Open Multicentre Study of the P2\textsubscript{T} Receptor Antagonist AR-C69931MX Assessing Safety, Tolerability and Activity in Patients with Acute Coronary Syndromes

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on behalf of the Investigators

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Key words
Platelet aggregation inhibitors, adenosine diphosphate, P2 receptors, unstable angina, heparin

Summary
Platelet aggregation is the central process in the pathophysiology of acute coronary syndromes. ADP contributes to thrombosis by activating platelets, and AR-C69931MX is a specific antagonist of this process acting at the P_{2\textsubscript{T}} receptor. At 5 hospitals, 39 patients with unstable angina or non-Q wave myocardial infarction, who were receiving aspirin and heparin, were administered intravenous AR-C69931MX with stepped dose increments over 3 h to a plateau of either 2 μg/kg/min for 21 h (Part 1; n = 12) or up to 69 h (Part 2; n = 13) or 4 μg/kg/min for up to 69 h (Part 3; n = 14). Safety parameters, platelet aggregation (PA) induced by ADP 3 μmol/L (impedance aggregometry), bleeding time (BT) and plasma concentrations of AR-C69931XX were assessed. AR-C69931MX was well tolerated. 33 patients completed the study. There were no deaths at 30 days and no serious adverse events attributed to AR-C69931MX. Trivial bleeding (56%) was common. At 24 h, mean inhibition of PA was 96.0 ± 8.6, 94.9 ± 14.4 and 98.7 ± 2.1% and BT was 9.5 ± 8.4, 14.0 ± 9.7 and 16.0 ± 11.1 min for Parts 1, 2 and 3 respectively. At 1 h post-infusion, mean inhibition of PA was 36.2 ± 39.2, 20.7 ± 25.9 and 40.7 ± 36.7% respectively. 90% patients had a plasma half-life for AR-C69931XX of <9 min. In conclusion, AR-C69931MX is a potent, short-acting platelet ADP receptor antagonist suitable for further studies as an antithrombotic agent.

Introduction
Platelet activation plays a dominant role in the pathogenesis of acute coronary syndromes, and the ideal antithrombotic strategy for treatment of these syndromes remains to be defined. Antiplatelet treatment with aspirin combined with anticoagulant treatment with heparin is standard therapy for reducing the occurrence of serious adverse cardiac events. Intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists have also shown benefits in some studies, particularly in the context of coronary intervention (1). ADP is an important platelet agonist that is secreted from platelet dense granules, where it is stored at high concentration, and secreted ADP amplifies the responses to other agonists that induce platelet secretion, such as thrombin and collagen (2, 3). ADP is also released from damaged erythrocytes and endothelial cells (3). Recent evidence indicates that there are three subtypes of ADP receptor on platelets, namely P2X\textsubscript{1}, P2Y\textsubscript{1} and P2\textsubscript{T} receptors (4). P2X\textsubscript{1} and P2Y\textsubscript{1} receptors are found in other tissues, whereas P2\textsubscript{T} receptors appear to be unique to platelets and megakaryocytes. Co-activation of P2Y\textsubscript{1} and P2\textsubscript{T} receptors is required for sustained ADP-induced platelet aggregation, whereas at present the functional significance of the P2X\textsubscript{1} receptor remains unclear (5-7).

