SCIENTIFIC LETTER

Is warfarin a contraindication to thrombolysis in acute ST elevation myocardial infarction?

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The use of thrombolysis to treat ST elevation myocardial infarction (MI) is well supported. Serious adverse events occur in 1–2% of patients.¹ Warfarin is increasingly prescribed to patients at high cardiovascular risk and it is inevitable that these patients will present with an MI that warrants thrombolytic treatment. The British National Formulary and the American Heart Association both advise that patients on warfarin present a relative contraindication to thrombolysis, but this has resulted in uncertainty in providing patients with the optimum medical management.

Streptokinase and tissue plasminogen activators activate the conversion of plasminogen to plasmin, which rapidly degrades formed thrombus. In contrast, warfarin inhibits the carboxylation of the vitamin K dependent clotting factors II, VII, IX and X (extrinsic system) rendering these factors inactive.

Anecdotally physicians differ in their advice regarding thrombolysis for patients prescribed warfarin. Before the present study, all acute care physicians and cardiologists at the University Hospitals of Leicester NHS Trust were surveyed anonymously about their use of thrombolysis for such patients. Three respondents (of 38 replies received) advised thrombolysis regardless of the international normalised ratio (INR). Of the others, 24 would advise thrombolysis only if the INR was less than 3. This was irrespective of grade and specialty.

Primarily, the objective of this study was to investigate the thrombolysis complication rate among patients prescribed warfarin at the time of admission for an MI. For this purpose, we retrospectively audited a large coronary care unit database covering seven years of recorded information.

METHODS

Data on all patients admitted to a coronary care unit from 1 January 1997 to 31 December 2003 were sufficiently complete to allow a robust study.

All patients given thrombolysis ($n = 2437$) were identified and data were extracted regarding demographics, medical history including drug history, diagnosis, vital signs on admission, treatment including thrombolytic agent and recorded complications including a requirement for repeat thrombolysis. Bleeding complications associated with thrombolysis were defined as proved or suspected intracranial haemorrhage (ICH), large or small gastrointestinal bleeding event and external haemorrhage, including haematuria and bleeding from the mouth or nose.

All patients who were taking warfarin and presenting with an MI were identified irrespective of their treatment ($n = 95$). This group comprised 50 patients who had been given thrombolysis. Sixty two patients had a final diagnosis of an ST elevation MI, but only 32 received thrombolytic agents.

RESULTS

Table 1 presents the basic demographic and presentation characteristics of warfarin and non-warfarin treated patients

who received thrombolysis. In the non-warfarin group, 150 patients (6.3%) had bleeding complications compared with four patients (8%) in the warfarin group. The four patients in the warfarin group were older than 75 years and had an admission blood pressure greater than 150 mm Hg systolic. Three INR values were documented: 2.9, 3.9 and 4—the second and third were associated with ICH and these patients died within 30 days. In addition, two patients had received thrombolysis twice: one complicated by a small gastrointestinal bleed and the other by an ICH. In comparison, the study identified six patients in the warfarin cohort who were older than 75 years and with an admission systolic blood pressure greater than 150 mm Hg, who did not have complications from thrombolytic drugs. Interestingly they had a mean initial INR of 1.5 (range 1.2 to 2).

There was a trend towards a greater occurrence of serious complications (ICH or large gastrointestinal bleeds) in the warfarin group (non-warfarin 1.47%, warfarin 4%) but was not significant.

In the second part of the analysis, those patients who had thrombolytic bleeding complications were analysed in more detail to determine whether any factors may have influenced this outcome. The 150 non-warfarin group patients with bleeding complications were compared with those who had not bled. Multiple regression analysis (SPSS V.11.0; SPSS, Chicago, Illinois, USA) indicated that age ($p < 0.001$), aspirin use ($p = 0.015$) and repeat thrombolysis ($p = 0.026$) significantly influenced the bleeding complication rate ($p < 0.001$, $r^2 = 0.4$; additional covariates were smoking and systolic blood pressure at presentation).

