

## Questionnaire study and audit of use of angiotensin converting enzyme inhibitor and monitoring in general practice: the need for guidelines to prevent renal failure

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### Abstract

**Objectives** To determine the current pattern of use of angiotensin converting enzyme inhibitor and monitoring of renal function in general practice and to audit all admissions to a regional renal unit for uraemia related to use of these drugs.

**Design** Postal questionnaire sent to 400 general practitioners; audit of clinical notes of all patients receiving these drugs in one large general practice; audit of all cases of uraemia (creatinine concentration >500  $\mu\text{mol/l}$ ) related to treatment presenting to hospital renal services over 12 months.

**Setting** General practices in the North Wales health authority and one in central Manchester. Regional renal unit in Salford.

**Main outcome measures** Proportion of general practitioners who regularly monitored renal function before and after initiation of angiotensin converting enzyme inhibitors. Indications for treatment and details of monitoring of renal function in patients receiving these drugs. Incidence of related uraemia and evidence of comorbid disease, other aetiological factors, delayed detection, and patient outcome.

**Results** 277 (69%) general practitioners replied; 235 (85%) checked renal function before but only 93 (34%) after the start of treatment, and 42 (15%) never checked renal function. Angiotensin converting enzyme inhibitors were prescribed for 162 patients from a total of 3625 aged >35 years (mean age 66.4 (SD 15.9) years). Monitoring of renal function occurred before treatment in 55 (45%) and after start of treatment in 35 (29%) of the 122 patients treated in general practice. Angiotensin converting enzyme inhibitors could be causally implicated in 9 (7%) of 135 admissions for uraemia (mean age 74.2 (7.2) v 62.1 (2.1) years;  $P < 0.01$ ). 3 patients had renovascular disease and 6 had congestive cardiac failure with another intercurrent illness. Renal function had not been checked in any patient after the start of treatment; mean duration of illness before admission was 10.5 (3.2) days. Mean length of hospital stay was 20.9 (10.4) days; there were 8 survivors.

**Conclusion** Cases of uraemia related to treatment with angiotensin converting enzyme inhibitors are still encountered and are often detected late because of lack of judicious monitoring of renal function in vulnerable,

often elderly, patients, especially at times of intercurrent illness. Guidelines for appropriate monitoring of renal function may help to minimise the problem.

### Introduction

Angiotensin converting enzyme inhibitors are implicated in the pathogenesis of some cases of acute renal failure.<sup>1</sup> Renovascular disease is common, and an increased prevalence is associated with ageing and comorbid vascular disease. Unsuspected severe disease (>50% renal arterial stenosis) was found at postmortem in 42% of patients aged >75 years<sup>2</sup> and during angiographic studies in 15% investigated for coronary artery disease<sup>3</sup> and 42% investigated for peripheral vascular disease.<sup>4</sup> Renovascular disease has recently been found in 34% of elderly patients with cardiac failure.<sup>5</sup> Angiotensin converting enzyme inhibitors are often indicated in all of these patient groups, and the risk of renal dysfunction is implicit in their association with renovascular disease.

Renal failure related to the use of angiotensin converting enzyme inhibitors, however, also occurs in the absence of severe renovascular disease. Vulnerable patients include those with hypovolaemia (for example, those receiving diuretics) or cardiac failure and elderly patients with intercurrent illness in whom compromised renal perfusion leads to dependence on the renin-angiotensin system for maintenance of glomerular filtration.<sup>6</sup> These conditions may supervene only many months after the initiation phase of treatment. Although renal complications of treatment are acknowledged by the pharmaceutical companies, the need for caution is generally specified only in patients with renovascular disease; monitoring guidelines do not legislate for that larger population without renovascular disease which is also vulnerable to these agents.

We performed three separate studies. The pattern of use of angiotensin converting enzyme inhibitors and monitoring in the community was determined by a postal survey of general practitioners in one health region and by detailed analysis of prescribing data within one large inner city practice. In the final study we audited admissions to a regional renal unit for uraemia from the point of view of use of angiotensin converting enzyme inhibitors to examine the scale of the problem.

## Methods

### Postal questionnaire to general practitioners

In November 1996 we sent a questionnaire to 400 general practitioners working within the North Wales health authority. The questionnaire comprised four questions regarding their use of angiotensin converting enzyme inhibitors and monitoring of renal function. What were the clinical indications for treatment in their practice? Was renal function usually checked before the start of treatment? Was renal function monitored after the start of treatment? Would they welcome clearer guidelines on the monitoring of renal function in patients treated with angiotensin converting enzyme inhibitors? The postal questionnaires were returned anonymously, and the data were aggregated.

