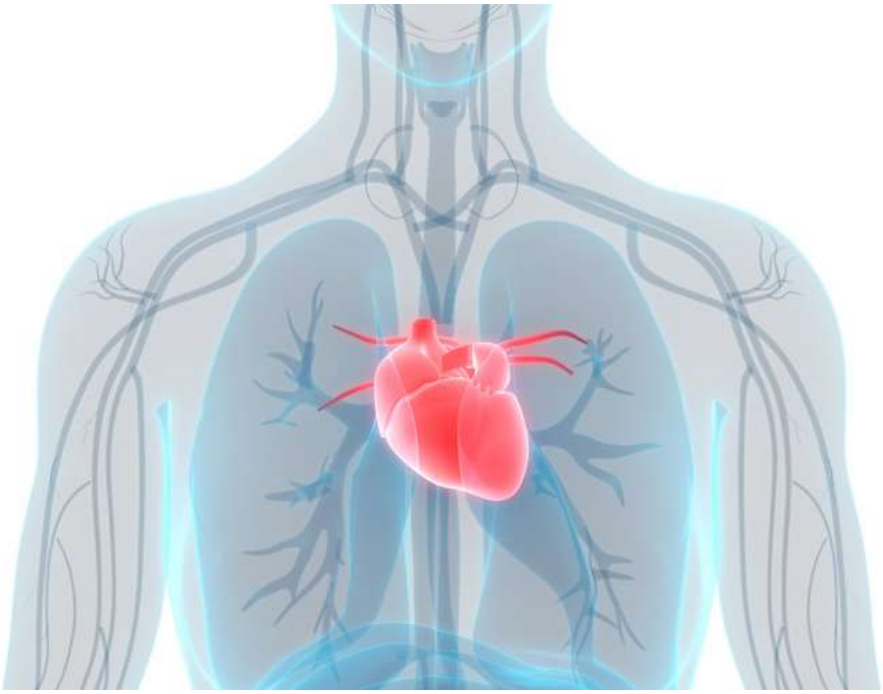

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Tolerance to an 8mg dose of perindopril for secondary prevention of coronary artery disease

teaser

This local study shows that after discharge from hospital the dose of perindopril is quite unlikely to be altered by the primary care physician to reach the target 8 mg dose. Enter the pharmacist

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Coronary artery disease (CAD) remains the leading cause of death in the Western world despite improved understanding of the pathophysiological mechanisms, improved methods for diagnosis and the availability of new treatments. Preventive measures can be aimed at preventing or delaying disease progression in high-risk patients or regressing an already well-established lesion in patients with pre-existing disease.[2]

Prevention strategies mainly involve lifestyle modifications, pharmacotherapy or invasive intervention. Pharmacotherapeutic options include aspirin, betaadrenoceptor blocking drugs and lipid-lowering drugs.[2] More effective secondary preventive strategies are needed, so angiotensin-converting enzyme (ACE) inhibitors are also being considered in preventive strategies.[3]

ACE inhibitors effectively reduce morbidity and mortality among patients with heart failure, left ventricular dysfunction, myocardial infarction and hypertension. The Heart Outcomes Prevention Evaluation (HOPE) study confirmed the benefits of ACE inhibition in patients aged 55 years or older at high risk of cardiovascular complications, characterised by a high prevalence of diabetes, hypertension, stroke and obstructive peripheral vascular disease. In addition to lowering blood pressure, ACE inhibitors possess direct cardiovascular protective effects through angiotensin II reduction and increased bradykinin availability. Consequently, ACE inhibition may result in antiatherosclerotic effects, reduced neointimal formation and improved endothelial function, plaque stabilisation and fibrinolysis. In animal models, ACE inhibitors reverse atherosclerosis.[3]

The EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) assessed the ability of the ACE inhibitor perindopril to reduce cardiovascular mortality and incidence of myocardial infarction and cardiac arrest in a broad population of patients with stable coronary heart disease and without heart failure or substantial hypertension.[3]