Thienopyridines, ticlopidine and clopidogrel, are platelet ADP receptor pathway antagonists that are pro-drugs for metabolites that act at the level of the P2\textsubscript{T} receptor (6, 8-10). Thienopyridines have been demonstrated to reduce the thrombotic complications of atherosclerotic disease (11, 12). However, they have a slow onset of action and their effects on platelets are irreversible (13). Furthermore, these agents yield only moderate inhibition of ADP-induced aggregation at current therapeutic doses (14). ATP is the natural antagonist of ADP-induced platelet aggregation and stable analogues of ATP that act as direct antagonists of the P2\textsubscript{T} receptor and are active in vitro represent an entirely novel class of antiplatelet therapy (15, 16). The ATP analogue AR-C69931MX (16) is a recently developed P2\textsubscript{T} receptor antagonist that has been found to be suitable for study in clinical trials. Animal studies of this agent suggest that it may effectively inhibit arterial thrombosis with less effect on bleeding time compared to glycoprotein IIb/IIIa antagonists (16). The P2\textsubscript{T} receptor plays a central role in amplifying platelet aggregation, secretion and procoagulant activity induced by agonists other than ADP, hence AR-C69931MX inhibits platelet responses to all natural agonists or their mimetics (7). We have assessed the effects of intravenous administration of AR-C69931MX to patients with unstable angina and non-Q wave myocardial infarction to determine its safety, tolerability and antithrombotic effects when given as adjunctive therapy to aspirin and heparin.

Methods
Study Population
Patients between 25 and 80 years of age admitted to 5 participating hospitals (4 in UK and 1 in Netherlands) with a diagnosis of unstable angina or non-Q...
wave myocardial infarction who were receiving aspirin, oral or parenteral nitrates and unfractionated or low-molecular-weight heparin were eligible for the study. They were also required to have one of the following: (a) ECG changes compatible with ischaemia, (b) a history of previous myocardial infarction, or previous abnormal coronary angiography, myocardial perfusion scintigraphy or exercise test, or (c) an increase in cardiac markers (CK, CK-MB or troponins) consistent with unstable angina or a non-Q wave myocardial infarction during the index admission. Exclusion criteria were acute ST elevation or new Q waves on ECG, uncontrolled severe cardiac failure, sustained arrhythmia, infection, cardiac tamponade, myocardial ischaemia not due to coronary disease, PTCA or CABG within the last 2 months, aortic aneurysm, shock or uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg), oral anticoagulant and/or fibrinolytic drugs within the last 10 days, history of intracranial bleeding or stroke, history of bleeding gastrointestinal disorder and/or endoscopically verified ulcer disease within the last 2 years, current or previous urogenital disorder, major surgery or trauma within the last 3 months, platelet count <100 x 10^9/L, any other condition associated with increased risk of bleeding, renal or liver failure, haemoglobin <10 g/dL, childbearing potential, drug or alcohol addiction, comorbidity likely to interfere with study procedures, and current treatment with ticlopidine, clopidogrel, dipyridamole, adenosine, dextran, prostacyclin, acibemb, or sulfinpyrazone. Patients receiving intravenous heparin were required to have a stable APTT value within the target range of 55-75 s prior to inclusion.

Study Objectives

The primary objectives of the study were: (a) To assess the safety and tolerability of AR-C69931MX when given as a continuous intravenous infusion for up to 72 h; and (b) to assess the effect of a range of doses of AR-C69931MX on platelet aggregation, bleeding time. The secondary objectives were: (a) To identify a dose of AR-C69931MX that provided 100% inhibition of platelet aggregation and bleeding time; (b) to determine the relationship between activity (ex vivo platelet aggregation and bleeding times) and plasma concentrations of AR-C69931XX (the free base of AR-C69931MX); and (c) to characterise the pharmacokinetic profile of AR-C69931XX in the target patient population.

Study Design

The study consisted of 3 parts with review of safety data after Part 1, prior to progression to Part 2, and after Part 2 prior to progression to Part 3. It was planned to treat 12 patients in Part 1, 12 patients in Part 2 and up to 24 patients in Part 3. In all parts, patients received open administration of intravenous AR-C69931MX with dose increases every hour for the first 3 h to reach a plateau dose infusion. In Parts 1 and 2, patients received AR-C69931MX 0.05, 0.2 and 0.5 μg/kg/min followed by a plateau infusion of 2 μg/kg/min for either 21 h (Part 1) or up to 69 h (Part 2) to total 24 or up to 72 h respectively. In Part 3, patients received AR-C69931MX 0.2, 1 and 2 μg/kg/min followed by a plateau infusion of 4 μg/kg/min for up to 69 h (total up to 72 h). A separate venous cannula was inserted in the contralateral forearm to the infusion for blood sampling.