Similarly, in the warfarin group, the four patients with bleeding complications were compared with those without complications. Multiple regression analysis indicated that only the INR ($p = 0.004$) and repeat thrombolysis rate ($p = 0.004$) significantly influenced the occurrence of bleeding complications ($p < 0.001$, $r^2 = 0.44$; additional covariates were age ($p = 0.082$) and systolic blood pressure at presentation ($p = 0.057$) and were just non-significant).

The final analysis sought to determine whether patients taking warfarin were denied thrombolysis. The warfarin group thrombolysis rate (51.6%) was significantly lower than that of the non-warfarin group (70.55%, $p = 0.002$). The reasons given for withholding thrombolysis (predominantly ineligible ECG, late presentation and uncontrolled blood pressure) were similar to the reasons given for the non-warfarin group. Only one patient was denied thrombolysis solely on the basis of existing warfarin treatment.

DISCUSSION

Only 1.47% of patients receiving thrombolysis had an ICH or large gastrointestinal bleed in this “real life” study of over

Abbreviations: GUSTO, Global Use of Strategies To Open occluded coronary arteries; ICH, intracranial haemorrhage; INR, international normalised ratio; MI, myocardial infarction

Table 1 Demographics, presentation and complications of patients who received thrombolytic drugs compared by warfarin prescription on admission

	Patient group	
	Warfarin	Non-warfarin
Number	50	2387
Men	64%	69%
White	88%	82.2%
Age (years)	72.82 (1.3)	65.6 (0.26)
Medical history		
Myocardial infarction	54%	21.7%
Stroke	16%	5.7%
Hypertension	44%	36.1%
Dyslipidaemia	20%	17.6%
Diabetes	24%	15.3%
Initial INR	2.4 (0.14)	NA
Systolic blood pressure (mm Hg)	141.4 (5.16)	139.4 (0.63)
Pulse (beats/min)	89.6 (3.77)	77.9 (0.52)
Anterior myocardial infarction	42%	40.8%
Streptokinase	58%	52.4%
Retepase	42%	47.6%
Door to needle time (min)	83.3 (8.94)	66.01 (1.33)
Bleeding complications	4 (8%)	150 (6.3%)
Cerebral haemorrhage	2 (4%)	25 (1.05%)
Large GI bleed	0	10 (0.42%)
Small GI bleed	2 (4%)	66 (2.76%)
External haemorrhage	0	49 (2.05%)
Allergic reaction to thrombolysis	2%	0.96%
Repeat thrombolysis	8%	8.2%

Data are mean (SEM).

GI, gastrointestinal; INR, international normalised ratio; NA, not applicable.

2000 patients; however, the risk of excessive bleeding was greatest among patients who were older, taking antiplatelets or treated with thrombolysis twice. Although there is no significantly increased risk of bleeding for patients taking warfarin, multiple regression analysis showed that repeat thrombolysis and a raised initial INR are key factors associated with an increased risk in this cohort. All patients who were taking warfarin and bled after thrombolysis, however, were older than 75 years and had an admission systolic blood pressure greater than 150 mm Hg.

The risk of bleeding while taking warfarin increases with age, high INR, recent onset of treatment and history of vascular disease.² The consequences of treating patients receiving full anticoagulant treatment with thrombolysis have been investigated only in relation to ICH,³ which identified a low body weight and age over 65 years as independent risk factors. ICH accounted for 45.3% of all

strokes (1.4% of patients) in GUSTO-1 (Global Use of Strategies To Open occluded coronary arteries) after thrombolysis and significant risk factors were increasing age, history of cerebrovascular disease or hypertension, diastolic blood pressure at presentation and combination thrombolytic treatment.⁴

Therefore, these study findings are comparable with other data. Although the number of adverse events within the warfarin group precludes providing definitive advice, the use of thrombolysis should not be contraindicated purely because a patient is concurrently receiving anticoagulants. Elderly patients with a raised admission blood pressure are at increased risk, and use of bedside INR monitoring may allow informed and immediate decisions regarding thrombolysis to be made; alternatively, primary percutaneous coronary intervention should be considered for those with a high INR. Although the efficacy of rescue percutaneous coronary intervention compared with repeat thrombolysis has yet to be fully established, this study suggests that repeat thrombolysis should be used with caution for patients taking warfarin.

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