baseline (but *not* outcome) data, maintaining trial discipline, and encouraging recruitment through its own networks of medical representatives and researchers. Whatever the cost of a trial, it should be compared with the cost of the disease being treated and, perhaps, against the cost of non-medical endeavours such as low altitude military aircraft training or unemployment benefit. By any such comparisons multicentre trials are usually extremely inexpensive and may lead to the rejection of expensive but ineffective treatments—for example, extracranial to intracranial bypass surgery for the prevention of stroke—and not always to the introduction of more expensive health care.

Writing the papers

Like the protocol, this is a job for the principal investigator, not a committee. Naturally, it will be necessary to have many discussions with the trial statistician and trial coordinator and comments and advice from all the collaborators as numerous drafts are produced. It is crucial, however, that in the end all the results are published under the name of all the collaborators; without them there would have been no trial at all, and they did the work. Although currently unfashionable in some quarters, the whole philosophy underlying multicentre trials is that group effort takes precedence over individual effort; only by acting as a group can the individuals get answers to therapeutic questions which affect their own individual patients. Of course, any centre can publish its *own* results but

there must be no “star billing” for authors when the results of the whole trial are presented.

Conclusions

Before starting a multicentre trial the following questions must be answered affirmatively: Is the therapeutic question really important, preferably even a burning issue? Are you sure there is no better way of answering it? Can you get enough centres together? Are you likely to get the resources? Have you got the time? Do you really want to do it? If so, then go ahead, but first visit one or two successful multicentre trial organisations which will give you far more idea of the problems and pleasures than I have been able to within the context of this article. Remember, only fools fail to learn from others’ mistakes. And once you get started, always keep thinking about how the trial can be done more efficiently and effectively, less expensively, more quickly with a greater recruitment rate and with less extra work being done by the collaborators. At the same time remember that esprit-de-corps is what counts more than anything else: look after it.

I thank other devotees of multicentre trials with whom I have worked and who commented on the manuscript (Livia Candelise, David Chadwick, Rory Collins, Barbara Farrell, Jan van Gijn, Adrian Grant, Peter Sandercock, and Brenda Smith), and also Richard Peto, who persuaded me and other clinicians, that really large sample sizes are crucial to make any sense of treatments which have modest yet clinically important benefits. But it is I who take the blame for all the opinions expressed in the article.

Lesson of the Week

Fibromuscular dysplasia of renal arteries: a neglected cause of acute loin pain

Simon J Stinchcombe, Adrian R Manhire, Michael C Bishop, Roger H S Gregson

An arterial lesion should be suspected in patients with acute loin pain if there is no evidence of ureteric obstruction on urography

Department of Radiology, Queen’s Medical Centre, Nottingham NG7 2UH
Simon J Stinchcombe, BM, senior registrar
Roger H S Gregson, FRCR, consultant

Departments of Radiology and Urology, City Hospital, Nottingham NG5 1PB
Adrian R Manhire, FRCR, consultant
Michael C Bishop, FRCS, consultant

Correspondence to: Dr Stinchcombe.

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Fibromuscular dysplasia of the renal arteries is usually associated with hypertension, but occasionally it may present with acute loin pain due to occlusion of the renal arteries or embolisation of small peripheral vessels. The presenting symptoms may then be indistinguishable from acute calculous obstruction or acute pyelonephritis. Early diagnosis of arterial occlusion is essential to prevent permanent damage to the kidney.

We report on three young previously fit patients who presented with acute loin pain, in whom renal infarction occurred in relation to fibromuscular dysplasia of the renal arteries. We also discuss how patients with loin pain should be investigated so that arterial occlusion can be diagnosed early.

Case 1

A 33 year old man was admitted with a four hour history of acute right testicular pain. Testicular torsion was diagnosed initially, but an exploratory operation disclosed no abnormality. Two days after admission he was still in pain, which had moved to the right loin, and he developed frank haematuria. Investigations disclosed a raised white cell count ($20.7 \times 10^9/l$) but normal plasma urea and electrolyte concentrations. Microscopic examination of the urine showed increased numbers of red and white cells and granular casts. Culture of his

urine gave negative results. On intravenous urography the right kidney was thought to be non-functioning. On ultrasonography the size of the kidney was normal with no dilatation of the pelvicaliceal system. Ureteric obstruction due to a radiolucent calculus was diagnosed, and he was treated conservatively.