Safety and Tolerability

Prior to this study, a pilot study was performed which did not involve administration of study medication but assessed the nature and range of coincidental fluctuations or abnormal findings in dipstick urinalysis, SDS-PAGE analysis for protein bands (a sensitive and early indicator of renal tract changes), urine cytology and serum creatinine in a similar cohort of patients (n = 25) as used in this study (using the same inclusion/exclusion criteria). The reason for conducting this pilot study was that background variability in these parameters had been noted in healthy volunteer studies and so it was important to assess the degree of variability in the target population in order to allow for accurate interpretation of the results obtained.

Standard clinical chemistry and haematology parameters were measured daily during infusion and at 24 h post-infusion. Urine samples were collected daily, and at 24 h and 7 days post-infusion, for dipstick urinalysis, SDS-PAGE analysis for protein bands, and cytology. All patients had continuous cardiac monitoring throughout the study with regular 12-lead ECG recordings and measurement of heart rate, BP and temperature.

Clinical events and status were determined at 30 days post-infusion by patient review.

Pharmacokinetics and Pharmacodynamics

At enrolment, patients were randomly assigned to either full pharmacokinetic analysis (17 samples) or partial pharmacokinetic analysis (9 samples) to measure plasma concentrations of AR-C69931XX, using a previously validated method. In brief, determination of AR-C69931XX in human plasma was performed using a dual solid phase extraction (SPE/SPE) high performance liquid chromatography (HPLC) method. The results from quality control samples, which were included in each analysis batch, were acceptable, giving confidence in the results obtained for test samples.

Platelet aggregation induced by ADP 3 μmol/L was assessed by whole blood impedance aggregometry (Chronolog), using unfractionated heparin sodium as anticoagulant (10 U/mL final concentration) and diluting blood with saline in 1:1 ratio. Duplicate measurements were performed at screening, then at 30 min after initiation of the three incremental and fourth (plateau) infusion doses. In Part 1 further measurements were made at 5 h and 23 h 50 min, and in Parts 2 and 3 at 5 h, 24 h, 48 h and 71 h 50 min. Post-infusion measurements were made at 20 min and 1 h in all Parts. Inhibition of platelet aggregation was determined relative to the screening impedance measurement.

Bleeding time measurements were determined prior to start of study infusion and 23 h after the start of the infusion in all parts. With the patient recumbent and the forearm level with the trunk, a distending venous pressure of 40 mmHg was applied with a standard sphygmomanometer cuff around the upper arm for 30 sec before and throughout the procedure. Using a standard lancet (Becton Dickinson 1.5 mm wide, 2.4 mm deep), 3 stabs were made into the volar surface of the forearm, not directly over superficial veins. Punctures were blotted every 15 sec and the time at which each ceased to bleed was recorded to the nearest 15 sec. If bleeding had not ceased at 30 min then the time was recorded as 30 min. The mean value of the 3 measurements was recorded.

Statistical Analysis

Pharmacokinetic and pharmacodynamic measures were determined as mean and standard deviation. Population pharmacokinetic analyses were carried out using the NONMEM software Version IV (NONMEM project group, California, USA). Pharmacokinetic modelling used both the PRED and the NMTRAN routine.

Results

Patients

A total of 39 patients (30 male, 9 female; mean age 62 years, age range 41-77 years) were administered AR-C69931MX, 12 in Part 1, 13 in Part 2 and 14 in Part 3. 33/39 patients completed the study and 6 patients discontinued the study early for reasons unrelated to the study medication: 3 patients developed pre-specified withdrawal criteria, either development of Q waves (1 patient) or decision to perform PTCA (2 patients, one of whom had back pain and ECG changes and was felt to require emergency PTCA); 1 patient withdrew himself without stating a reason; 1 patient was discharged early from hospital; 1 patient was withdrawn by the Investigator prior to angiography to reduce bleeding risk. The intensive requirements of the study caused slow recruitment so that enrolment was terminated before Part 3 was completed but once
sufficient data had been accrued. All 39 patients received aspirin, heparin and nitrates. Other cardiovascular medications at entry included β-blockers (79%), calcium channel blockers (51%), statins (31%), ACE inhibitors (23%) and potassium channel activators (13%).

