PRELIMINARY REPORT

Effect of an α_2 agonist (mivazerol) on limiting myocardial ischaemia in stable angina

K Fox, H J Dargie, D P de Bono, M F Oliver, E Wülfert, T Kharkevitch

Abstract

A specific α_2 agonist, mivazerol, known to be effective in reducing myocardial ischaemia when given intravenously immediately before an exercise tolerance test, produced a significant increase in exercise duration and time to the onset of angina when given orally over a two week period to 25 patients with stable angina. A non-significant trend to reduction in electrocardiographic signs of ischaemia was also noted. The clinical relevance of this improvement now needs to be tested in larger numbers.

(*Heart* 1999;**82**:383–385)

Keyword: α_2 agonist; sympathetic activity; myocardial ischaemia; stable angina; exercise tolerance test

Department of Cardiology, Royal Brompton and Harefield NHS Trust, London, UK
K Fox

Clinical Research Initiative in Heart Failure, University of Glasgow, Glasgow, UK
H J Dargie

Faculty of Medicine, Clinical Sciences Wing, Glenfield General Hospital, University of Leicester, Leicester, UK
D P de Bono

Cardiac Medicine, National Heart & Lung Institute, Imperial College of Science, Technology and Medicine, Dovehouse Street, London SW3 6LY, UK
M F Oliver

Research and Development, Cardiovascular Department, UCB SA Pharma Sector, Braine-l'Alleud, Belgium
E Wülfert
T Kharkevitch

Professor de Bono died since this article was submitted for publication.

Correspondence to:
Professor Oliver.

Accepted for publication
4 March 1999

The hyperadrenergic response to stress and exercise can precipitate angina in patients with critically reduced myocardial blood flow resulting from advanced coronary atherosclerosis. Reduction of sympathetic outflow together with reduced myocardial demand, such as may be achieved through β receptor blockade, can modify the extent of myocardial ischaemia and hence ameliorate anginal symptoms. However, drugs which block β receptors can also depress myocardial function and lead to a number of adverse effects such as exhaustion, reduction of mental acuity, and breathlessness.

The possibility that reduction of sympathetic activity could also be achieved by activation of α_2 receptors deserves investigation. A new agent, mivazerol, which appears to act experimentally on peripheral α_2 receptors and at the spinal level, has this therapeutic potential. Studies of this specific α_2 agonist have shown, in conscious dogs in which transient occlusion of the left anterior descending coronary artery was induced, that electrocardiographic signs of myocardial ischaemia and coronary sinus lactate output were reduced.[1] As these dogs were maintained at a constant heart rate through pacing, this apparent beneficial effect was not a function of reduced heart rate.

Anti-ischaemic effects have been shown when mivazerol was given intravenously and orally to patients with stable angina immediately before treadmill exercise tolerance tests.[2] In these patients, all parameters of myocardial ischaemia were improved during the exercise tests. Heart rate increases during exercise were unaffected by the α_2 agonist.

These data suggest that mivazerol may inhibit increases in sympathetic tone and that it might be a valuable antianginal drug in patients. This report describes the effects of daily administration of mivazerol in 25 patients with stable angina.

Study design and conduct

Three centres were invited to participate in the study. The plan was to recruit 36 male patients, 12 from each centre, in order to provide 90% power for statistical analyses. In two of the centres it was not possible to identify an appropriate number of eligible patients; therefore the intention to treat analysis comprises 25 eligible patients.

The patients selected had stable angina for at least three months, myocardial ischaemia was documented by a positive exercise tolerance test (ST depression of 1.5 mm or more). No episode of unstable angina or myocardial infarction had occurred within the preceding three months.

Two "training" exercise tolerance tests and qualification exercise tolerance tests were given one week apart, the last on the day before the start of the study. Patients who fulfilled this qualification phase, with the development of myocardial ischaemia, entered a four week double blind crossover treatment phase (either two weeks on mivazerol or two weeks on placebo, or vice versa). Two further exercise tolerance tests were then undertaken on the 14th and 28th days of the study. Randomisation of treatment was done for each centre. A tablet of mivazerol 1200 μg, or an identical placebo, was taken twice daily over this two week period.

Total exercise duration was the primary efficacy end point. Time to 1 mm ST depression and time to the onset of angina were secondary end points. Haemodynamic parameters, number of angina attacks, and the number of glyceryl trinitrate tablets taken each week were also considered as secondary end points.

Informed consent was given and the study was approved by all three ethics committees.

