Gupta+Adgey pg 36-42:Gupta+Adgey pg 36-42 24/2/06 9:33 am Page 1

Meeting the NSF targets for door-to-needle time in acute myocardial infarction – the role of a bolus thrombolytic

VELMURUGAN C KUPPUSWAMY, DANIELA WEBBE, SANDEEP GUPTA

Abstract

Coronary heart disease (CHD) remains the leading cause of premature death in the United Kingdom.[1] The mortality from myocardial infarction (MI) can be reduced by reperfusion of the infarct-related artery with thrombolytic agents.[2,3] The best results for survival are achieved in those patients who are thrombolysed early.[4,5] We set out to investigate whether the time between arrival to hospital of a patient with acute MI and administration of thrombolytic therapy (door-to-needle time) could be improved by the introduction of a bolus thrombolytic in the accident and emergency (A&E) department in a busy inner city hospital. This study of 13 months' duration compared the door-to-needle times and the proportion of patients thrombolysed within 30 minutes before and after the introduction of a bolus thrombolytic agent – reteplase. The findings demonstrated a 37% reduction in door-to-needle time (from 27 minutes to 16 minutes) and a 22% improvement in the proportion of patients thrombolysed within 30 minutes (from 68% to 86%) with reteplase. Our findings suggest that bolus thrombolytic agents such as reteplase can be used in a strategy to meet the National Service Framework (NSF) targets for door-to-needle time.

Key words: thrombolysis, bolus thrombolytic, reteplase, tissue plasminogen activator.

Br J Cardiol 2006;**13**:36–41

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

Introduction

Coronary heart disease remains the leading cause of premature mortality in the United Kingdom.[1] Recent evidence suggests that approximately 300,000 patients suffer a myocardial infarction (MI) annually and about a third of them die before they reach the nearest hospital.[1-2] Those who survive are at an increased risk of mortality in the first 12 hours following MI.[3] Compelling evidence suggests that the elevated risk of mortality from MI is reduced by early administration of thrombolytic drugs.[4] Furthermore, survival outcomes are time-dependent (i.e. the time elapsed between the onset of symptoms and the initiation of thrombolysis), with the best results achieved in patients who were thrombolysed earliest.[5,6] Although primary percutaneous coronary intervention (PCI) remains an option, it is beyond the scope of this article.

Delays in the initiation of thrombolysis may occur before and/or after a patient is admitted to hospital. Pre-hospital delays are particularly relevant in rural areas where patients may be far away from the nearest district hospital and in cases where patients delay seeking help and present late. Atypical symptoms and non-diagnostic electrocardiograms (ECGs) on presentation may further delay the time between the patient reaching hospital and the initiation of reperfusion therapy – defined as "door-to-needle time". A number of previous audits have demonstrated that door-to-needle times in unequivocal MI for many hospitals in the country lie outside the National Service Framework (NSF) for Coronary Heart Disease (CHD) target of 30 minutes.[7-9]

Multiple strategies have been implemented to reduce pain-to-needle times with varying success: pre-hospital thrombolysis by paramedics;[10,11] patient fast-tracking from accident and emergency (A&E) to the coronary care unit (CCU);[12] changing the site of thrombolysis from CCU to A&E[13] and the employment of specialist thrombolysis nurses in A&E who can diagnose acute MI and thrombolyse.[14-18] An additional strategy adopted in many centres to minimise in-hospital treatment delay is the use of a bolus agent (such as reteplase or tenecteplase) in place of an infusion agent like tissue plasminogen activator (t-PA) for its logistic advantage.[19] This article will focus on the application of such an approach at Whipps Cross University Hospital, London, as a strategy for meeting the NSF door-to-needle targets.

Methods

We conducted a prospective study of a 13-month period between September 2002 and September 2003. Data were collected as part of the hospital's ongoing participation in the Myocardial Infarction National Audit Project (MINAP). The audit standard used was the NSF for CHD target for thrombolysis that states at least 75% of patients diagnosed with an acute MI should be thrombolysed within 30 minutes of arrival at the hospital.[19] The 'door' time is defined as the time of arrival at the hos-

Department of Cardiology, Whipps Cross University Hospital, Whipps Cross Road, Leytonstone, London, E11 1NR.
Velmurugan C Kuppuswamy, Research Fellow in Cardiology
Daniela Webbe, Clinical Principal Pharmacist
Sandeep Gupta, Consultant Cardiologist
Correspondence to: Dr S Gupta
(email: sgupta111@aol.com)