Safety and Tolerability

(i) Clinical adverse events. There were no deaths at 30-day follow-up and there were no major or minor bleeds as defined by TIMI criteria (17). 3/39 patients during treatment, and 4/39 patients during follow-up, experienced adverse events which were classified as ‘severe’ (chest pain, indication for PTCA, development of Q waves on ECG, or heart failure), and all these events were considered by the investigators as unlikely to be related to the study treatment. The most frequently reported adverse events emerging during treatment (reported by 2 or more patients in any part of the study) are shown in Table 1. Since this was not a double-blind, randomised control study, it is not certain what proportion of these events were related to the study medication. However, trivial bleeding was common (22/39), predominantly consisting of slight bleeding at injection sites, microscopic haematuria or purpura and not associated with any significant fall in haematocrit. This was anticipated in view of the mechanism of action of the drug and the effects on bleeding time (shown below).

(ii) Clinical chemistry and haematology. 8/39 patients (21%) had raised ALT (SGPT) levels during treatment, 3 in Part 2 and 5 in Part 3 and some of these patients also had raised AST (SGOT) levels. Only in one case were creatine kinase levels also raised. The maximum increase in ALT was from 22 IU/L at baseline to 130 IU/L during treatment, representing a maximum increase to 2.6 times the upper limit of normal. No clinical consequences of these elevations were observed.

15/39 patients (38%) had creatinine or urea values above the upper limits of normal at some point in the study; 10 of these had abnormal values at baseline and there were no significant increases. The data showed a similar pattern in all parts of the study and to that collected in the pilot study. Other biochemical and haematological parameters showed no significant effect of AR-C69931MX infusion; in particular, there were no cases of thrombocytopenia induced by AR-C69931MX and no changes in mean haematocrit.

(iii) Urine tests. Urine SDS-PAGE results showed additional protein bands for 10/39 patients (26%), these abnormalities being present in 5 patients prior to treatment. In the pilot study, SDS-PAGE results were abnormal in 5/25 patients (20%). Urine cytology was classified as either normal or ‘no significant abnormality’ (Class 1) in all patients apart from one sample at 7-day follow-up that was classed as showing a Class 3 abnormality (atypia). In the pilot study, 2/25 patients had Class 2 abnormalities and 1/25 patients had a Class 3 abnormality. Overall, the urine tests did not suggest adverse renal effects of AR-C69931MX infusion.

(iv) Haemodynamic and ECG monitoring. There were no clinically significant mean changes in blood pressure or pulse rate in any part of the study. ECG changes were those expected for the patient population under study.

Pharmacokinetics and Pharmacodynamics

(i) Pharmacokinetics. The pharmacokinetic profile of AR-C69931XX is illustrated in Fig. 1 (d-f). The elimination of plasma AR-C69931XX is biphasic. Estimates of the mean population pharmacokinetic parameters indicated that clearance of AR-C69931XX was rapid (44.3 ± 6.4 L/h) while the initial volume of distribution was small (5.10 ± 1.77 L), indicative of containment to the plasma. The estimated mean population half-life was less than 5 min, with 90% patients having a half-life less than 9 min. The mean volume of distribution at steady state was 13.37 L. Clearance did not appear to change with either the infusion duration or the infusion rate, with no extension of the secondary phase of clearance at the longer infusion durations. Unexpected falls in plasma level of AR-C69931XX, noted particularly in Step 4 (3.5 h) in Part 3, were most likely due to underdelivery of drug occurring as a result of the complex study protocol with regular changes of infusion syringe in the first 4 h of the study.