A letter was also sent to 10 pharmaceutical companies that market angiotensin converting enzyme inhibitors, asking whether specific guidelines for renal function monitoring were available for their medical representatives to advise general practitioners on request.

### Audit of prescribing and monitoring

One general practice in central Manchester was selected for detailed audit as it had a large number of patients, was of acknowledged quality, and possessed a suitable patient database. The database was interrogated to identify all patients receiving angiotensin converting enzyme inhibitor currently (December 1996) or within the previous 12 months; the age distribution of the patient population; and all patients with a diagnosis of hypertension or cardiac failure.

The clinical records of all patients being treated with angiotensin converting enzyme inhibitors were retrieved to ascertain the clinical indication for treatment; whether treatment was initiated in the community or in hospital; whether, in the patients receiving treatment initiated in general practice, renal function was assessed within the 3 months before the start of treatment; and whether renal function was checked within 3 months after start of treatment.

### Incidence of severe uraemia in patients presenting to a regional renal unit

A prospective audit of all new cases of severe uraemia (creatinine concentration >500 µmol/l or urea >35 mmol/l) presenting acutely to the renal department of Salford Royal Hospitals NHS Trust (catchment population for renal disease 1-1.25 million) was undertaken for the 12 months from June 1995. Patients with either acute or acute-on-chronic renal failure were included; aetiological factors for uraemia were determined; and cases in which angiotensin converting enzyme inhibitor treatment seemed important in the pathogenesis were evaluated in more detail. Thus clinical characteristics, patient and renal outcome, and details of monitoring by general practitioners were all documented.

### Ethical considerations and statistical analysis

The study was reviewed by the local research ethics committee, which advised that a formal ethical application was not required.

Means and standard deviations are displayed when appropriate. Differences in categorical data were

**Table 1** Characteristics of prescribing of angiotensin converting enzyme inhibitors and monitoring of renal function by general practitioners in North Wales

Characteristic	No of general practitioners (n=277)
Indications for treatment:	
Hypertension	277
Cardiac failure	271
Diabetic nephropathy	166
Practitioners who usually monitored renal function:	
Before start of treatment	235
After start of treatment	93
At no stage of treatment	42
Practitioners who would welcome guidelines for monitoring renal function	234

analysed with the  $\chi^2$  test. For continuous data, means were compared by *t* tests.

## Results

### Postal questionnaire to general practitioners

Completed questionnaires were returned by 277 (69%) general practitioners. Their practice with respect to monitoring of renal function is shown in table 1. Only 93 (34%) checked renal function regularly after treatment with angiotensin converting enzyme inhibitors was started, and 42 (15%) admitted to never assessing it at any stage. Although 234 (84%) practitioners would welcome clear guidelines for monitoring of renal function when they prescribe these drugs to their patients, only one of the pharmaceutical companies provided such information.

### Audit of prescribing and monitoring

Although the practice served a large student population, which swelled its numbers during term time, it also included 3625 city dwelling patients aged >35 years, and this typical subset of patients was used for audit. There were 390 (10.8%) patients with hypertension in this group and 117 (3.2%) with cardiac failure. Angiotensin converting enzyme inhibitors were prescribed to 162 (4.5%) patients (mean age 64.4 (SD 15.9) years, range 22-93 years), of whom 64 (40%) were aged 70 years or more. The  $\geq 70$  years group represented 36% of all patients with hypertension and 60% of the patients with heart failure in the practice.

Table 2 shows the indications for treatment and data on renal function monitoring. Treatment with angiotensin converting enzyme inhibitors was initiated by the general practitioner in 122 (75%) cases. No assessment of renal function was undertaken within the first 3 months of treatment in 87 (71%) patients. An increase of over 10% in creatinine concentration was observed in 15 (12%) patients at some stage during the 12 month audit period; surprisingly, these drugs were continued in 11 without any further monitoring of renal function.

