END OF STUDY REPORT

Study Title: Study of the effect of morphine on prasugrel absorption in patients with prior history of ST elevation myocardial infarction.

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Chief Investigator: Dr Alison Morton

Sponsor: Sheffield NHS Teaching Hospitals Foundation Trust

List of Principal Investigators and Sites	**DR ALLISON MORTON, SHEFFIELD NHS TEACHING HOSPITALS FOUNDATION TRUST**
List of Publications (or plans for publications) including those for patients (if applicable)	**PRESENTED IN THE YOUNG INVESTIGATORS SESSION AT EUROTHROMBOSIS 2013 – PAPER CURRENTLY BEING DRAFTED FOR SUBMISSION**
Study Start Date **Study End Date**	**1 FEBRUARY 2012** **5 JUNE 2013**
Study Design	Open-label, cross over study of 12 patients in two phases. Administration of prasugrel 60 mg and either morphine or saline; crossover after 3 weeks washout to prasugrel 60 mg and either saline or morphine. Patients randomly allocated to saline/morphine or morphine/saline sequence of administration. Visit 1 Preliminary screening visit. Written informed consent obtained. Venesection performed to check serum biochemistry (urea, electrolytes, creatinine, liver enzymes) and full blood count. Following this visit, the blood results were reviewed and if patients still met the inclusion and exclusion criteria then, within 3 weeks, they attended for Visit 2. Visit 2. Whole day visit. Participants had an intravenous cannula placed in a forearm vein or vein in the elbow for obtaining serial blood samples and another intravenous cannula in the other forearm for administration of intravenous study medication. Participants had pupil size, blood pressure and pulse rate at baseline recorded. Blood samples were

	also taken for platelet function. Participants received an intravenous 2.5mg dose of morphine or placebo (saline) followed after 5 minutes by a further matching 2.5 mg dose of morphine or saline if respiratory rate was > 10/minute and oxygen saturation was > 95%. Patients who had a respiratory rate < 10/minute or oxygen saturation < 95% after the initial dose of morphine did not receive further intravenous study medication. Cyclizine 50mg was administered intravenously if needed for control of nausea. All patients then received a 60mg oral dose of prasugrel 10 minutes after administration of the intravenous morphine/saline. They had blood pressure, pulse rate, respiratory rate and oxygen saturations measured every 5mins for the first 15 minutes and then prior to blood sampling unless clinically indicated to be performed more frequently. Patients had pupil size recorded and blood samples taken for platelet function measurements taken at the following time points: 1) prior to any study medication 2) immediately after morphine/saline administration but prior to prasugrel administration 3) 0.5, 1, 2, 4 and 6 hours post prasugrel dose Plasma was collected and stored at 80 degrees centigrade prior to analysis of prasugrel and its active metabolite levels by mass spectroscopy. Visit 3: 24 hours post prasugrel dose patients underwent further venesection for platelet function measurements. After a washout period of 3 weeks (+ 1 week) following the dose of prasugrel, patients then crossed over from the morphine or saline group to saline or morphine respectively and attended again for Visits 4 and 5. Visit 4: Repeat of procedures at Visit 2. Visit 5: Repeat of procedures at Visit 3.
No. of Patients	**12**
Main inclusion/exclusion criteria	**INCLUSION:** 1. Admission to hospital with a STEMI >12m prior to recruitment 2. The patient must have given written (personally signed and dated) informed consent before completing any study related procedures (i.e. any assessment or evaluation that would not have formed part of their normal medical care). 3. The patient must be between 18 75 years of age. 4. Female participants must be postmenopausal, defined as 'when a woman has experienced twelve consecutive months of amenorrhea (lack of menstruation) without a period'. 5. Willing and able to provide informed consent 6. Previous prasugrel and morphine sulphate use with no adverse effect. This will be ascertained from the medical notes when screening for potential participants. 7. Body weight > 60kg

	Patients take Prasugrel for 1 year following their STEMI. As we require patients not to be on the drug when recruited, **EXCLUSION** 1. The patient has any other medical condition or abnormality (e.g. malignancy or complication) that in the opinion of the investigator would impact upon the safety or efficacy of the study treatment or any study assessments. 2. The patient is enrolled in another research project, unless it is a study administering questionnaires/interviews only. 3. Active respiratory disorder, resting oxygen saturation < 95% or decompensated congestive cardiac failure 4. Current use of antiplatelet or anticoagulant drugs apart from aspirin 75 mg daily, or receipt of any dose of clopidogrel, prasugrel or ticagrelor in the last 2 weeks 5. Current use of opiate analgesia 6. Any condition that the investigator believes may place the patient at substantially increased risk of bleeding, such as active bleeding, iron deficiency anaemia, uncontrolled hypertension, history of stroke, transient ischaemic attack or intracranial bleeding, or active cancer (other than localised skin cancer). 7. Age > 75 years 8. Body weight less than 60 kg 9. Active liver disease 10. Haemoglobin < 10 g/dl or platelet count < 100 x 109/dl 11. Serum Creatinine >180micromol/L 12. Drug or alcohol (> 40 units/week) misuse 13. Psychiatric or neurological illness that could interfere with compliance with the study protocol or impair understanding of the study 14. Insufficient forearm veins for intravenous cannula insertion 15. Female participants must not be pregnant or trying to conceive.
Investigational Medicinal Product(s) (including comparator, if applicable) and mode of administration	Test IMP - 60mg Efient (Prasugrel hydrochloride); film-coated tablet Test IMP – 2.5mg x 2 Morphine Sulphate: intravenous Test IMP – Sodium chloride 0.9% solution for injection
Duration of Treatment	**1 DAY**
Primary and Secondary Objective(s)	To assess the effects of morphine on the absorption and onset of action of prasugrel in patients with a prior history of STelevation Myocardial Infarction (STEMI).
Endpoints/ Outcome Measure(s)	**PRIMARY OUTCOME:**

	VerifyNow P2Y12 PRU measurement at 2 hour post dose. **SECONDARY OUTCOME:** Estimated time to PRU less than 150; maximal LTA response to ADP 20 microM at 2 hour post dose; final LTA response to ADP 5 microM at 2 hour post dose.
Statistical Methods	Paired ttest to compare the primary endpoint in the morphine and control phases and significance attached to P value less than 0.05. If the primary endpoint is significantly different between the two groups then the secondary endpoints will be assessed in order until such time as a nonsignificant P value is reached, again with significance $P < 0.05$. Observational longitudinal analyses will be conducted to assess the individual relationships between time to recovery of baseline pupil size and time to PRU less than 150.
Conclusions	This study has shown a significant reduction in the mean PRU at 2h post dose when patients receive morphine therapy (89.9 (14.5) vs 60.1 (42.9). This implies that morphine does delay the onset of action of Prasugrel. This may have significant clinical implications for patients undergoing primary percutaneous coronary intervention and futher confirmatory larger studies are being planned

Authorised by: Dr Allison C Morton

Signature:

Date: _16th April 2014