(ii) Platelet aggregation. The effects of AR-C69931MX infusion on ADP-induced platelet aggregation at different sampling timepoints are illustrated in Fig. 1 (a-c). A clear dose-dependent effect on platelet aggregation is seen. The mean level of inhibition was similar for the infusion doses 0.2 and 2 g/kg/min in all 3 Parts regardless of the infusion dose in the preceding step(s) indicative of the rapid onset of effect and rapid achievement of steady state level of inhibition (within 30 min of onset of infusion). The proportion of patients with 100% inhibition of aggregation during plateau infusion was 7/11 (64%) in Part 1, 10/13 (77%) in Part 2 and 12/14 (86%) in Part 3. All patients had >80% inhibition of aggregation at infusion rates of 2 and 4 μg/kg/min. The level of inhibition of aggregation remained constant throughout the study in all Parts and there was a rapid decline in inhibitory effect of AR-C69931MX following termination of infusion regardless of the duration or dose of infusion. 23/33 (70%) patients recovered more than 60% of their baseline aggregation response by 1 h post-infusion.

Combined analysis of AR-C69931XX plasma levels and effects on platelet aggregation induced by ADP 3 μmol/L yielded an estimated mean IC50 value of 7.72 ± 9.11 ng/mL.

### Table 1  Summary of the most frequently reported adverse events occurring during treatment according to study part

<table>
<thead>
<tr>
<th></th>
<th>Part 1</th>
<th>Part 2</th>
<th>Part 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=13)</td>
<td>(n=14)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>At least one AE</td>
<td>8 (67%)</td>
<td>11 (85%)</td>
<td>14 (100%)</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0 (0%)</td>
<td>6 (46%)</td>
<td>4 (29%)</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Purpura</td>
<td>0 (0%)</td>
<td>3 (23%)</td>
<td>5 (36%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>3 (25%)</td>
<td>1 (8%)</td>
<td>1 (7%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>1 (8%)</td>
<td>2 (15%)</td>
<td>2 (14%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>AST (SGOT) increased</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
<td>3 (21%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (8%)</td>
<td>2 (15%)</td>
<td>1 (7%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (21%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>LDH increased</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (14%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>ASPPT increased</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (14%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Other lab test abnormal</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

1Injection site reactions consist of slight bleeding at injection sites (8/39) or phlebitis at a cannula site (1/39).

### Table 2  Effect of AR-C69931MX infusion on bleeding time

<table>
<thead>
<tr>
<th></th>
<th>Part 1</th>
<th>Part 2</th>
<th>Part 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=13)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>Bleeding time at baseline</td>
<td>3.1 ± 1.4</td>
<td>2.6 ± 1.7</td>
<td>3.1 ± 1.9</td>
</tr>
<tr>
<td>Bleeding time at 23 hours</td>
<td>9.5 ± 8.4</td>
<td>14.0 ± 9.7</td>
<td>16.0 ± 11.1</td>
</tr>
<tr>
<td>Ratio (treatment/pretreatment)</td>
<td>2.9 ± 2.0</td>
<td>5.2 ± 3.0</td>
<td>6.9 ± 6.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD
(iii) Bleeding time. The effects of AR-C69931MX on bleeding time (assessed after 23 h of infusion) are shown in Table 2. The differences in bleeding time between different parts were not significant due to the small sample size and wide inter-individual differences, although there was a trend for longer bleeding time for patients in Parts 2 and 3 compared to Part 1. There was not expected to be any difference between patients in Parts 1 and 2 as these patients had received the same dose of study drug at the point that the bleeding time was assessed. Amongst those patients who had bleeding times assessed whilst on treatment, there were fewer patients in Part 1 (1/11) who received low-molecular-weight heparin compared to Part 2 (10/13) with the remaining patients receiving unfractionated heparin infusion. All patients in Part 3 re-
received low-molecular-weight heparin. Combined analysis of the results for Parts 1 and 2 showed that the group receiving unfractionated heparin had a lower mean bleeding time compared to those receiving low-molecular-weight heparin (increase in bleeding time from baseline of 5.0 ± 6.2 min vs. 13.9 ± 7.8 min; p = 0.004, Wilcoxon test). The increase in bleeding time seen in patients in Part 3 was 12.9 ± 10.8 min, similar to that seen with the patients in Parts 1 and 2 who received low-molecular-weight heparin. Some of the highest bleeding times were seen in those patients who had received subcutaneous injection of low-molecular-weight heparin 2-5 h previously. Analysis of the relationship between bleeding time and plasma AR-C69931XX concentration showed that there was little correlation between these two variables (Fig. 2), adding further weight to the conclusion that the type of heparin co-administered with AR-C69931MX could be the main determinant of bleeding time rather than the plasma AR-C69931XX concentration.