### Severe uraemia in association with angiotensin converting enzyme inhibitors

During the 12 month audit period 135 patients (mean age 62.1 (2.4) years; range 17-92 years) with severe uraemia were accepted by the unit. Causes of renal failure included prerenal uraemia or acute tubular necrosis (45), uraemic presentation of chronic renal

**Table 2** Prescribing of angiotensin converting enzyme inhibitors and monitoring of renal function in 3625 patients aged over 35 years in one Manchester health centre

Detail	No of patients receiving treatment (n=162)
Patients receiving treatment:	
Treatment started by GP	122 (75% of all receiving treatment)
Treatment started in hospital	40 (25%)
Indications for treatment:	
Hypertension (n=390)	118 (73% of all receiving treatment)
Cardiac failure (n=117)	38 (24%)
After myocardial infarction	6 (4%)
Patients receiving treatment started by GP (n=122) who received renal function monitoring:	
Within 3 months before start of treatment	55 (45%)
At any stage before start of treatment	60 (49%)
Within 3 months after start of treatment	35 (29%)
At any stage after start of treatment	76 (62%)

failure (19), diabetic nephropathy (15), acute vasculitis or glomerulonephritis (14), renovascular disease (14), and urinary tract obstruction (12).

In nine patients (four men) angiotensin converting enzyme inhibitors were considered to be important in the pathogenesis of the uraemia. They were considerably older (mean age 74.2 (7.2 years), range 64-88 years;  $P < 0.01$ ) than the overall group of patients with uraemia. Severe renovascular disease was shown at angiography in three patients (two had bilateral disease, the other a unilateral renal artery occlusion), all of whom received treatment for hypertension. The six others had normal renal vasculature and were receiving treatment (and concomitant diuretics) for heart failure; two of these patients also received non-steroidal anti-inflammatory drugs. Eight patients had received angiotensin converting enzyme inhibitors for more than 6 months, but only four had had renal function assessed before treatment; three of these four patients had moderate chronic renal failure (serum creatinine  $< 150 \mu\text{mol/l}$ ). No patients had renal function monitored after the treatment was started.

The illnesses precipitating admission were exacerbation of heart failure (two patients), influenza (three), pneumonia (two), and gastroenteritis (one). The other patient had bilateral renovascular disease and was admitted with uraemia only 4 weeks after starting treatment. The mean duration of these patients' illness in the community, before admission, was 10.5 (3.2) days. On admission, angiotensin converting enzyme inhibitors were discontinued, and all patients were optimally hydrated; only one patient required haemodialysis and there were eight survivors, all of whom left hospital with chronic renal failure (mean creatinine concentration  $254 (74) \mu\text{mol/l}$ ). The mean length of stay in hospital was 20.9 (10.4) days.

## Discussion

These three divergent studies confirm that monitoring of renal function in patients treated with angiotensin converting enzyme inhibitors remains inadequate and cases of uraemia still commonly occur. This is of concern as current recommendations say that all patients with heart failure should be considered for treatment with angiotensin converting enzyme inhibitors<sup>7</sup> and that major cost benefits may be derived by starting treatment in the community.<sup>8</sup> There is no disputing the morbidity and survival advantages that such treatment conveys,<sup>9</sup> but these recommendations must

be accompanied by clear guidelines that encourage the detection of renal dysfunction and the most vulnerable patients at the earliest possible stage.

As the first study shows, such guidelines are usually not forthcoming from pharmaceutical companies, and most protocols within the medical literature make no provision for detecting late deterioration of renal function,<sup>7-10</sup> which seems to be the key area of patient management being overlooked. Although we accept that self reporting of clinical behaviour is often unreliable, it was surprising that only a third of the general practitioners who responded to the postal questionnaire admitted to monitoring renal function after initiation of angiotensin converting enzyme inhibitors, and nearly one in seven never checked function at any stage before or after treatment. It is unlikely that the practice of the 30% non-respondents would improve the results of this survey. Audit of the Manchester practice showed that even when there was an intention to monitor, renal function was actually assessed in few patients. Furthermore, although renal dysfunction was observed in 15 of 122 patients who received treatment initiated in general practice, most continued to receive treatment without further monitoring or investigation. Major concern derives from the 44 elderly patients ( $> 70$  years) in the practice who started treatment in the community, of whom 16 (36%) never had renal function monitored at any stage.