Table 1 Mean haemodynamic values during exercise tolerance test

	Placebo				*Mivazerol*			
	HR (bpm)	*SBP (mm Hg)*	*DBP (mm Hg)*	*RPP (bpm × mm Hg)*	*HR (bpm)*	*SBP (mm Hg)*	*DBP (mm Hg)*	*RPP (bpm × mm Hg)*
Each minute								
Min 0	73.4	135.2	79.8	9853.6	64.6	123.7	77.4	8026.9
Min 1	91.4	–	–	–	84.8	–	–	–
Min 2	101.1	–	–	–	95.1	–	–	–
Min 3	103.6	153.3	83.2	15896.5	96.8	141.6	79.0	13787.6
Min 4	112.6	–	–	–	107.0	–	–	–
Min 5	118.7	–	–	–	111.9	–	–	–
Min 6	119.3	163.8	85.7	19826.0	115.2	156.4	82.2	18225.3
Specified time points								
Time to 1 mm ST depression	116.8	–	–	–	111.1	–	–	–
Time to onset of angina	117.3	153.3	85.4	18660.3	114.0	155.8	82.2	17934.6
Total exercise duration	128.8	171.7	83.2	22535.8	127.0	165.3	83.5	21086.1
Maximum common time	123.9	–	–	–	116.4	–	–	–

HR, heart rate: SBP, systolic blood pressure; DBP, diastolic blood pressur; RPP, rate–pressure product.

For total exercise duration, time to 1 mm ST depression, and time to onset of angina, parametric and non-parametric analyses were made. The analysis carried out on the patients' results in the two centres with small numbers implies a large confidence interval (CI) but, despite this, similar results were found for all patients analysed.

Results

Heart rate, systolic blood pressure, and rate–pressure product were lower during the two weeks of exercise tolerance tests in the mivazerol treated group (table 1).

TOTAL EXERCISE DURATION

Total exercise duration was longer in the mivazerol treated group compared with the placebo treated group (table 2). In parametric analysis the difference between the mivazerol and placebo treated groups was 38 seconds (95% CI 17 to 60 seconds) ($p < 0.002$); in non-parametric analysis, the difference was 40 seconds (95% CI 13.5 to 63.5 seconds) ($p = 0.004$).

TIME TO ST DEPRESSION

There was no significant difference between the mivazerol and placebo treated groups in the time before ST depression of 1 mm developed during the exercise tolerance test at two weeks (table 2).

TIME TO ONSET OF ANGINA

Time to onset of angina was 32 seconds longer in the mivazerol treated group during the exercise tolerance (non-parametric analysis $p = 0.03$). Figure 1 shows the number of patients having not developed angina pectoris at each minute of exercise tolerance test under mivazerol and placebo. There was no significant period nor interaction effect for all these parameters.

Table 2 Non-parametric analysis: median differences of total exercise duration, time to 1 mm ST depression, and time to onset of angina

	Difference (95% CI)	*p Value*
Total exercise duration (s) (n = 25)	40 (13.5 to 63.5)	0.004
Time to 1 mm ST depression (s) (n = 24)	15 (−0.5 to 30.0)	NS
Time to onset of angina (s) (n = 25)	32 (3.0 to 66.0)	0.03

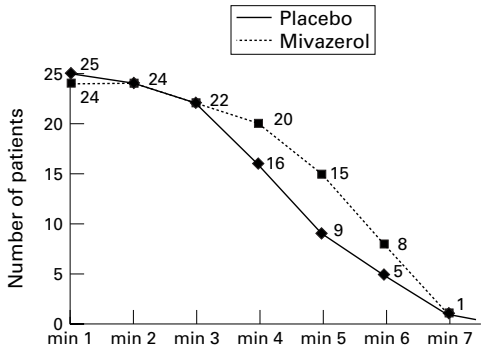

Figure 1 Number of patients without angina pectoris at each minute of the exercise tolerance test.

Discussion

Oral administration of the α_2 adrenergic agonist, mivazerol, for two weeks at a dose of 1200 µg daily to patients with stable angina led to an increase in the total duration of exercise during a standardised exercise tolerance test. There was also improvement in the time before the onset of angina but no improvement in the time for the development of 1 mm ST depression during exercise.

These results, although highly significant, are in absolute terms consistent with a small improvement in exercise capacity. They support the earlier finding that the intravenous and oral administration of mivazerol given acutely had a positive effect in patients with angina.[2]

Whether these results can be translated into clinical benefit, or could be improved by a different dose schedule or dose, remains to be evaluated by longer clinical studies.

Recently, the European mivazerol trial (EMIT)[3] has shown that mivazerol, administered during anaesthesia and surgery on a double blind placebo controlled basis, led to a significant reduction in all cause and cardiac mortality in patients undergoing major reconstructive vascular surgery.

