Assessment of the practicality and safety of thrombolysis with anistreplase given by general practitioners

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SUMMARY

Background. *Recent guidelines recommend that patients with obvious acute myocardial infarction receive thrombolysis, unless contraindicated, within 60–90 minutes of summoning assistance. If this target is to be achieved, an increasing number of general practitioners are likely to be involved in the administration of thrombolytic agents.*

Aim. *This study aimed to assess the practicality and safety of thrombolysis with anistreplase when given by general practitioners.*

Method. *An observational study was conducted in 805 general practices throughout the United Kingdom. Between March 1991 and September 1992, a total of 3383 patients with a clinical diagnosis of myocardial infarction were recruited — 888 by 344 general practitioners who wished to include anistreplase in their management of myocardial infarction ('user' group) and 2495 by 776 general practitioners who did not wish to use anistreplase but who were willing to provide information about their cases ('comparison' group).*

Results. *More than half the patients were seen within two hours of onset of symptoms. A high frequency of contraindications to thrombolysis, diagnostic uncertainty, and other, mainly practical, reasons limited the number of occasions on which anistreplase was administered. Thus, only 310 patients were given anistreplase in the community. The general practitioners in the study used anistreplase safely. Their diagnostic accuracy was high (of the 310 patients given anistreplase 69% had a definite, possible or probable myocardial infarction, 4% a definite non-cardiac diagnosis), the number of patients given anistreplase in spite of a documented contraindication was small (seven patients), and the doctors appeared to be aware of potential bleeding problems associated with thrombolysis. In all cases, the complications of acute myocardial infarction appeared to be managed appropriately.*

Conclusion. *General practitioners can use anistreplase both appropriately and safely in the early management of acute myocardial infarction. Recognized contraindications to thrombolysis and practicalities of diagnosis and drug administration may, however, limit the number of occasions on which anistreplase is used.*

Keywords: myocardial infarction; thrombolytic therapy; immediate care; general practitioner role; medical decision making.

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Introduction

IN April 1989, the Royal College of General Practitioners was approached by Beecham Research (now part of SmithKline Beecham) to see whether it would be willing to conduct a post-marketing surveillance study of anistreplase. Several clinical trials had already shown the therapeutic potential of thrombolysis,[1-5] and greater benefits appeared to be achieved by the early rather than later administration of thrombolytic preparations.[4] It was thought that this evidence might encourage some general practitioners to start providing thrombolysis in the community. Although general practitioners could legitimately have done so (all of the marketed agents are licensed for use by any qualified medical personnel), at the time all of the safety data relating to these agents were derived from hospital-based studies. Indeed, uncertainty about the safety and efficacy of pre-hospital thrombolysis was highlighted in guidelines on the role of general practitioners in managing patients with myocardial infarction, produced by a British Heart Foundation working group in 1989.[6] The RCGP was also concerned that the introduction of domiciliary thrombolysis should be carefully monitored, particularly in view of the uncommon but serious side events associated with these preparations.

The RCGP myocardial infarction study was therefore conducted in order to assess the practicability and safety of anistreplase when administered by general practitioners in the community in the early management of suspected myocardial infarction. A secondary objective was to obtain contemporary information about other aspects of the management of myocardial infarction by general practitioners.

A number of randomized clinical trials of the pre-hospital use of thrombolysis have subsequently been published.[7-11] A meta-analysis of the five trials found a significant 17% relative reduction in mortality at one month among those given thrombolysis prior to hospital admission.[10] A clear trend of greater benefit from earlier treatment was also found in an overview which included hospital based trials of fibrinolytic therapy.[12] The Grampian region early anistreplase trial has been the only trial to investigate the early administration of anistreplase by general practitioners compared with its later use by hospital physicians.[9] Domiciliary thrombolysis resulted in a median time saving of two hours and significant reductions in measures of cardiac damage and three month mortality.[9] These benefits have continued to be apparent; at the end of one year mortality among patients treated at home was halved.[13]