In spite of the rather low-risk population in EUROPA compared with HOPE, there was a significant 20% reduction in the composite endpoint (death from cardiovascular causes, infarction and resuscitated cardiac arrest), with a 2% absolute risk reduction observed in the treated group compared with the control group. More importantly, these results were observed in patients who received optimal therapy, including antiplatelet agents, beta-adrenoceptor blocking drugs and statins.[4]

The EUROPA study also concluded that perindopril 8mg daily is beneficial for preventing cardiac events in all stable CAD patients, including those with previous revascularisation.[5]

Perindopril is generally well tolerated in patients with hypertension, heart failure or CAD. In a large postmarketing surveillance study in 47,351 hypertensive patients (mean age 61 years) receiving perindopril 2¨C8 mg once daily for one year, 16% of patients spontaneously reported adverse events and 5% of patients withdrew due to adverse events. Generally, adverse events were mild and transient, with cough (characteristic of ACE inhibitors), gastrointestinal disturbances and asthenia/fatigue (all <10%) most commonly reported. In clinical trials, cough (possibly or probably related to the study drug) was the most common adverse event causing withdrawal from perindopril therapy (1.2¨C3.2% of recipients).[6]

In the EUROPA trial perindopril was well tolerated. At the end of the study, 81% of perindopril-treated patients were still in the study, with 93% receiving the 8mg daily dose.[7] Treatment withdrawals in patients treated with perindopril 8mg/day or placebo were mainly for cough (2.7% vs 0.5%), hypotension (1.0% vs 0.3%) or drug intolerance (not defined, 2.4% vs 1.3%). The adverse event profile of perindopril is generally similar to that of other ACE inhibitors, although in studies of patients with heart failure first-dose hypotension occurred less frequently with perindopril than with captopril, enalapril or lisinopril.[6]

Aims

The aims of this study were to assess the early tolerance of patients who had undergone a coronary artery bypass graft (CABG) to a rapid increase in the dose of perindopril from 2mg to 8mg over a period of three days postoperatively as opposed to a period of one month as seen in the EUROPA study; to assess the long-term tolerance of the 8 mg dose of perindopril by comparing the incidence and severity of side-effects, namely dry cough, experienced by those patients taking 2 mg and 4mg perindopril with those patients taking 8 mg; and to establish the number of patients on perindopril 8 mg within 18 months post-CABG.

Method

Patients

From November 2003 to June 2004, patients who had undergone CABG surgery at the Cardiovascular and Thoracic Surgery Unit (CTU) at St Luke's Hospital, Malta, and who were then commenced on perindopril following the intervention, were identified.

Exclusion criteria included previous intolerance to ACE inhibitors; severe renal impairment (high preoperative creatinine ¨C that is, greater than 150¦Ìmol/l); or the need for postoperative dialysis.

Study design

The escalation of dose from 2mg to 8mg perindopril was rapid and carried out over the three postoperative days while the patient was still in hospital, where close monitoring of blood pressure and renal function was straightforward.

Perindopril was administered when the patient was weaned off any inotropes, usually on the first postoperative day. The starting dose was 2mg. Hourly blood pressure and urine output recordings were made. If urine output

exceeded 1ml/kg/min and the systolic blood pressure did not fall below 100mmHg, the perindopril dose was increased to 4 mg daily on the second postoperative day. Diuretics were prescribed sparingly for oliguria, and an inadequate response was taken as an indication for not increasing the perindopril dose. In patients whose systolic blood pressure consistently failed to exceed 100mmHg, the dose was not increased. Electrolytes, urea and creatinine were measured daily. If the creatinine trend was downwards the dose was increased until 8mg was reached, as long as the patient was still hospitalised.