The collaborating centres were Royal Brompton Hospital, London, Western Infirmary, Glasgow, and Glenfield Hospital, Leicester. This study was supported by a scientific grant from UCB SA Pharma Sector, Belgium.

1 Kharkevitch T, Noyer M, Guyaux M, *et al*. Mivazerol, a new alpha2-adrenergic agonist with anti-ischaemic effects in animal models of myocardial ischaemia. *J Cardiothorac Vasc Anesth* 1994;**8**(suppl 2):86.
2 Wright RA, Decroly P, Kharkevitch T, *et al*. Exercise tolerance in angina is improved by mivazerol, an alpha-2 adrenoceptor agonist. *Cardiovasc Drugs Ther* 1993;**7**:929–34.
3 Oliver MF, Goldman L, Julian DG, *et al*. Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: the European mivazerol trial (EMIT). *Anesthesiology*. [In press.]

Electronic pages: *www.heartjnl.com*

This issues launches a new venture for *Heart* with the publication of some electronic only articles. *Heart* has had a full text web site since the end of 1998[1] and the volume of traffic indicates that it is extremely popular (about 15 000 pages viewed each week).

The number of articles submitted to *Heart* has greatly increased over the past few years (between 5% and 15% increase each year and still rising). This could lead either to an increased rejection rate or a longer lag time from acceptance to publication; neither of which is desirable. The publication of electronic only material on *eHeart* means that more articles can be published without increasing the number of pages in each issue of the printed journal. This follows the model of other medical journals including *Pediatrics,* which has been successfully publishing electronic only articles since January 1997.[2]

Case reports can be a valuable contribution to medical research and education[3]; however, they often find it hard to gain space in already overstretched medical journals. In future *Heart* will publish the majority of accepted case reports and similar communications online only. The first three appear as an extension of this issue and summaries appear below. These articles will be indexed in *Index Medicus* and other services exactly the same way as papers appearing in the printed version, and they will be included in search engines such as MEDLINE.

We predict that this is just the first stage in making better use of the flexibility and power of the internet, and we envisage publishing other electronic only articles as well as supplementary data to printed articles, in a similar vein to our sister journal the *BMJ* (www.bmj.com). We welcome your comments on this new venture and any other suggestions you might have (http://www.heartjnl.com/cgi/feedback).

1 Davies MJ. The world wide web takes Heart: www.heartjnl.com [editorial]. *Heart* 1998;**81**:1.
2 Anderson K, Lucey JF. Pediatric electronic pages: looking back and looking ahead [editorial]. *Pediatrics* 1998;**102**:124–8.
3 Vandenbroucke JP. Case reports in an evidence-based world [editorial]. *J R Soc Med* 1999;**92**:159–63.

Staphylococcus capitis **endocarditis: two cases and review of the literature**

J A T Sandoe, K G Kerr, G W Reynolds, S Jain

Two cases of native valve endocarditis caused by *Staphylococcus capitis* are presented; both in patients with aortic valve disease. The patients were cured with prolonged intravenous vancomycin and rifampicin without recourse to surgery during the acute phase of the illness. Five of the six previously described cases of endocarditis caused by this organism have occurred on native valves and have responded to medical treatment alone. (*Heart* 1999;**82**:e1) www.heartjnl.com/cgi/content/full/82/3/e1

Hereditary cardiac amyloidosis associated with the transthyretin Ile122 mutation in a white man

J D Gillmore, D R Booth, M B Pepys, P N Hawkins

An 83 year old white man with atrial fibrillation was hospitalised following a cerebral infarct. Echocardiography was characteristic of cardiac amyloid deposition and subsequent tests confirmed amyloidosis of transthyretin (TTR) type, in association with the Ile122 mutation of the TTR gene, previously reported only in African-Americans in whom it occurs with an allele frequency of 2%. Haplotype analysis did not suggest a different founder than for the African Ile122 mutation. (*Heart* 1999;**82**:e2) www.heartjnl.com/cgi/content/full/82/3/e2

Intravascular ultrasound in the diagnosis of the no-reflow phenomenon after primary angioplasty for myocardial infarction

J Trevelyan, M Been

The diagnosis of the no-reflow phenomenon remains one of exclusion. This is the first published description of the use of IVUS to examine the distal vessel in the setting of a no-reflow phenomenon. IVUS may be a useful tool to detect residual high grade distal stenosis as a cause of the no-reflow phenomenon, which may be an underrecognised cause of failed reperfusion following balloon angioplasty for acute myocardial infarction. (*Heart* 1999;**82**:e3) www.heartjnl.com/cgi/content/full/82/3/e3