Gupta+Adgey pg 36-42:Gupta+Adgey pg 36-42 24/2/06 9:33 am Page 2

Table 1. Month-by-month comparison of door-to-needle times (minutes) by the nurse-led thrombolytic service

Infusion (t-PA) thrombolytic (n=38)				Bolus (reteplase) thrombolytic (n=30)			
Month	**n=**	**Mean (SD)**	**Median (IQR)**	**Month**	**n=**	**Mean (SD)**	**Median (range)**
1	9	19 (12)	17 (13)	1	4	8 (1.2)	8 (2.5)
2	10	21 (18)	15 (17)	2	4	20 (10)	19 (19)
3	5	26 (11)	33 (-)	3	1	-	-
4	5	26 (39)	38 (73)	4	3	20 (13)	14 (-)
5	9	42 (23)	45 (39)	5	5	15 (5)	18 (10)
				6	3	21 (12)	15 (-)
				7	3	27 (16)	22 (-)
				8	7	14 (2.5)	15 (3)

Key: SD = standard deviation; IQR = interquartile range

Figure 1. Mean door-to-needle times for both systems of thrombolysis delivery. Error bars show mean (within one standard error of the mean [SEM])

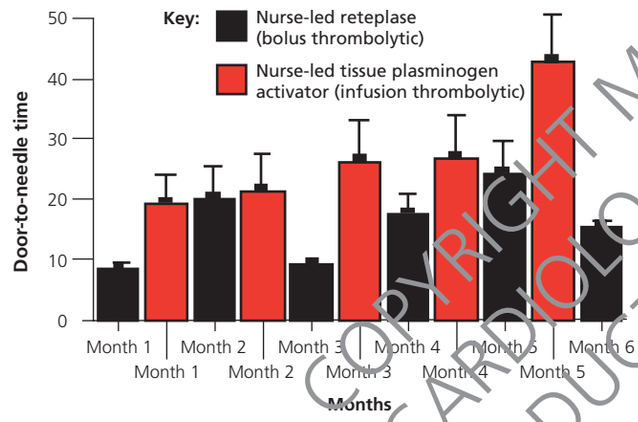
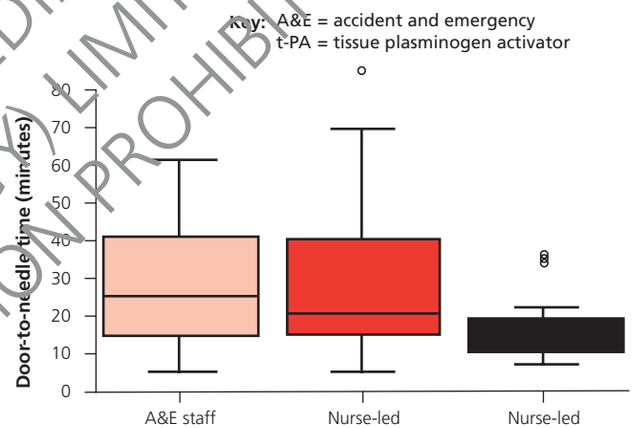


Figure 2. Boxplot and the whiskers showing the mean door-to-needle time with the standard error for the three systems of thrombolysis



COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

pital as recorded by the paramedic crew, or time of registration in A&E for self referrals and the 'needle' time is defined as the time of initiation of thrombolysis.

The current system of thrombolysis at Whipps Cross University Hospital is a thrombolytic nurse-led service in A&E between the hours of 9 am to 5 pm. It was initiated in September 2002 as a strategy to meet the NSF target. During the 'out of hours' period, the hospital reverts back to the traditional system, which is thrombolysis by A&E staff and/or the on-call medical team. Reteplase was introduced in place of t-PA in February 2003 as an additional step towards achieving the NSF target. The objective of this audit was to compare the impact of reteplase to the current performance of t-PA. Patients presenting with a non-diagnostic ECG, with relative contraindications to thrombolysis and/or previous thrombolysis with streptokinase were excluded. The audit also looked at our performance during the out of hours service.

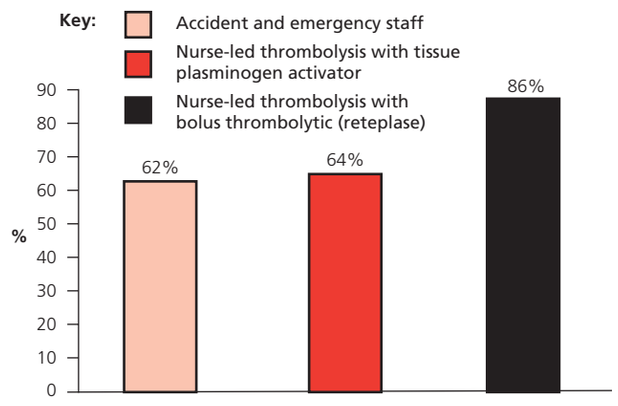
Results

A total number of 139 patients were thrombolysed during the audit period. Of this total, 24 patients were excluded. Of the remaining 115 patients, 38 and 30 were thrombolysed with t-PA and reteplase respectively by the nurse; 26 and 21 were given t-PA and reteplase respectively by A&E staff during the out of hours period.