The next day he developed a temperature of 38°C , and despite 24 hour treatment with intravenous antibiotics he did not improve. A right retrograde pyelogram was normal, but a $^{99\text{m}}\text{Tc}$ diethylenetriaminepenta-acetate ($^{99\text{m}}\text{Tc}$ DTPA) renogram showed that there was no perfusion of the right kidney. Renal angiography showed that the right renal artery was completely occluded by thrombus 3 cm from its origin; there was some irregularity of the wall of the left main renal artery, and two stenoses were seen in one of the segmental vessels. The findings were consistent with a diagnosis of fibromuscular dysplasia. Despite the five day interval after the onset of symptoms we attempted to revascularise the kidney with intra-arterial streptokinase 5000 units/hour. The thrombus in the right main renal artery was dissolved, disclosing a 75% stricture, which was treated with balloon angioplasty. Unfortunately pericatheter thrombus formed, which embolised distally, and peripheral perfusion to the kidney could not be restored. The patient was given long term anticoagulant treatment and discharged. Detailed investigation subsequently failed to disclose

any other cause for arterial thrombosis or embolism. At follow up 18 months later he was well and normotensive.

Case 2

A 33 year old man was admitted with a five day history of left loin pain; he had previously been well. On examination his blood pressure was 190/100 mm Hg, and he was tender in the left flank. A full blood count and plasma urea and electrolyte concentrations were normal and urine analysis showed no abnormality on admission, but microscopic haematuria and proteinuria were subsequently detected. An intravenous urogram was normal but a ^{99m}Tc dimercaptosuccinate (^{99m}Tc DMSA) renal scintigram showed absence of activity in the lower lateral part of the left kidney, which suggested renal infarction. A further smaller cortical defect was seen in the right kidney. Renal angiography disclosed a series of strictures and aneurysmal dilatations of the arteries supplying the lower pole of the left kidney (fig 1). One segmental artery was completely occluded just distal to a stricture. Angiography also confirmed considerable loss of renal parenchyma with defects seen in the nephrogram phase. On superior mesenteric angiography a similar pattern was seen with strictures interspersed with dilatations of the artery (fig 2). These findings represent a form of fibromuscular dysplasia sparing the main renal artery but affecting the segmental arteries. The patient was treated with atenolol 100 mg, chlorthalidone 25 mg, and slow release nifedipine 20 mg in the mornings. He was discharged and two years subsequently remained well receiving antihypertensive treatment.

Case 3

A 24 year old man was admitted with a six hour history of left loin pain. On examination he was tender in the left flank and had a blood pressure of 190/100 mm Hg. A full blood count and determination of erythrocyte sedimentation rate and plasma urea and electrolyte concentrations showed no appreciable abnormalities, but an increased number of red cells were seen on microscopic examination of his urine. The intravenous urogram showed a faint nephrogram with no pyelogram on the left side. The right kidney

FIG 1—Selective left renal angiogram showing changes of fibromuscular dysplasia in arteries supplying lower pole of kidney (case 2). A segmental artery is occluded and defects are visible in nephrogram

FIG 2—Superior mesenteric angiogram showing changes of fibromuscular dysplasia (case 2)

was normal. Two days later he was still in pain, had developed a fever, and his blood pressure had increased to 200/130 mm Hg. He was treated with atenolol 100 mg in the mornings and cefuroxime 750 mg thrice daily. There was no pelviciceal dilatation on renal ultrasonography. His symptoms continued, and a subsequent isotopic renogram showed that there was no perfusion of the left kidney. Angiography was performed seven days after admission; the left renal artery was completely occluded by thrombus. Treatment with intra-arterial streptokinase was started at 50 000 units/hour; 24 hours later the main renal artery was patent on renal angiography. Although there was some filling of the intrarenal vessels, no pyelogram was seen. His symptoms settled and he was discharged.

Seven months later his hypertension had become difficult to control, and a further isotopic renogram showed that the left kidney was virtually non-functioning, so he had a left nephrectomy. His left kidney was severely scarred, and the renal artery was pulseless and cord like. On histological examination the left main renal artery and some branch arteries showed changes of fibromuscular dysplasia of the intimal fibroplasia type. Evidence of ischaemia and infarction were seen in the renal parenchyma. He was subsequently discharged; at follow up two months later he was completely well and normotensive taking a small dose of captopril.

Discussion

Acute occlusion of the renal arteries is unusual but may occur in various clinical settings. Emboli to the renal arteries are usually cardiac in origin and are most commonly associated with atrial fibrillation. In older age groups arterial thrombosis is commonly secondary to atherosclerosis whereas in younger patients it is more likely to be secondary to trauma or inflammatory conditions such as polyarteritis nodosa and systemic lupus erythematosus.¹ Fibromuscular dysplasia is an unusual cause of acute renal arterial occlusion but is important as it may occur in young patients who are otherwise completely well.

Patients with acute occlusion of a major renal artery typically present with loin pain, though this symptom may be absent in a quarter of cases.² Frank haematuria is unusual, but most patients have microscopic haematuria, and pyuria is seen in 80% of cases.¹ Nausea and vomiting are common, but fever and hypertension may be prominent.

