A randomised controlled study of ramipril dose-escalation packs in clinical practice

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Abstract

The benefits of angiotensin-converting enzyme (ACE) inhibitors occur early in the treatment period and may be dose-dependent. The utilisation of ACE inhibitors in cardiovascular patients is often suboptimal. This current study evaluates the clinical use of a specific ACE inhibitor dose-escalation pack.

Fifty hospital in-patients with a definite indication for ACE inhibitor therapy were randomised to receive either a dose-escalation pack or 'usual' initiation and escalation of ramipril. Patients and general practitioners received an information sheet outlining the benefits and risks of ACE inhibitors and the need for monitoring of serum urea and electrolytes. The groups were matched for age, gender, deprivation score and blood pressure. One patient died in each group and one patient withdrew from the control group. More patients in the dose-escalation group reached target dose by six weeks (72% *vs.* 33%; p< 0.01) and three months (67% *vs.* 35%; p<0.05). At three months, there were no differences in serum creatinine, urea or potassium (all p>0.05). Cough was the most commonly reported side effect although there was no difference in its incidence between the dose-escalation and control groups (8% *vs.* 6%, p>0.05). This study demonstrates that the use of a specific dose-escalation pack for the ACE inhibitor ramipril is a simple, reliable and safe mechanism for reaching a target dose. This approach could find utility with other drug therapies.

Key words: angiotensin-converting enzyme inhibitor, dose, escalation.

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Introduction

Angiotensin-converting enzyme (ACE) inhibitors have mortality and morbidity benefits in a number of cardiovascular diseases.[1-6] These benefits occur early and may be dose-dependent,[7] suggesting that prolonged delay in initiation and dose-escalation of ACE inhibitor therapy may be disadvantageous. Despite this, the utilisation of drug therapies in high-risk cardiovascular patients is suboptimal.[8,9] In keeping with these data, a pilot survey in our hospital of 140 patients two months following a myocardial infarction, revealed that only 35% who were prescribed an ACE inhibitor were at a dose of proven benefit.

The reasons for poor implementation of ACE inhibitor therapy are probably multiple, and include uncertainty regarding target dose, concerns regarding side effects and organisational problems where dose-escalation of ACE inhibitor is omitted due to insufficient review of the patient's medications.

This current study evaluates the clinical use of a specific ACE inhibitor dose-escalation pack designed to increase ACE inhibitor dose to a target dose previously proven to have morbidity and mortality benefits for patients with cardiovascular disease.[2]

Methods

Subjects

Fifty hospital in-patients with a definite indication for ACE inhibitor therapy were studied. Patients were eligible if it was the intention of the physician to prescribe ramipril to a target dose of 10 mg and if a 'test' dose of 1.25 or 2.5 mg had been tolerated. Patients were excluded if they were already prescribed an ACE inhibitor, had a history of renal failure, significant aortic stenosis or had previously failed to tolerate an ACE inhibitor. Written informed consent was obtained from each subject. The study was undertaken with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki.

Ramipril dose-escalation pack

Escalation packs were donated by Aventis. These contained 7 x 2.5 mg, 15 x 5 mg and 7 x 10 mg ramipril capsules in separate boxes for each dose. In these packs the box containing 2.5 mg capsules is available first. The subsequent higher doses cannot be accessed until this box has been removed, thus reducing the likelihood of patients taking the capsules out of sequence.

Study design

Subjects were enrolled in hospital and randomised to receive either a dose-escalation pack or 'usual' initiation and escalation of ramipril. Patients and general practitioners received an information sheet outlining the benefits and risks of ACE inhibitors

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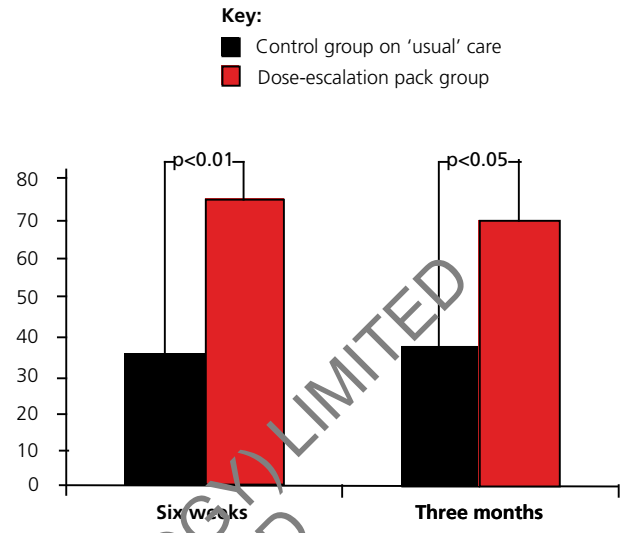
Table 1. Patient baseline demographics and primary reason for initiation of ACE inhibitor therapy