Looking at the nurse-led service, table 1 gives a month-by-month breakdown of door-to-needle times and figure 1 shows the month-by-month comparison of the mean door-to-needle times. Thrombolysis with reteplase achieved a significantly faster door-to-needle time, with a median of 16.9 minutes (95% CI between 13.5 and 20.4) compared with 27.2 minutes (95% CI between 20.9 and 33.4) for t-PA. The difference between the two means was 10.3 minutes (Independent student *t*-test = 95% CI 3.1 to 17.2 and p<0.005) (figure 2). The nurse-led service

Gupta+Adgey pg 36-42:Gupta+Adgey pg 36-42 24/2/06 9:33 am Page 3

Figure 3. The proportion of patients thrombolysed within the National Service Framework target of 30 minutes



Key messages

- Outcome following acute MI is time-dependent – the earlier the reperfusion, the better the survival
- Thrombolysis of the infarct-related artery remains the best strategy in place for patients with acute MI in rural parts of the country and in some cites
- Evidence suggests that the door-to-needle time in many NHS Trusts is well below national targets
- Bolus thrombolytic therapy may have a logistical advantage over existing agents and may reduce time delay
- Our audit demonstrated that a bolus thrombolytis may reduce the door-to-needle time by a third and improve the proportion of patients thrombolysed within three minutes by a fifth, thus achieving national targets

using reteplase thrombolysed a statistically significant proportion of 86% of patients (26 of 30) within 30 minutes of arrival to the hospital, compared with 64% of patients (24 of 38) who were thrombolysed with t-PA (difference = 22%) (figure 3).

Of the patients thrombolysed with reteplase by the A&E staff during the out of hours period, the mean door-to-needle time was 40 minutes with 61.5% of patients being thrombolysed within 30 minutes. Of the patients thrombolysed with t-PA, the door-to-needle mean was 39.6 minutes and 62% of patients were thrombolysed within 30 minutes. There was no statistically significant difference between the two agents. Figure 2 compares the mean door-to-needle times of the three systems: nurse-led thrombolysis with t-PA, nurse-led thrombolysis with reteplase, and thrombolysis by A&E staff with either agent.

Discussion

The early reperfusion of the infarct-related coronary artery is the gold standard in the management of acute MI. The rate of survival achieved by reopening the occluded arteries is time dependent, with the greatest results seen in patients thrombolysed within 60 minutes of onset of symptoms (call-to-needle time), which led the Department of Health to enforce national targets of achieving a 60-minute call-to-needle time and a 30-minute door-to-needle time. Furthermore, the government has emphasised that at least 75% of eligible patients should receive thrombolysis within 30 minutes of their arrival at hospital.

Many hospitals have implemented mechanisms to improve their current performances and to move towards achieving the national targets. Multiple strategies such as pre-hospital thrombolysis, fast tracking and the introduction of a nurse-led A&E thrombolytic service in A&E have been explored. Although there had been significant improvements in both the mean time and the proportion of patients being thrombolysed within the door-to-needle target time, Whipps Cross audit data still showed that nationally proposed standards were not being met before the introduction of our current protocol.

The introduction of a bolus agent to the nurse-led thrombolytic service has significantly impacted patient care at Whipps Cross University Hospital. We have demonstrated that our strategy is an effective means of reducing door-to-needle time. Not only was door-to-needle time reduced with the bolus agent, compared to use of the infusion agent, it was also more consistent as demonstrated by minimal standard errors (figure 2). In addition, we were able to achieve and exceed the NSF target to treat eligible patients within 30 minutes. Although the study noted no difference between the two agents during the out of hours service, it has clearly demonstrated that the system of nurse-led thrombolysis with a bolus agent is superior to both nurse-led thrombolysis with an infusion agent and to thrombolysis by the A&E staff with either agent.

Limitations

This is a prospective audit that monitored the impact of the change in clinical practice. It is possible that the data-set may be incomplete and that some of the improvements witnessed may have been a result of the audit process rather than an improvement in clinical care – the Hawthorne effect. The increased use of reteplase in the post-change period may have contributed to the improved door-to-needle times – secondary to the logistical advantage reteplase has over steptokinase. Finally, the influence of ongoing staff education and positively changed attitudes after meeting the door-to-needle time targets should not be ignored.

