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Lamifiban

A Viewpoint by David J. Moliterno

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Among the leading scientific advancements in contemporary cardiovascular medicine are the recognition of the pivotal role of platelets in atherothrombosis and the introduction of platelet IIb/IIIa receptor antagonists in the treatment of coronary arterial plaque rupture associated with acute coronary syndromes and percutaneous coronary revascularisation. Lamifiban is among the most potent members of the small-molecule class of IIb/IIIa inhibitors developed for intravenous administration. Unlike antibody agents to the IIb/IIIa receptor, which tightly bind to platelets and have a long biological half-life and a relatively lower presence in the plasma, small-molecule IIb/IIIa antagonists (peptidomimetics) are competitive inhibitors, have a short half-life, are present in relatively higher proportion as free in the circulation and are primarily excreted unchanged by the kidney. These kinetics make lamifiban's antiplatelet effect highly dependent on renal function. In brief, the antiplatelet effect of peptidomimetics is directly proportional to the percentage of the 50 000 to 80 000 IIb/IIIa receptors occupied per platelet, and in turn, the percentage of receptors bound is directly related to plasma drug concentration and ultimately to renal function.

In PARAGON A, while low dose lamifiban was consistently more efficacious than high dose lamifiban in reducing the occurrence of death or nonfatal myocardial infarction relative to control, post hoc analyses have shown that the greatest predictor of favourable outcome was the plasma concentration of lamifiban. Steiner et al.[1] analysed plasma lamifiban concentrations among 810 patients in PARAGON A and showed the relative reduction in death or nonfatal infarction compared with control to be 40% at 30 days for those with plasma lamifiban concentrations between about 20 and 42 μg/L (fig. 1). PARAGON B is currently enrolling 4000 patients with unstable angina or myocardial infarction into this phase III study specifically administering lamifiban according to each patient's creatinine clearance.

If lamifiban continues to follow the successful path of other developed IIb/IIIa receptor antagonists, it should be a particularly useful agent, since it is among the most potent antagonists, the only one to be prospectively administered according to renal function, and it has an extensively studied oral congener, sibrafiban. While the acute coronary syndromes are a logical arena for this compound, it should be similarly beneficial in other situations involving arterial thrombosis such as percutaneous coronary revascularisation, cerebrovascular ischaemia and peripheral vascular disease.

Reference

1. Steiner B, Hofer U, Wittke B, et al. Plasma concentration of lamifiban and glycoprotein IIb-IIIa receptor occupancy best predict clinical outcome in patients with unstable angina: results from PARAGON A. Eur Heart J 1998; 19: 598

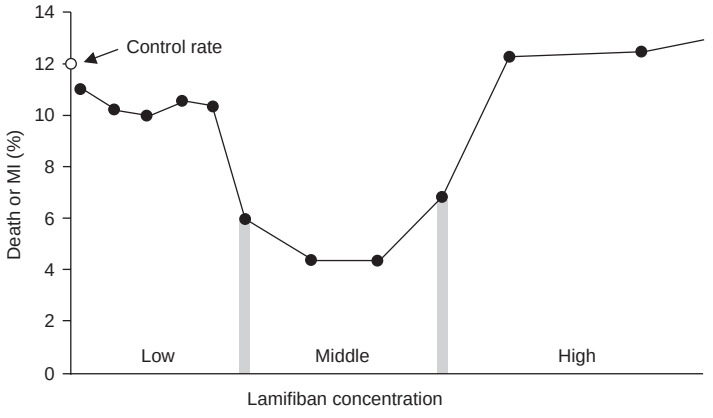

Fig. 1. In 810 patients in PARAGON A, the plasma concentration in a middle range (about 20-40 μg/L) was found to be associated with the lowest 30-day incidence of death or myocardial (re)infarction relative to control. **MI** = myocardial infarction.