	Dose-escalation pack n=50 (sem)	'Usual' care n=50 (sem)	p value
Age (years)	64±2	66±2	0.6
Male	17	18	
Depcat score	3.9±0.2	4.0±0.1	0.6
Systolic BP	127±3	129±5	0.5
Diastolic BP	73±2	73±3	0.5
Urea (mmol/L)	5.3±0.3	7.0±0.5	0.02
Creatinine (µmol/L)	100±4	103±4	0.2
Potassium (mmol/L)	4.4±0.1	4.1±0.1	0.04
Primary reason for initiation of ACE inhibitor therapy			
Coronary artery disease	21	22	
Post-CABG	0	1	
Hypertension	1	1	
Cerebrovascular disease	0	1	
Diabetes	2	0	
Heart failure	1	0	

Key: BP = blood pressure; ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft

Figure 1. Percentage of patients receiving 10 mg ramipril



Key messages

- The use of a specific dose-escalation pack for the ACE inhibitor ramipril is a simple, reliable and safe mechanism for reaching target dose of ACE therapy
- This approach could find utility with other drug therapies

and the need for monitoring of serum urea and electrolytes. General practitioners and patients were informed by letter that ramipril was being initiated at a low dose and that the dose should be increased. Patients were instructed to attend their general practitioner for blood tests and medication review at one week after discharge. Patients randomised to 'usual' care received a one-week supply of ramipril on discharge along with an immediate discharge letter. Each patient underwent a telephone questionnaire by a blinded investigator (SAE) at six weeks and three months. Data were analysed by chi-squared test and Student's t-test, where appropriate, and significance taken at the 5% level.

Results

Table 1 shows the groups were matched for age (64±2 *vs.* 66±2 years; p=0.6), sex (17 *vs.* 18 male), deprivation score (3.9±0.2 *vs.* 4.0±0.1; p=0.6), systolic blood pressure (127±3 *vs.* 129±5 mmHg; p = 0.5), diastolic blood pressure (73±2 *vs.* 73±3 mmHg; p=0.5) and creatinine (100±4 *vs.* 103±4 µmol/L; p=0.2). There were small initial differences in serum urea (5.3±0.3 *vs.* 7.0±0.5 mmol/L; p=0.02) and potassium (4.4±0.1 *vs.* 4.1±0.1 mmol/L; p=0.04). One patient died in each group and one patient withdrew from the control group. More patients in the dose-escalation group reached target dose by six weeks (72 *vs.* 33%; p<0.01) and three months (67 *vs.* 35%; p<0.05) (figure 1). A total of 82% of patients had attended their general practitioner for a blood test by six weeks and 88% by three months, at which times there were no differences in serum creatinine, urea or potassium (all p>0.05). In addition, no patient in the study had an increase in serum creatinine of > 20 µmol/L, urea of > 4 mmol/L or potassium > 1.2 mmol/L. Cough was the most commonly reported side effect, although there was no difference in the incidence between the dose-escalation and control groups (8 *vs.* 6%; p>0.05).

Discussion

This study has demonstrated that a simple, inexpensive dose escalation pack can be used safely to nearly double the number of patients receiving optimal doses of ACE inhibitor by six weeks, and this difference was sustained at three months after discharge. The use of the dose-escalation pack appeared to be well tolerated by patients, as judged by similar levels of side effects and withdrawals from the placebo and active groups. Interestingly, in our control group, the proportion of patients receiving maximum dose of ACE inhibitor at the end of the study was no higher than in the initial pilot survey. This occurred despite comprehensive discussions with each patient on the potential benefits of ACE inhibitors and a letter being sent to

each GP informing of the need to increase ACE inhibitor dose. The reasons for the lack of dose escalation in the control group are unclear but suggest a reluctance of general practitioners to increase doses of ACE inhibitor given that similar numbers of patients in each group attended their general practitioner for blood tests.

Conflict of interest

This was an independent investigator-led study. There was no funding for this study. Dose-escalation packs were donated by Aventis, who also made available a laptop computer for the duration of the study.

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