The primary endpoint was early tolerance to the increase in dose of perindopril from 2 mg to 8mg over three days, early after CABG, using blood pressure and renal function (serum creatinine) as the main parameters. For those patients discharged from hospital on lower doses of perindopril (2mg and 4mg) records of their hourly blood pressure charts and daily renal function tests were examined, to identify reasons for early intolerance.

The secondary endpoint was the long-term tolerance of perindopril in patients, and this was assessed during the first follow-up (eight months). The occurrence and severity of side-effects were compared in patients receiving 8 mg or lower doses of perindopril. A self-administered, mailed questionnaire was developed to collect data on the perindopril dose patients were taking and any side-effects. The questionnaire included 19 close-ended and one open-ended question and was compiled in English and Maltese. Patients were assigned to Group 1 if taking 2mg or 4 mg perindopril daily and to Group 2 if taking 8 mg perindopril daily. A pilot study using 10 patients led to slight modifications to make the questionnaire more patient-friendly and easily understood.

All patients were subsequently sent this modified postal questionnaire, in September 2004 (up to eight months post-CABG).Those patients who did not return the questionnaire by March 2005 were contacted by telephone and given the option to complete the questionnaire
over the telephone or have a replacement questionnaire sent to them.

A second follow-up (up to 18 months post-CABG) was undertaken to establish the number of patients taking 8mg within 18 months of the CABG. The aim was to investigate whether patients discharged from hospital on 8 mg perindopril remained on this dose long-term and whether those discharged on 2mg and 4mg doses had had their dose increased to 8mg. All participating patients were contacted by telephone by the principal investigator (EM) for the second follow-up, in September 2005. Four patients who could not be reached by telephone were sent a letter explaining that the study was in its final phase and were asked to state the dose of perindopril they were taking.

Ethical approval

All participants received the normal treatment plan as established by guidelines at St Luke's Hospital. Patients were contacted for follow-up and received information about the study prior to completing the questionnaire. No added intervention specifically related to the study was carried out. All patient information was treated in strict confidence, and no study details were stored with the clinical data.

Statistical analysis

The data collection instrument and all data for each patient were coded. Data were analysed using SPSS version 14.

Descriptive statistics were used in the analysis of patient demographics, patient lifestyle, concomitant diseases and concurrent medications, the use of perindopril, incidence and severity of side-effects and drug discontinuation where relevant. The incidence and severity of side-effects experienced by Groups 1 and 2 were compared using the Pearson chi-square test. Results were considered significant if $p<0.05$.

Results

Of the 55 patients identified for participation for the study, 52 were included. For the first follow-up 45 questionnaires were returned. The remaining 10 patients were contacted by telephone in March 2005, and 94.5% of patients were eligible to participate.

[[Fig 3]]

For the second follow-up, of the 46 patients still taking perindopril, 42 were reached by telephone and four were sent follow-up letters. Two of these letters were returned. The response rate at this point was 95.7% Table 1).

Thirty-nine patients (75%, n=52) were discharged from hospital on 2mg or 4mg perindopril, while 13 patients (25%, n=52) were discharged on 8mg. The sole reason for early intolerance among the patients discharged on lower doses of perindopril was a mean systolic arterial blood pressure that failed to consistently exceed 100mmHg. In such cases there was no attempt to increase the dose further.

As patients were mobilised their blood pressure naturally recovered and they tolerated perindopril better. After eight months post- CABG, 25 patients (54.3%, n=46) were taking 2 mg or 4mg perindopril, 21 patients (45.7%, n=46) were taking 8mg, and six patients (11.5%, n=52) had discontinued perindopril. Four of these patients (66.7%) were on 2mg or 4mg, and the other two patients (33.3%) were on 8 mg perindopril before discontinuation. The main reason for discontinuing perindopril was severe dry cough (three patients). Accelerated heartbeat, allergy and rash occurred in other patients.