Acknowledgements

The authors would like to thank all emergency care department and coronary care unit staff for their support throughout this audit, with particular thanks to: Ms Rhona Schwartz, cardiac

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

Gupta+Adgey pg 36-42:Gupta+Adgey pg 36-42 24/2/06 9:33 am Page 4

nurse specialist, who collected the data, and Mr Terry Coker, MINAP data input administrator.

Conflict of interest

SG has received honoraria for speaker meetings related to thrombolytic agents and myocardial infarction. VCK and DW: none declared.

References

1. British Heart Foundation. *Coronary heart disease statistics.* London: British Heart Foundation, 2004.
2. Chambless L, Keil U, Dobson A *et al.* for the WHO MONICA Project. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985-1990. *Circulation* 1997;**96**:3849-59.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**ii**:349-60.
4. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. *Lancet* 1988;**i**:545-9.
5. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311-22.
6. Boersma E, Maas ACP, Deckers JW *et al.* Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**:771-5.
7. Birkhead JS, on behalf of the joint audit committee of the British Cardiac Society and a cardiology committee of Royal College of Physicians of London. Time delays in provision of thrombolytic treatment in six district hospitals. *BMJ* 1992;**305**:445-8.
8. Hood S, Birnie D, Swan L *et al.* Questionnaire survey of thrombolytic treatment in accident and emergency departments in the United Kingdom. *BMJ* 1998;**316**:274.
9. Department of Health. *National Service Framework for Coronary Heart Disease* (Modern standards and service models). London: Department of Health, 2000.
10. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian Region Early Anistreplase Trial. *BMJ* 1992;**305**:548-53.
11. Gupta S. Pre-hospital thrombolysis in acute MI: has its time come? *Cardiology News* 2003;**6**:6-9.
12. Flisher D. Fast track: early thrombolysis. *Br J Nurs* 1995;**4**:562-5.
13. Hourigan CT, Mountain D, Langton PE *et al.* Changing the site of delivery of thrombolytic treatment for acute myocardial infarction from the coronary care unit to the emergency department greatly reduces door to needle time. *Heart* 2000;**84**:157-63.
14. Hughes C, Scott K, Saltissi S *et al.* The effect of an acute chest pain nurse (ACPN) on door to needle times at an inner city teaching hospital. *Heart* 1997;**77**(suppl 1):49.
15. Wilmshurst P, Purchase A, Webb C *et al.* Improving door to needle times with nurse initiated thrombolysis. *Heart* 2000;**84**:262-6.
16. Moorhby A, Rowe H, Walsh F *et al.* Closing the audit loop: nurse led thrombolytic therapy. *Heart* 1997;**77**(suppl 1):192.
17. Caunt J. The advanced nurse practitioner in CCU. *Care of the Critically Ill* 1996;**12**:136-9.
18. Quinn T. Can nurses safely assess suitability for thrombolytic therapy? A pilot study. *Intens Crit Care Nurs* 1995;**11**:126-9.
19. Leah V, Clark C, Doyle K, Coats TJ. Does a single bolus thrombolytic reduce door to needle time in a district general hospital? *Emerg Med J* 2004;**21**:162-4.

COPYRIGHT MEDIVIEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

COMMENTARY

Which lytic?

Due to impressive improvements in the delivery of thrombolysis over the past few years, most patients who suffer an ST elevation myocardial infarction (STEMI) in the UK now receive reperfusion therapy within 60 minutes of calling for help.[1]

Which thrombolytic they receive, however, remains something of a lottery.

The newer bolus thrombolytics tenecteplase and reteplase have become increasingly popular in recent years, administered either as part of a fast-track in-hospital protocol or by a paramedic before the patient reaches hospital. Other patients receive alteplase, delivered by an initial intravenous (IV) bolus injection, followed by an IV infusion. Meanwhile streptokinase infusions remain the low-cost option widely used by many hospitals.

Some would argue that the choice of thrombolytic matters far less than the speed with which it is given. Certainly the 'hypothetical curve', created by Gersh *et al.* from an analysis of recent reperfusion trials, emphasises that speed is of the essence in the care of acute myocardial infarction.[2] They showed that during the first two to three hours after symptom onset, reperfusion produces a striking benefit in terms of mortality and myocardial salvage. Thereafter, the benefit decreases steeply with time.