Acute occlusion of the renal arteries may therefore

FIG 3—Proposed investigation of patients with acute loin pain

occur in any age group, without a clinically obvious predisposing cause, and the symptoms may be indistinguishable from acute ureteric obstruction or acute pyelonephritis. Acute renal thromboembolism is diagnosed on the day of admission in less than 30% of cases and often considerably later.² If, however, irreversible renal damage is to be prevented an early diagnosis is necessary, and acute renal thromboembolism therefore must be considered in all patients with loin pain if ureteric obstruction cannot be confirmed radiologically.

Figure 3 illustrates the way in which we think patients with acute loin pain should be investigated. After initial clinical assessment the first radiological investigation should be an intravenous urogram. Acute ureteric obstruction may be diagnosed on the basis of an increasingly dense nephrogram and a delayed pyelogram; delayed films taken several hours later may be necessary to confirm ureteric obstruction.

In patients with acute loin pain a non-functioning kidney on intravenous urography may be due to occlusion of the renal artery, renal vein thrombosis, acute suppurative pyelonephritis, or ureteric obstruction.³ A faint nephrogram may be seen despite complete occlusion of the renal artery because of the blood supply through capsular vessels. If the kidney is non-functioning on intravenous urography it is vital to diagnose any arterial occlusion without delay, as prompt intervention is necessary to prevent total renal infarction. Abdominal ultrasonography should be performed urgently to confirm the presence of renal tissue, allow the size of the kidney to be measured, and to exclude hydronephrosis. Doppler ultrasonography with colour flow mapping may be useful in diagnosing acute renal ischaemia, but as yet its value is unproved. If the kidney is very small further investigation is not warranted. If the kidney is of normal size and not hydronephrotic a renal arteriogram with venography, if necessary, is urgently indicated. Although a non-functioning kidney on intravenous urography with no pelvicaliceal dilatation on ultrasonography does not exclude acute ureteric obstruction, a retrograde pyelogram is indicated only if a normal examination will not delay the arteriogram.

The urographic signs of acute segmental renal infarction are variable. The kidney may be non-functioning owing to intense vascular spasm or acute tubular necrosis.² Classically, a triangular nephrographic defect with its base in the subcapsular region is seen,⁴ but high dose nephrotomography is often required to detect this. The kidney may appear swollen with a diminished pyelogram but the urogram can be entirely normal even when sizable renal infarcts are shown by scintigraphy.⁵

If the urogram is abnormal but there is no evidence of obstruction a renal arteriogram is indicated unless there is a strong clinical suspicion of acute pyelonephritis, either because of coexisting symptoms of cystitis or because organisms have been detected in the urine.

It is not feasible to perform angiograms on all patients with loin pain and a normal intravenous urogram; these patients should be reviewed on the basis of the results of urine analysis. If the pain is still thought to be of renal origin and there is no evidence of acute pyelonephritis either renal scintigraphy or a computed tomography should be performed. A ^{99m}Tc diethylenetriaminepenta-acetate (^{99m}Tc DTPA) renogram will show defects in perfusion of the kidney and provide information about renal function. A ^{99m}Tc dimercaptosuccinate (^{99m}Tc DMSA) renal scintigram will detect cortical scarring secondary to infarction. Renal scintigraphy with ^{99m}Tc glucoheptonate is more sensitive in detecting segmental renal infarction than intravenous urography.⁵ The appearances of major renal infarction on contrast enhanced computed tomography are characteristic, with a sharply defined low density area and a high attenuation cortical rim.^{4,6} Computed tomography may detect segmental renal infarction,⁴ although the appearances with smaller areas of ischaemia may not be diagnostic.⁶ The decision whether to perform isotopic renography or computed tomography will depend on the local availability of these modalities.

If renal ischaemia is shown by isotopic renography or computed tomography in young patients further investigations are always indicated to detect an underlying cause. Renal angiography may detect vascular abnormalities that are amenable to treatment.

We thank Mr J Lemberger for allowing us to publish details of case 3.

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ANY QUESTIONS

Is there any epidemiological evidence that the incidence of acute illnesses has a seasonal variation?

Many illnesses exhibit seasonal variation. Asthma peaks in early summer and autumn,¹ and myocardial infarction and ischaemic heart disease are more likely to present during cold weather. Acute respiratory infections, which account for about 20% of all consultations in general practice, peak in the first quarter of the year. The incidence of viral illnesses is generally lowest during late summer.² Though external temperature may be relevant

to the periodicity of some illnesses, this is only one of the variables associated with the seasons. The notion of a direct relation (positive or negative) between external temperature and illness does not have any substantial support.—D M FLEMING, deputy director, Royal College of General Practitioners Birmingham research unit

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