The importance of these observations is reflected in more recent guidelines from a British Heart Foundation working party which recommended that patients with obvious acute myocardial

infarction receive thrombolysis, unless contraindicated, within 60–90 minutes of summoning assistance.[14] If this target is to be achieved, an increasing number of general practitioners are likely to be involved in the administration of thrombolytic agents. Indeed, the guidelines specifically state that general practitioners should initiate thrombolytic therapy in areas where transport times to hospital are prolonged, or where delays in hospital are great.[14] The RCGP myocardial infarction study provides the first data about whether general practitioners can administer thrombolysis safely when providing routine clinical care rather than when participating in a formal clinical trial.

Method

All of the doctors participating in the study were volunteers who responded to a letter of invitation sent to every general practitioner in the United Kingdom between March and June 1991. Two groups of doctors were recruited: 1339 who stated that they wished to include, where possible, the use of anistreplase in their management of myocardial infarction ('user' group), and 2237 who did not wish to use anistreplase but who were willing to provide information about their cases of myocardial infarction ('comparison' group). In all, 344 doctors in the user group (based in 253 practices) and 776 doctors in the comparison group (552 practices) recruited patients.

Participating doctors were asked to record on special forms brief details of all patients seen with symptoms suggestive of myocardial infarction. If the clinical diagnosis, which may or may not have included supportive evidence from an electrocardiogram carried out in the home, was not thought to be myocardial infarction no further information was collected. If myocardial infarction was thought to have occurred, the doctors supplied details of patients' clinical condition and pre-hospital management, including their eligibility for thrombolysis. No further information was collected for patients in whom thrombolysis was contraindicated. The remaining patients, as well as those given anistreplase at home in spite of a documented contraindication, were observed for a total of 12 months. Information collected during follow up and recorded on follow-up forms included the final diagnosis and treatments received in hospital.

Since the study was an observational study of current practice, it was important that any changes that might occur as a result of participation in the investigation were minimized. In particular, anistreplase was to be used in accordance with the published data sheet which does not require an electrocardiogram for the confirmation of the diagnosis prior to its administration. Participating doctors, however, were advised when recruited of the benefits of having access to defibrillation equipment when attending patients suspected of having a myocardial infarction and were recommended, in the absence of any contraindication, to give such patients 150 mg of dispersable aspirin by mouth. The doctors were also reminded that all injections should be given intravenously, both for efficacy and in order to avoid haematoma formation following thrombolysis.

Patient recruitment began in March 1991 and finished on 30 September 1992. The original intention was that each group of doctors would recruit 5000 patients over a two-year period. Patient recruitment, however, was slower than expected, particularly by doctors in the user group. By July 1992, it was obvious that the study would not recruit the expected numbers. Since sufficient information about the feasibility of using anistreplase and about other aspects of the current management of myocardial infarction had already been collected, the study's steering committee decided to stop patient recruitment in September 1992.

The doctors who chose to be in each group were likely to be different in a number of ways, including their interest in cardiology. Care, therefore, should be taken when comparing the experience of patients recruited by each set of doctors. Although the patients in the comparison group provided information about the frequency of events that occur during the early stages of myocardial infarction, they did not constitute a formal control group in the conventional, clinical trial, sense. For this reason, formal statistical tests were not performed on observed differences between groups. Life table analysis was used to calculate 28-day mortality rates.

The independent RCGP clinical research ethics committee gave ethical approval for the study, which was deemed by the Medicines Control Agency to fulfil the quadripartite agreement for the conduct of postmarketing surveillance studies.[15]

Results

A total of 3596 patients with chest pain were recruited (1015 in the user group and 2581 in the comparison group), of whom 3383 were managed as if they had myocardial infarction (888 in the user group and 2495 in the comparison group).

The patients recruited in each group were similar in terms of age, smoking habits, and past medical history (Table 1). There was a greater proportion of men in the user group given anistreplase than in the user group not given thrombolysis or in the comparison group.

