

Warning re: New Anti-Platelet Drugs and potential hazards of Surgery and Major Regional Intraspinal Analgesia

The past few years have seen the introduction of several new platelet inhibiting agents brought about by research in coronary artery stenting and prevention of arterial thrombosis and embolism. ABCIXIMAB, TIROFIBAN, TICLODIPINE, CLOPIDOGREL are examples. (1), (2), (3) Aggressive marketing has encouraged their wide spread use. Of particular interest is CLOPIDOGREL which has two trade names viz: ISOCOVER and PLAVIX.

(Ticlopidine, trade name Tilodene, has similar pharmacology but has a greater side effect profile discouraging it's use).

CLOPIDOGREL is a thienopyridine derivate that exerts its effect via a low affinity type 2 purinergic receptor that inhibits the binding of ADP to the glycoprotein IIb/IIIa complex and its subsequent activation to bind fibrinogen and cause platelet aggregation. Maximum efficacy occurs 2-4 days after therapy commences and the platelet effect is irreversible lasting 10 days (life of the platelet). Therefore it would be prudent to cease this agent 7 - 10 days prior to surgery if their medical risks have been considered.

CLOPIDOGREL and TICLODIPINE require metabolism by hepatic cytochrome P450-1A for activation to an unknown active metabolite. Active metabolites are primarily excreted renally. CLOPIDOGREL exists in the circulation bound to platelets and as **free drug for approximately 18 hours** assuming normal renal function. **Therefore, exogenous transfused platelets will be inhibited and rendered ineffective if administered within 18 hrs of the last dose**, assuming normal pharmacokinetics. At least 24 hrs would seem a minimal period to postpone surgery after the last dose.

Furthermore, the practice of administering both Clopidogrel and Aspirin appears to be gaining popularity making the risks of surgery and intraspinal analgesia potentially greater still.

Anecdotal reports of uncontrollable haemorrhage during surgery associated with very recent administration are occurring and caution should be exercised even if the drug has been stopped within 7-10 days of surgery, as with Aspirin. Also spontaneous subdural haemorrhages are being reported. One report of intraspinal haematoma (4) has occurred after cervical epidural anaesthesia in a patient on a NSAID, Clopidogrel and Aspirin.

There are also articles that reject the association between earlier anti-platelet agents and the development of intraspinal haematomas. (5) These however, do not cite experience with the latest agents.

A careful risk/benefit analysis should therefore be undertaken for patients on these new anti-platelet agents alone and in combination with other agents when considering surgery and intraspinal analgesic techniques.

References:

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