Discussion

This multicentre study demonstrates that the platelet P2Y receptor antagonist AR-C69931MX is well tolerated as an adjunct to standard therapy, including aspirin and heparin, in patients with unstable angina or non-Q-wave MI, yielding effective and stable inhibition of ADP-induced platelet aggregation over a prolonged infusion of up to 72 h. AR-C69931MX rapidly reaches steady state plasma level and inhibition of platelet aggregation, within 30 min of onset of infusion, without the need for a bolus dose, and the plasma half-life is remarkably short, being less than 9 min in most patients. Thus, the effects of AR-C69931MX on platelets are rapidly reversed following termination of infusion. The pharmacokinetic and pharmacodynamic profiles of AR-C69931MX may be ideal in the management of patients with acute coronary syndromes in which thrombotic complications and progression of the disease process are most likely at the onset of the syndrome, such that it is preferable to attain the target antithrombotic effect as rapidly as possible (18). Furthermore, the very short half-life allows for rapid reversal of antithrombotic effect should bleeding complications arise or if haemostasis is required for urgent interventional treatment. These properties clearly distinguish AR-C69931MX from the thienopyridines, which have a slow onset of action and irreversible effect on platelets (13). The high levels of inhibition of ADP-induced platelet aggregation achieved in this study contrast with more modest levels of inhibition achieved by the thienopyridines (~40-50% inhibition for ADP 2 and 5 μM), although different aggregation methodologies have been used (14). Direct comparisons of the effects of clopidogrel and in vitro AR-C69931MX in both healthy volunteers (19) and patients undergoing coronary stent implantation (20) confirm that substantially greater inhibition of ADP and TRAP-induced platelet aggregation can be achieved by AR-C69931MX compared to clopidogrel.

Safety issues. The inhibitory effects of AR-C69931MX are associated with a significant increase in bleeding time when this agent is administered in addition to aspirin and heparin, reflecting the important role ADP plays in haemostasis. This was commonly accompanied by trivial bleeding, particularly oozing from subcutaneous injection sites, but was not associated with any more substantial bleeding complications in this study. The higher bleeding times seen in patients receiving low-molecular-weight heparin, compared to those receiving unfractionated heparin, may partly reflect the study design, since many bleeding time measurements were made in the morning, several hours after patients had received subcutaneous injection of low-molecular-weight heparin. Levels of anti-Xa activity peak between 2 and 5 h after subcutaneous injection (21). The pharmacokinetic profiles of subcutaneous low-molecular-weight heparins and the bleeding arising from their injection sites may favour the intravenous route of administration when heparins are given with combinations of antiplatelet agents that yield substantially more powerful antiplatelet effects than aspirin alone.

Significant increases in serum transaminases were seen in this study during the course of AR-C69931MX infusion. The modest extent of these increases, with predominant elevation of ALT rather than AST, does not suggest gross hepatocellular necrosis and may indicate only cell leakage of enzymes (22). Raised transaminases are a recognised effect of heparins and other drugs (23) and, since this was not a placebo-controlled study, it is not possible to determine whether the observed increases were attributable to AR-C69931MX. This adverse effect will therefore need to be scrutinised in further ongoing studies of AR-C69931MX. Preliminary data from a phase II double-blind placebo-controlled study of AR-C69931MX showed no difference between the drug-treated and placebo groups in elevation of serum transaminases (24).