A greater proportion of patients in the user group had a documented contraindication than those in the comparison group (28.8% versus 23.3%). The main difference was in the proportion of patients reported by general practitioners to have active gastrointestinal or internal bleeding: doctors recorded this contraindication for 12.5% of contraindicated patients in the user group compared with 4.6% of contraindicated patients in the comparison group. Fewer patients in the user group had a history of

Table 1. Characteristics of patients recruited to the study.

	% of patients		
	User group		
	Anistreplase given (n = 310)	Anistreplase not given (n = 578)	Comparison group (n = 2495)
Age at recruitment (years)			
⩽49	9.4	9.9	7.7
50–69	49.0	47.8	50.1
70+	41.0	41.7	41.8
Not known	0.6	0.7	0.3
Sex			
Male	72.3	66.6	65.3
Female	27.7	33.4	34.7
Smoking habits at recruitment			
Smoker	28.7	25.3	27.0
Non-smoker	63.9	66.8	62.6
Not known	7.4	8.0	10.4
Past medical history			
Previous myocardial infarction	24.8	24.4	25.1
Angina/coronary heart disease	14.8	14.0	15.2
Peripheral vascular disease	2.6	2.6	1.9
Hypertension	12.9	14.5	12.0
Diabetes mellitus	3.9	6.6	5.1

n = total number of patients in group.

cerebrovascular disease than those in the comparison group (27.3% versus 31.2%).

Just over half the patients in each group were seen within two hours of the onset of symptoms (Table 2). The median time interval between the onset of symptoms and the doctor's arrival was 90 minutes for patients in the user group and 100 minutes for patients in the comparison group. Data were not collected on the time between onset of symptoms and call for help, or on the response times of the general practitioners.

Community use of anistreplase

Of the 888 patients with a working diagnosis of myocardial infarction in the user group, 310 (34.9%) were given anistreplase in the community by 182 general practitioners. Seven of the 310 patients had a contraindication to thrombolysis (four had had previous cerebral thrombosis or ischaemia, and three transient ischaemic attacks). Of the 310 patients given anistreplase 214 (69.0%) had an electrocardiogram taken beforehand; 151 of these patients (70.6%) subsequently had their diagnosis confirmed in hospital. In the comparison group, 506 patients without a contraindication to thrombolysis (20.3%) had an electrocardiogram taken; 228 of these patients (45.1%) had a hospital-confirmed infarction. Most of the 961 doctors who performed an electrocardiogram (80.9%) felt it to be helpful, irrespective of whether they wished to provide thrombolysis. Copies of the domiciliary electrocardiograms were not collected, so an independent assessment of the tracings was not possible.

The general practitioners in the user group were asked to detail why they decided not to use anistreplase in certain patients (Table 3). In a large proportion of patients treatment was not possible because of a recognized contraindication or diagnostic uncertainty. Practical problems associated with anistreplase, particularly the need for storage in a refrigerator, were also important. Thus, in 130 of the 888 cases (14.6%) the drug was not available. In some of these cases, the doctors did not think from the preliminary information provided that the patient was likely to be having an infarction, and so they did not take the drug with them. On other occasions the doctors were diverted from another visit while on call and were unable to return home or to the surgery to obtain the anistreplase from the refrigerator. Twenty seven patients were not given anistreplase because of a condition which, although not a recognized contraindication, made the general practitioner feel that its use was inappropriate. For example, one doctor felt that the patient's unexplained anaemia may have been due to occult gastrointestinal bleeding and therefore he did not wish to administer anistreplase. Many of the conditions mentioned (including history of peptic ulcer, indigestion, post-operative bleeding problems, epistaxis and current use of steroids or anti-inflammatory drugs) suggested that the doctors were keenly aware of possible haemorrhagic problems associated with thrombolysis.

Table 2. Interval between the onset of symptoms and the doctor's arrival.

