Clinical implications

- Many patients with coronary artery disease suffer from intractable angina pectoris in spite of optimal medical and surgical therapy
- Spinal cord stimulation has proved to be an effective method to relieve angina pectoris in these patients; the anti-anginal effect seems, from earlier studies, to be associated with a reduction in myocardial ischaemia
- This study confirms that spinal cord stimulation has an anti-ischaemic effect in angina pectoris that can be induced by atrial pacing—this effect is probably mediated by a reduction in myocardial oxygen consumption.
- Myocardial ischaemia during treatment with spinal cord stimulation gives rise to anginal pain—that is, the treatment does not conceal symptoms of myocardial ischaemia
- Spinal cord stimulation seems to be a therapeutic possibility in patients with angina pectoris when conventional strategies of management have been exhausted

increased tolerance to atrial pacing, improved myocardial lactate metabolism, and decreased magnitude and duration of ST segment depression at comparable pacing frequencies, suggesting antianginal and anti-ischaemic effects of the treatment. These effects seem to be related to a decrease in myocardial oxygen consumption. At the maximum pacing rate all patients experienced anginal pain, myocardial lactate extraction changed to production, and the magnitude of ST segment depression and myocardial oxygen consumption increased to the same values as during control pacing, indicating that myocardial ischaemia during treatment with spinal cord stimulation gives rise to anginal pain. Thus, the treatment does not deprive the patient of a warning signal during myocardial ischaemia.

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Adverse drug reactions: who is to know?

Martin Cook, R E Ferner

Dudley Road Hospital, Birmingham B18 7QH
Martin Cook, *medical student*
R E Ferner, *consultant physician*

Correspondence to:
Dr R E Ferner.

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Adverse drug reactions can be difficult to detect, and patients may be adamant that an event is due to drug treatment when few experts would agree. None the less, it is at least prudent to discover whether patients believe that they have suffered from previous treatment, and it can be imperative to do so if the patient is not to be exposed to needless risk. Once a reaction has been elicited it should be recorded.[1]

To study how effectively adverse reactions are elicited in hospital we compared the number of reactions recorded in routine medical notes and on prescription charts with the numbers discovered using a simple questionnaire. We also examined whether doctors recorded reports on well established reactions more often than unlikely ones.

Subjects, methods, and results

The subjects were 437 patients (254 men and 264 surgical patients) on the general medical, general surgical, and orthopaedic wards who were sufficiently awake and lucid to answer questions. An interpreter helped when necessary. Each patient was asked: Have any medicines or tablets ever disagreed with you or caused an allergy? If so, what was the drug, and what happened? Have you ever needed treatment by a doctor or at a hospital for a reaction to a medicine or tablet? If so, what was the drug, and what happened? Are you able to take aspirin or penicillin? When a

Number of adverse drug reactions and the number considered likely

	All drugs	Penicillin	Aspirin	Codeine	Co-trimoxazole
Elicited by questionnaire:					
Total	97	39	14	6	5
Likely	74	28	12	6	5
Recorded in medical notes:					
Total	53	24	5	4	3
Likely	42	20	4	4	3

reaction was disclosed the medical records were examined to see if it had been noted. There are spaces to record "drug allergy" and "contraindicated drugs" on prescription charts and inside the back cover of medical notes at our hospital. These too were examined. Reactions listed in standard texts[2,3] were regarded as likely and others as unlikely.

Seventy seven patients reported 97 adverse drug reactions on direct questioning (table). The current medical history recorded only 53 of these, and the prescription chart only 17 of the 53. None of the reactions was recorded inside the back cover of the clinical notes. Important reactions included facial swelling with penicillins (4), gastrointestinal bleeding with aspirin (3) or other non-steroidal anti-inflammatory drugs (1), and pulmonary embolism with oral contraceptives (1). The reactions elicited by questionnaire appeared likely in 74 cases, of which 42 were recorded in the current notes, though for likely penicillin reactions 20 out of 28 were recorded. The question "Have you ever needed treatment by a doctor or at a hospital for a reaction to a medicine or tablet?" did not add to information from the other questions.

Comment

The simple questions, Have any medicines or tablets ever disagreed with you or caused an allergy? and Are you able to take aspirin or penicillin? identified 97 reactions. Most (76%) of these were likely to have been related to the drug, so that the questionnaire was reasonably specific for adverse reactions, which are anyway difficult to diagnose.[4] Doctors recorded only half of the reactions elicited by the questionnaire, and they did not preferentially record well established reactions.