## Extent of the problem

Some authors believe that the problem of renal dysfunction relating to use of angiotensin converting enzyme inhibitors is overstated<sup>11</sup>; they refer to data from large trials in cardiac failure, usually those involving younger patients.<sup>9</sup> We would argue that the risk of renal dysfunction increases significantly in elderly patients, a fact borne out by our current and previous<sup>1</sup> experiences and by the Elite study, in which 10.5% of elderly patients receiving captopril or losartan developed an increase of over 10% in serum creatinine concentration.<sup>12</sup> In our third study the nine (7%) patients whose uraemia could be attributable to treatment with angiotensin converting enzyme inhibitors were older than the other patients with uraemia. Most had been receiving treatment for many months and had no evidence of renovascular disease, but events which precipitated uraemia were usually identifiable. This elaborates an important point: although these drugs may be well tolerated by patients for many months or years, severe late renal dysfunction may complicate intercurrent illness (for example, influenza, pneumonia, gastroenteritis) when renal haemodynamic stress is increased by hypovolaemia and worsening cardiac function; these are the patients who require careful monitoring.

The nine patients admitted to our unit with uraemia related to treatment with angiotensin converting enzyme inhibitors required a total of 189 bed days, many of which were high dependency. Given the high use of these drugs in the community and the scale of inadequate monitoring identified by this study, it could be argued that the consequences of inadequate monitoring are of minor impact to secondary care. The overall consumption of resources attributable to inadequate monitoring is undoubtedly much greater, however, as many such elderly patients with uraemia are

## Key messages

- Admissions for uraemia that are related to use of angiotensin converting enzyme inhibitors are still commonplace, but many cases are preventable by judicious testing of renal function
- The most vulnerable patients are elderly people and those with heart failure, chronic renal impairment, or renovascular disease; acute deterioration of renal function often accompanies an intercurrent illness in such patients
- Despite widespread recognition of this risk of treatment with angiotensin converting enzyme inhibitors many general practitioners still do not regularly monitor renal function even in the most vulnerable patients
- Adoption of simple guidelines for monitoring of renal function would reduce this cause of morbidity and admission to hospital and may reduce costs

admitted under the care of geriatricians and other medical teams and are not referred on to renal services because of comorbidity and general frailty.

## Possible guidelines

Our postal survey indicates that most general practitioners would welcome clear advice regarding monitoring of renal function in patients receiving angiotensin converting enzyme inhibitors (or angiotensin receptor blockers). We recommend that patients should be screened for risk factors predisposing them to uraemia (for example, old age, peripheral vascular disease, low cardiac output, or concomitant treatment with non-steroidal drugs or high dose diuretics). Renal function should be checked before and 7-10 days after treatment is started in all patients and thereafter regularly (for example, annually) only in those with risk factors. Most importantly, it should be assessed in all patients, especially the vulnerable, at times of relevant intercurrent illness (and if concomitant drug treatment is modified). Withdrawal from treatment should be considered if there are unexpected increases in serum creatinine concentration above the normal range or by

25% of the baseline value, or both. It is recognised, however, that the benefits of treatment to some patients outweigh this renal dysfunction (for example, those with severe cardiac failure) so that treatment should be continued, albeit with diligent monitoring. Patients with unexplained baseline renal dysfunction or with measurable dysfunction accompanying treatment should be considered for further renal investigation.

Contributors: PAK had the original idea to amalgamate the three audits, performed the audit of acute renal failure, and wrote the manuscript. MK developed the questionnaire for general practitioners and performed the audit of general practitioner prescribing in North Wales. PMacD performed the audit of prescribing and monitoring angiotensin converting enzyme inhibitors in the Manchester practice. MOR contributed to the design of the study and reviewed the manuscript. PAK is guarantor for the study.

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### A grateful patient Not what he wanted

He was in his 60s and bedridden with congestive cardiac failure; I was new to the practice, having bought it in 1947 after service in the army abroad and a spell working in hospital. Brash and enthusiastic, I was dismayed to find that he was being treated with bottles of medicine given by my predecessor, who the patients believed would shortly be returning. With my zeal for scientific medicine at its height, I prescribed digoxin and diuretics (in those days by injection), and was tremendously encouraged by the response. A phenomenal diuresis followed—it didn't occur to me to think how uncomfortable this might have been for him—and the oedema and dyspnoea rapidly improved. After a week or so he was able to come downstairs during my visits.

My pleasure at his recovery was shortlived. "You have been very kind to me, doctor," he said, "and I'm very grateful, but when is my doctor coming back?" I was startled, and asked why he wanted to know. "Well, you see," he replied, "she understands my case."

I cannot recall what happened after this—perhaps the painful memory has been suppressed, but 50 years later I still feel ashamed and continue to puzzle over the incident. One thing is quite clear: I had not provided what he wanted.

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