After 18 months post-CABG, 18 patients (43.9%, n=41) were taking 2mg or 4mg perindopril, 21 patients (51.2%, n=41) were taking 8mg, one patient (2.4%, n=41) was taking 6 mg and one patient (2.4%, n=41) was taking 12mg. Three patients (6.8%, n=44) who discontinued perindopril between eight and 18 months post-CABG were on 8mg perindopril. For these patients, dry cough accounted for 75% of reasons for discontinuation (n=4). One patient discontinued perindopril for two reasons: dry cough and sleep disturbances.

Of those patients taking 2mg or 4mg perindopril, five (20%, n=25) had dizziness and seven (28%, n=25) had a dry cough. All patients with dry cough stated that the cough was mild. Nine patients (36%, n=25) had sleep disturbances. Of those patients taking 8mg, five (23.8%, n=21) had dizziness, nine (42.9%, n=21) had a dry cough: seven (77.8%, n=9) had a mild dry cough, while two (22.2%, n=9) had a severe dry cough. Ten patients (50%, n=20) had sleep disturbances.

There was no significant difference in the incidence of dizziness, dry cough and sleep disturbances or in the severity of dry cough between Group 1 and Group 2 patients (p-values were 0.755, 0.292, 0.345 and 0.182, respectively).

At the end of the study 62% of patients (n =8) discharged from hospital on 8 mg remained on this dose long term and 33% of patients (n=13) discharged from hospital on 2mg or 4mg had their dose increased to 8mg up to 18 months post-CABG.

Discussion

Many factors contributed to the response to perindopril after surgery. Most patients were kept purposely dehydrated in an effort to counteract inflammatory oedema. Inanition, analgesics and postural hypotension all contributed to low blood pressure. Moreover, the postoperative use of diuretics often resulted in low plasma sodium as part of a broad electrolyte loss, exacerbating the hypotensive response to perindopril. Normal saline given intravenously and hyperosmotic (20%) albumin solution were used to counteract this. Perindopril

administration was delayed until patients were weaned off all inotropes.

There was no statistically significant difference in the incidence of dizziness (p=0.755), dry cough (p=0.292) or sleep disturbances (p=0.345), or in the severity of dry cough (p=0.182), between patients taking 2mg or 4mg perindopril and those taking 8mg. Therefore the higher 8mg dose is not associated with a higher incidence of or more severe side-effects, and is likely to be as well tolerated among the Maltese population as the 2mg and 4mg perindopril doses in the EUROPA study. At the end of the three-year study, approximately 80% of patients were still on blinded perindopril ¨C a similar percentage to that in the placebo group. Moreover, after four years, 93% of patients were still receiving the target dose of 8mg perindopril.[7] At the end of this local study, only 51% of patients were found to be taking perindopril 8mg.

This could be due to the fact that only a third of those patients discharged from hospital on 2mg or 4mg perindopril went on to have their dose increased to 8mg up to a year and a half following surgery. In Malta, two months after their intervention patients attend an outpatient consultation clinic at which the perindopril dose is reviewed. Not all patients are reviewed personally by the consultant, and junior doctors may be more hesitant to increase the perindopril dose to 8mg.

This local study shows that after discharge from hospital the dose of perindopril is quite unlikely to be altered by the primary care physician to reach the target 8mg dose. However, with increased awareness of the advantages of the 8mg dose, namely the fact that it once a day prevents one cardiovascular death, nonfatal myocardial infarction or cardiac arrest among every 50 patients with coronary disease treated for four years, one would expect this situation to change for the greater benefit of patients.

Hospital pharmacists could be involved in contacting patients who are discharged from hospital on a dose less than 8mg to investigate whether the dose is being optimised. On presentation of a prescription for perindopril at a dose less than 8mg, community pharmacists could also contact the patient's primary care physician to discuss the possibility of increasing the dose.

Although the study sample was big enough to allow statistical analysis, results would likely have been more accurate if a larger sample had been used. Another limitation was the fact that the author did not attempt to contact patients' primary care physicians to verify reasons given for why, in specific cases, the perindopril dose was not increased to the recommended 8mg.

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