We have no evidence that any patient came to harm as a result of the imperfect recording of adverse drug reactions, but we believe that knowing a patient's history of such reactions is important to protect both the patient and the doctor. Doctors should be encouraged to ask the simple questions which we used when admitting patients, and to record the data they obtain. A hazard label for the front of the notes and the prescription chart might be helpful.

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Homozygous deletion of gene for glutathione *S*-transferase M1 in bladder cancer

Ann K Daly, David J Thomas, Jane Cooper, William R Pearson, David E Neal, Jeffrey R Idle

Pharmacogenetics Research Unit and Department of Surgery, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH
Ann K Daly, *lecturer in pharmacogenetics*
David J Thomas, *research registrar*
Jane Cooper, *research technician*
David E Neal, *professor of surgery*
Jeffrey R Idle, *professor of pharmacogenetics*

Department of Biochemistry, University of Virginia, Charlottesville, VA 22908, United States
William R Pearson, *associate professor*

Correspondence to:
Dr Daly.

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The glutathione *S*-transferase enzyme GSTM1 has a polymorphic expression, with about half of people from various racial groups lacking enzyme activity.[1] The enzyme detoxicates several carcinogens including benzo[*a*]pyrene-4,5 oxide and it has been suggested that smokers who lack glutathione *S*-transferase activity are at increased risk of developing lung cancer, particularly adenocarcinoma.[2] Enzyme deficiency seems to be due to deletion of the coding gene GSTM1, and simple polymerase chain reaction assays to detect this deletion have been developed.[3]

The main risk factors for transitional cell carcinoma of the bladder are smoking and occupational exposure to carcinogens.[4] In view of the reported association between glutathione *S*-transferase and susceptibility to lung cancer, we examined whether lack of the enzyme was also associated with susceptibility to bladder cancer.

Subjects, methods, and results

We recruited 53 patients with transitional cell carcinoma of the bladder (34 men, 19 women; mean age 75) and 52 control patients (45 men, seven women; mean age 70) from Freeman Hospital Urology Department, Newcastle upon Tyne. The control patients were either having transurethral resection of the prostate for bladder outflow obstruction or were receiving treatment for stones, stress incontinence, unstable bladder, or neuropathic bladder, and all had had cystoscopy to exclude a bladder tumour. We also recruited 58 healthy volunteers from staff and students of Newcastle University (24 men, 34 women). The study was approved by the local ethics committee, and patients and volunteers gave informed consent.

We detected deletion of GSTM1 in leucocyte DNA by a polymerase chain reaction assay using the primers GCTTCACGTGTTATGGAGGTTC(fromintron6of GSTM1)andGAGATGAAGTCCTTCAGATTT(from exon 7), which gave rise to a 160 base pair product in subjects who were heterozygous or homozygous wild type (GSTM1 positive).[3] As a control, we also ran an assay for the non-polymorphic gene GSTM2 (for muscle specific glutathione *S*-transferase) in parallel using as primers CCAGAATACCTGCAGGCACTC (exon 6) and GTATGACAAATCTGTGGTGTCC (intron 6). Conditions for both assays were 40 cycles of 1 min at 95°C, 1·5 min at 47°C, and 2 min at 70°C. All assays were repeated at least twice.

The table summarises the results. Forty six per cent of the healthy controls and 40% of the patient controls had the GSTM1 gene compared with only 15% of patients with bladder tumour. There was a significant difference between the patients with cancer and the two control groups ($\chi^2=8{\cdot}41$, $p<0{\cdot}005$ for patient controls and $\chi^2=12{\cdot}67$, $p<0{\cdot}001$ for healthy controls). Compared with the patient control group the relative risk was 1·42 (95% confidence interval 1·12 to 1·79) and odds ratio 3·81 (1·53 to 9·34). This odds ratio is greater than the ratios calculated in the previous study

Presence of GSTM1 gene in patients and controls

Group	No of subjects	No (%) with gene	No (%) without the gene
Bladder tumour	53	8 (15)	45 (85)
Patient controls	52	21 (40)	31 (60)
Healthy controls	58	27 (47)	31 (53)