Time interval (hours)	Cumulative % of patients[a]	
	User group (*n* = 862)	Comparison group (*n* = 2429)
<1	*31.7*	*29.2*
<2	*53.4*	*52.6*
<3	*64.0*	*64.6*
<4	*71.1*	*71.1*
4+	*100*	*100*

n = total number of patients in group. [a]Time of onset of symptoms and/or doctor's arrival missing for 92 patients.

Table 3. Reason why anistreplase was not given by doctors in the user group.

	% of patients[a] (*n* = 888)
Recognized contraindication	*28.0*
Uncertain diagnosis	*21.3*
Patient died before treatment possible	*1.2*
One or more other reason specified:	*30.1*
Anistreplase not available	*14.6*
History of condition thought to preclude use	*3.0*
Treatment thought to be inappropriate	*3.0*
Adverse clinical state of patient	*1.8*
Other practical reasons	*1.7*
ECG did not confirm myocardial infarction	*1.6*
Prompt admission thought to be preferable	*1.5*
Patient being managed at home	*0.9*
Cardiac arrest before treatment	*0.7*
Other miscellaneous reasons	*1.7*
No reason given	*0.3*

n = total number of patients in group. ECG = electrocardiogram. [a]More than one reason could be given.

Important events after all prehospital treatments

The doctors were asked for details of any clinically significant event following treatment (Table 4). In no case could causality be determined since a number of factors, such as differences in the time of administration of therapy and other treatments given, could have influenced the frequency of reported events. Most of the reported episodes (93.7%) related to the period between administration of treatment and the transfer of the patient to hospital (that is, getting into the ambulance).

Hypotension and/or bradycardia was reported more frequently in patients given anistreplase than in the other groups (Table 4). Six of the 10 patients given anistreplase who had bradycardia were also given atropine, compared with none of the two patients in the user group not given anistreplase, and five of the 16 patients in the comparison group. Atropine was also administered more often to hypotensive patients given anistreplase (six/20) compared with those not given anistreplase (zero/two) and those in the comparison group (one/13). Tachycardia and an irregular pulse were more frequent in patients given anistreplase.

There were no cases of anaphylaxis. Events which might represent an allergic reaction (such as shock, unconsciousness, drowsiness, dizziness, breathlessness or chest tightness) were infrequent in all groups.

Haemorrhagic events were uncommon. One patient had a subdural haematoma approximately six hours after the administration of anistreplase. The event occurred after the blood pressure rose to high levels (230/140 mmHg); the patient vomited, became comatose and died without regaining consciousness. The haematoma (confirmed by computerized tomography) was thought to be due to the sudden uncontrollable rise in blood pressure. The certified cause of death was acute subdural haematoma, with acute myocardial infarction the underlying cause. Another patient had a transient ischaemic attack after treatment with anistreplase. This resolved with no ill effects.

Details of the four patients who experienced backache soon after receiving anistreplase have been published elsewhere.[16]

Nine of the patients given anistreplase at home (2.9%), 12 patients in the user group not given anistreplase (2.1%) and 42 patients in the comparison group (1.7%) were reported to have had a cardiac arrest in the community. Nine of these 63 events occurred in the ambulance. The user doctors successfully resuscitated 12 of the 18 patients who arrested at home (67%), and the comparison doctors successfully resuscitated 18 of the 36 cases

Table 4. Important events documented by general practitioners after all prehospital treatments.

	% of patients		
	User group		
	Anistreplase given (n = 310)	Anistreplase not given (n = 578)	Comparison group (n = 2495)
Hypotension without bradycardia	4.5	0.3	0.4
Hypotension with bradycardia	1.9	0	0.2
Bradycardia without hypotension	1.3	0.3	0.5
Tachycardia	3.2	0.9	0.5
Cardiac arrest	2.9	2.1	1.7
Irregular pulse, including atrial fibrillation	2.3	0.9	0.2
Hypertension	0	0.2	0
Cardiac failure/ cardiogenic shock/ shock/peripheral circulatory failure	0.6	1.9	1.1
Unconsciousness/ drowsiness/vasovagal attack/dizziness	1.0	0.7	1.1
Tremor/spasm/fit	1.3	0	0.1
Breathlessness/ chest tightness/ respiratory arrest	1.9	0.5	0.4
Backache	1.3	0	0
Vomiting blood/ unspecified haemorrhage	0.6	0	0
Subdural haematoma/ transient ischaemic attack	0.6	0	0

n = total number of patients in group.

occurring in their presence (50%). In many instances the general practitioner was assisted by ambulance staff.