In essence, Gersh *et al.* are simply proving the old adage that 'time is muscle' and that the earlier we can achieve patency in STEMI patients the better. This was also demonstrated in the GUSTO 1 (Global Use of Strategies To Open occluded coronary arteries) study where mortality was lowest (4.4%) among patients with normal coronary flow at 90 minutes and highest (8.9%) among patients with no flow.[3]

However, data from GUSTO 1 also showed that the choice of thrombolytic had a direct influence on the level of patency achieved. There was a 2.5 times greater likelihood of achieving 90-minute TIMI 3 flow with accelerated tissue

Gupta+Adgey pg 36-42:Gupta+Adgey pg 36-42 24/2/06 9:33 am Page 5

plasminogen activator (t-PA) compared with streptokinase.[4] In patients with anterior myocardial infarction, streptokinase was associated with a 45–48% reduced likelihood of TIMI 3 flow 90 minutes post-thrombolytic therapy over the entire range of patient body weights examined compared with accelerated t-PA.

The superiority of t-PA over streptokinase in achieving patency is thought to be due to its greater specificity for fibrin and its ability to lyse more highly cross-linked fibrin.

The choice of thrombolytic can also directly influence the time it takes to initiate treatment once the patient has called for help. Use of a bolus thrombolytic, for instance, will shorten the time to treatment by at least the 30 minutes it takes to prepare an infusion. Bolus thrombolytics may also help to reduce medication errors and can be used to initiate treatment before the patient has even arrived at hospital.

According to the Joint Royal Colleges Ambulance Liaison Committee, over 1,000 STEMI patients in England received paramedic-led pre-hospital thrombolysis in the first half of 2005.[5] In all, over 3,000 patients have now received such treatment and 27 of the country's 31 ambulance services are now trained to give thrombolysis. Pre-hospital thrombolysis clearly reduces delay and also reduces mortality. One meta-analysis found a 17% improvement in survival among patients who receive thrombolysis before they reached hospital.[6]

Within hospital, bolus agents are also ideally suited to the fast-track protocols that have been instrumental in the recent reductions in door-to-needle times.

So, if bolus thrombolytics are to be considered the first-line treatment of choice, does it matter which one we use? Both tenecteplase and reteplase are derivatives of t-PA but there are a number of crucial differences in their molecular structure.

Reteplase is a single chain deletion mutant of t-PA in which the fibronectin finger region is deleted. Best results are achieved with a double bolus of 10 units each, 30 minutes apart.

In contrast, tenecteplase is not a deletion mutant of t-PA. Its fibrin selectivity remains relatively high. Its plasma half-life of approximately 20 minutes allows for single bolus treatment.

The ideal thrombolytic

Clearly it is preferable for there to be some consistency in the thrombolytic treatment we offer our STEMI patients, wherever they receive it. This requires us to decide what we want from a thrombolytic agent and which of the currently available options comes closest to this ideal. Most cardiologists would agree that the ideal thrombolytic would achieve maximum patency in the shortest possible time and have minimal bleeding complications. It would be easily administered as a bolus, have a prolonged half-life and be highly specific for fibrin.

Based on these characteristics, it is no surprise that tenecteplase has recently become the most frequently used thrombolytic agent for STEMI in the UK. We may also need to question whether there is any justification for the continued use of streptokinase.

Jennifer Adgey

After all, if you had to have a thrombolytic, which one would you choose?

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

Conflict of interest

JA has received research grants from Roche and Boehringer Ingelheim.

References

1. MINAP Steering Group. *How the NHS manages heart attacks.* MINAP Fourth Public Report, 2005. (www.rcplondon.ac.uk)
2. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. *JAMA* 2005;**293**:979-86.
3. GUSTO-1. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators *N Engl J Med* 1993;**329**:1615-22.
4. Lundergan CF, Reiner JS, McCarthy WF, Coyne KS, Califf RM, Ross AM. Clinical predictors of early infarct related artery patency following thrombolytic therapy: importance of body weights, smoking history, infarct related artery and choice of thrombolytic regimen: The GUSTO 1 experience. *J Am Coll Cardiol* 1998;**32**:641-7.
5. Ambulance Service Association/Joint Royal Colleges Ambulance Liaison Committee. *Thrombolysis update.* ASA/JRCALC Clinical Effectiveness Programme, August 2005. (www.asancep.org.uk)
6. EMIP Investigators. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. *N Engl J Med* 1993;**329**:383-9.

Jennifer Adgey
Consultant Cardiologist
Regional Medical Centre,
Royal Victoria Hospital,
Grosvenor Road, Belfast, BT12 6BA.

Br J Cardiol 2006;**13**:41–2