

In case surgery is postponed the patient will be advised to continue Aspirin or Flurbiprofen until the next admission. If any inquiry patient should contact the Anticoagulant nurse (01493 453213).

Patient under Clopidogrel and/or aspirin who needs a replacement therapy are considered as "high-risk if postponed" and should not be cancelled in bed bureau. The mention "high-risk if postponed" will take place at the pre-assessment clinic.

It is the responsibility of the surgeon who has admitted the patient to ensure that antiplatelet therapy is restarted post-operatively (within 24-48h, if haemostasis is intact).

4. EVIDENCE

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