Admission to hospital

Of the 310 patients given domiciliary thrombolysis, 287 (92.6%) were transferred to hospital, 20 were cared for in a community hospital (6.5%) and three (1.0%) were kept at home. Treatment with anistreplase at home was associated with a small delay in admission to hospital: the median time interval between the doctor's arrival and transfer to hospital was 45 minutes for 304 patients given anistreplase, 30 minutes for 509 patients in the user group not given anistreplase and 30 minutes for 2340 patients in the comparison group. The median time interval between the onset of symptoms and transfer to hospital was 150 minutes for 813 patients in the user group (irrespective of whether anistreplase was given), and 135 minutes for 2340 patients in the comparison group.

Final diagnosis for patients given anistreplase

In 198 of the 310 patients given anistreplase (63.9%), the infarction was subsequently confirmed by electrocardiogram changes, cardiac enzymes and/or other investigations. Another 17 patients (5.5%) were thought to have had a probable or possible myocardial infarction. Other cardiac conditions, such as unstable angina, ischaemic heart disease, left ventricular failure and atrial fibrillation, were given as the final diagnosis in a further 62 patients (20.0%). Some of the patients given angina as the final diagnosis were thought by the general practitioner or their hospital colleagues to have had an impending infarction aborted by the early administration of anistreplase. There was, however, no objective confirmation of these clinical impressions.

Thirteen of the patients given anistreplase (4.2%) had a non-cardiac final diagnosis — musculoskeletal pain (three), chest infection (three), peptic ulcer (two), oesophagitis (two), exacerbation of chronic obstructive airways disease (one), alcohol abuse (one) and possible fractured rib (one). In a further 14 patients (4.5%) the hospital doctor was unable to reach a definitive diagnosis. No information was available from the general practitioner on the final diagnosis for six patients (1.9%).

28-day mortality rates

Sixty patients could not be included in the life table analysis because of incomplete data (14 deaths occurred in these patients; five in the user group not given anistreplase and nine in the comparison group). When all available information was analysed, patients in the user group not given anistreplase appeared to have a poorer 28-day mortality rate (76 deaths; 18.7%) than those given anistreplase (37 deaths; 12.7%), or those in the comparison group (284 deaths; 13.9%). However, when deaths occurring before treatment would have been possible were excluded, the differences in 28-day mortality rate narrowed: patients in the user group not given anistreplase 65 deaths (16.8%), in the user group given anistreplase 37 deaths (12.7%) and in the comparison group 270 deaths (13.4%).

Discussion

The earlier recommendations of a British Heart Foundation working group[6] have been updated.[14] The new guidelines stress that a variety of options need to be developed to ensure that patients with myocardial infarction receive rapid diagnosis and treatment.[14] Optimal care will include the rapid provision of basic and advanced life support, adequate analgesia, aspirin, adequate diagnosis and, when indicated, thrombolytic therapy. In some cases, particularly when journey times or hospital delays are prolonged, general practitioners may need to provide thrombolysis. It is important to know, therefore, whether such therapy can be used practically and safely in the community.