Therapeutic potential. It may be questioned what advantages P2Y receptor antagonism by AR-C69931MX might have over the more developed strategy of GPIIb/IIIa antagonism? Since the glycoprotein IIb/IIIa receptor is the final common pathway for platelet aggregation, it can be postulated that antagonism of this receptor may be superior to the strategy of blocking receptors of platelet activation, such as the ADP receptors. However, there is wide interindividual variation in response to given doses of GPIIb/IIIa antagonist and a relatively narrow therapeutic window in terms of safety and efficacy (25-31) and GPIIb/IIIa antagonists have relatively limited effects on platelet activation and secretion compared to their effects on aggregation (32). These limitations might explain why GPIIb/IIIa antagonists have had only modest benefits in the conservative medical management of acute coronary syndromes (33-35). On the other hand, secreted ADP serves as an amplification system for responses to other agonists such that antagonism of ADP receptors has a broad inhibitory effect on platelet responses to all agonists (2, 7, 8). AR-C69931MX is an effective inhibitor of platelet P-selectin expression, granule secretion and procoagulant responses induced by strong agonists such as TRAP, characteristics that may prove ideal in the treatment of arterial thrombosis (7). Furthermore, there is a limit to the extent to which increasing concentrations of AR-C69931MX will inhibit platelet responses and this is likely to yield a wider therapeutic window compared to GPIIb/IIIa antagonists (7, 36). Animal studies of AR-C69931MX and the GPIIb/IIIa antagonist lamifiban, studying stenosed femoral artery in a dog model of arterial thrombosis.
bositis, showed that the prolongation of bleeding time was substantially less for AR-C69931MX than lamifiban at doses which completely inhibited cyclical flow reduction (16). These animal studies suggest that P2Y1 receptor antagonism may target and effectively treat arterial thrombosis with less effect on haemostasis than effective doses of GPIIb/IIIa antagonists. The tolerability of AR-C69931MX in this study provides the first evidence in support of this hypothesis, although clearly much larger clinical studies are required to investigate the clinical effects of this agent and to compare these effects with those of other antithrombotic agents.

Conclusions. AR-C69931MX is a potent and effective inhibitor of ADP-induced platelet aggregation in patients with acute coronary syndromes. It has both a rapid onset of action, rapidly achieving steady state plasma levels and inhibitory effects that remain stable over a 72 h period, and a very short half-life. It was well tolerated by patients in this study as adjunctive therapy to aspirin and heparin, with no major or minor bleeding (TIMI criteria) although injection site bleeding was common. AR-C69931MX infusion was associated with a significant rise in bleeding time. Overall, these properties indicate that AR-C69931MX is suitable for further investigation as an antithrombotic agent.

Appendix

Co-ordinating Investigator: RW Wilcox
Centres, Principal Investigators and Co-Investigators: Principal investigator cited first, number of patients treated in brackets.

Netherlands: Medisch Spectrum Twente, Enschede (6): GP Molhoek, P Slinkman
United Kingdom: University Hospital, Nottingham (13): RG Wilcox, RF Storey; Hairmyres Hospital, East Kilbride (11): KG Oldroyd, BD Vallance; Western Infirmary, Glasgow (6): WS Hillis, G McCann, D Muir, L Swan; Glenfield Hospital, Leicester (3): AH Gershlick, J Baron.

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References

7. Storey RF, Sanderson IM, White AE, May JA, Cameron KE, Heptinstall S. The central role of the P2Y1 receptor in amplification of human platelet acti-


36. Storey RF, Curry SN, Heptinstall S. In vitro evidence supporting direct platelet P2Y receptor antagonism as an alternative strategy to glycoprotein IIb/IIIa receptor antagonism. Heart 2000; 83 (Suppl.1): 17.

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