The data presented here suggest that general practitioners often have the opportunity to provide thrombolysis soon after myocardial infarction occurs; just over half of the patients were seen within two hours of onset of symptoms. The number of occasions on which domiciliary thrombolysis is likely to be given, however, may be more limited. In this study, a quarter of all patients thought to have had a myocardial infarction had a recognized contraindication to thrombolysis. In addition, for 9% of patients recruited by user doctors, the patient had a history of a condition thought to preclude use (for example, indigestion or current use of steroids or anti-inflammatory drugs), treatment was thought inappropriate, the patient was in an adverse clinical state or prompt admission was thought to be preferable. Although some of these conditions might be thought to be of dubious significance, many of the general practitioners were working in areas where their hospital colleagues gave little support and occasionally declared active opposition to the concept of domiciliary thrombolysis. It is perhaps not surprising, therefore, that some general practitioners were cautious in its use. Diagnostic uncertainty also precluded the use of thrombolysis in a large number of patients. The practitioners clearly demanded a higher level of certainty for the administration of a thrombolytic than simply a working diagnosis of myocardial infarction.

In addition to these clinical factors, the study highlighted a number of important practical problems associated with anistreplase. The need to store anistreplase in a refrigerator often resulted in the drug not being available when the doctors attended patients with chest pain. Furthermore, many doctors were reluct-

ant to keep the drug both at their surgery and at their home because of its expense. The availability of a cheap, thermostable, rapidly administered preparation would offer a clear advantage over anistreplase and may help the wider adoption of domiciliary thrombolysis.

The diagnostic accuracy of the general practitioners who used anistreplase was good; 69% of the patients given anistreplase in the community had a subsequent confirmation of a definite, probable or possible myocardial infarction and few had a definite non-cardiac diagnosis. Other studies which did not require electrocardiogram confirmation of diagnosis for patient recruitment have found comparable rates of diagnostic accuracy. In the Anglo-Scandinavian study of early thrombolysis, 72% of the patients had a subsequent confirmation of myocardial infarction,[5] and in the Grampian region early anistreplase trial the figure was 78%.[9] None of the studies, including our own, was able to determine how many patients initially thought not to have myocardial infarction actually had the condition (the diagnostic false negative rate).

Seven patients in this study were given anistreplase in spite of there being a documented contraindication. Further enquiry revealed that in each case the doctor made a careful clinical judgement that the benefits of thrombolysis outweighed any possible risks of such treatment. General practitioners, who often have detailed knowledge of their patients acquired over a prolonged period of time, may be in a better position to make these difficult decisions than hospital colleagues. They may also be in a better position to exclude thrombolysis from the management of patients who do not have a recognized contraindication but who might be more likely to bleed after such treatment.

The frequency of reported adverse events following anistreplase was low. In most cases, the event appeared to have been handled appropriately. The high rate of success in resuscitating patients who had a cardiac arrest was particularly noteworthy. This was reassuring in view of the significant but small increased risk of ventricular fibrillation following thrombolysis reported by the European myocardial infarction project group,[10] and the observation that domiciliary thrombolysis inevitably resulted in a small delay in the patient's admission to hospital. These findings also emphasize the critical need for defibrillation equipment to be available when attending all patients suspected as having had a myocardial infarction, irrespective of the treatments offered. The observation that in many cases the practitioner was helped by ambulance colleagues highlights the benefits of both groups attending patients with chest paint.[14,17]

Since the start of the RCGP myocardial infarction study, thinking about the early use of thrombolysis has matured in the light of accumulating data. The role of the general practitioner in providing thrombolysis has become clearer[14] and more hospital doctors are supportive of the concept of pre-hospital thrombolysis.[14,18,19] At present, however, few general practitioners provide thrombolysis and only a minority feel that the provision of such treatment is part of their job.[20] This position may have to change if the targets set by the British Heart Foundation working party are to be met.[14,19] Support from hospital colleagues will be important: a recent survey of general practitioners revealed that most were unwilling to use thrombolysis unless encouraged to do so by their local cardiologist.[18]

This study has shown that many general practitioners had the opportunity to provide early thrombolysis. In addition, those who chose to do so appeared to do so carefully. The frequency of adverse events was low, and those that did occur were handled appropriately by the participating general practitioners. Further study is needed, however, in order to ascertain whether this continues to be the case if the community use of thrombolysis becomes more widespread.

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