Not all travellers need immunoglobulin for hepatitis A

Viral hepatitis A occurs endemically in most parts of the world, especially where there is overcrowding,¹ and studies on the prevalence of antibody to hepatitis A in Europe have shown higher concentrations among those who live in Mediterranean countries.²⁻⁶ It is an infection often associated with travel: in West Germany and Switzerland over 60% of acute cases have a history of recent travel abroad,⁷ and in the west of Scotland 20% of cases are in returning travellers.⁸ The beneficial effect of human normal immunoglobulin in preventing hepatitis A has long been recognised,⁹ and it is commonly given to intending travellers to countries where there might be increased exposure to hepatitis A.¹⁰ The dramatic upsurge in the number of people travelling from Britain—22.1 million visits abroad were made by British citizens in 1984, 12% to destinations beyond Europe¹¹—has increased the need to protect travellers from hepatitis A.

Do all such travellers need immunoglobulin? A random serum survey of 511 travellers predominantly from the west of Scotland conducted between 1979 and 1983 showed that 64% already had antibodies to hepatitis A—30% of those aged 10-19 rising to 89% of those over 60 (personal observations). This is similar to the prevalence reported in random testing of blood donors in 1980 from the same area and in comparable age groupings.¹² Thus many intending travellers already possess antibody and are presumably not at risk from hepatitis A.

Added to this is the question of expense. An injection of normal immunoglobulin costs £3-£9 depending on the manufacturer and dose (250 mg intramuscularly for six weeks' protection and 750 mg for six months' protection¹³); and in certain circumstances a fee of £3.45 may be claimed by doctors from the health board.¹⁴ Last year the West of Scotland Blood Transfusion Service distributed 1249 phials, most to immunise prospective travellers (Scottish National Blood Transfusion Service, personal communication). When this cost is balanced against that of antibody testing (from £8 down to £4 depending on laboratory throughput (Hepatitis Reference Laboratory, Glasgow, personal communication) there is a distinct economic benefit in selective screening before immunising as opposed to immunising the putative traveller at risk. Using such information, Larouze *et al* have devised a formula that enables the cost benefit to be calculated.¹⁵ This benefit accrues with increasing age in the traveller, length of stay abroad, and frequency of visits abroad; implementing a screening policy also minimises unnecessary immunisation and makes for effective use of a limited resource.

JONATHAN H COSSAR
Research associate
DANIEL REID
Consultant epidemiologist

Communicable Diseases (Scotland) Unit,
Ruchill Hospital,
Glasgow G10 9NB

- 7 Frosner GG, Roggendorf M, Frosner H-R, *et al*. Epidemiology of hepatitis A and B infection in western European countries and in Germans travelling abroad. In: Szmuness W, Alter HJ, Maynard JE, eds. *Viral hepatitis*. Philadelphia: Franklin Institute Press, 1982:157-68.
- 8 Follett EAC, McMichael S. Acute hepatitis A infection in W Scotland. *Scott Med J* 1981;26:135-7.
- 9 Pollock TM, Reid D. Immunoglobulin for the prevention of infectious hepatitis in persons working overseas. *Lancet* 1969;i:281-3.
- 10 Walker E, Williams G. ABC of health travel. *Br Med J* 1983;286:631.
- 11 Business Statistics Office. *Business monitor annual statistics. Overseas travel and tourism*. London: HMSO, 1985. (MA6.)
- 12 Follett EA, Barr A, Crawford RJ, Mitchell R. Viral hepatitis markers in blood donors and patients with a history of jaundice. *Lancet* 1980;i:246-9.
- 13 British National Association and Pharmaceutical Society of Great Britain. *British National Formulary. No 12*. London: BMA, Pharmaceutical Society of Great Britain, 1986:398.
- 14 Scottish Home and Health Department. *Statement of Fees and Allowances Payable to General Medical Practitioners in Scotland*. Edinburgh: SHHD, 1986: para 27/sched 1, item 16. (Circular No 1979 (PCS) 12.)
- 15 Larouze B, Gaudoubert C, Foulon G, Mercier E, Ancelle JP. Screening for Hepatitis A antibody before prescribing standard immunoglobulin for Europeans staying in tropical areas. *Lancet* 1984;i:449-50.

The cost of unnecessary tests by day or night

Undoubtedly some of the tests done by pathology laboratories are unnecessary, although it is impossible to know how many. When money is short it is tempting to predict how much would be saved if the unnecessary tests were not performed,^{1 2} but several traps await those who attempt this calculation.

Laboratory costs, like those of most hospital departments, can be divided into those that are fixed and independent of the workload and those that are variable and directly proportional to the number of requests received. Precisely defining these two components is difficult because some costs are best described as semivariable. Variable costs are usually equated with direct consumable costs, and in clinical chemistry they are about 10-12% of the revenue expenditure.³ Consequently the relation between workload and expenditure is not a simple direct proportion, and the savings from deleting unnecessary tests⁴ are invariably less than those expected from a simple analysis. Thus Winkelman⁵ found that reductions of 10% and 50% in laboratory tests resulted in savings of 3.9% and 21.5% respectively; indirect costs, which are the largest component of laboratory expenditure,³ will be unaffected by small short term changes in workload.

The cost of laboratory work done out of hours is a tempting target for the cost cutting manager because it is readily identifiable in most laboratory budgets. In practice this is the on call labour cost, not the total cost; and it is obviously a variable cost so that only proportional savings would result from reducing the work. Gray *et al* have drawn attention to another trap for the unwary. In Britain payment to laboratory staff for out of hours work is based on the call, which is usually for several requests on different patients. On average one out of hours on call payment may cover two or three requests⁶⁻⁸—so that a 40% reduction in workload may result in only a 4% decrease in calls.⁸ Several methods of reducing out of hours demands have been proposed, including using guidelines⁹ and the monitoring of requests by senior laboratory staff,⁸ but there is no evidence that these have produced worthwhile savings.¹⁰ Using commonsense clinical criteria, Gray *et al* found that 16% of requests were unnecessary, but deleting these would have reduced on call labour costs by less than 5%.⁶ This casts doubt on the widely held belief that on call services are abused and expensive. The total cost of handling a typical request out of hours is probably about 50% more than that incurred within normal working hours,³ which can be considered good value and is unlikely to encourage doctors to reduce their demands.

- 1 Zuckerman AJ. The three types of human viral hepatitis. *Bull WHO* 1978;56:1-20.
- 2 Carreno V, Vasquez M, Ortiz F, Hernandez Guio C. Anti-HAV prevalence in healthy people in Spain. [Abstract.] *Gastroenterology*, 1980;79:1101.
- 3 Papaevangelou GJ, Gourgouli-Fotiou KP, Vissoulis HG. Epidemiologic characteristics of hepatitis A virus infections in Greece. *Am J Epidemiol* 1980;112:482-6.
- 4 Frosner GG, Papaevangelou G, Buter R, *et al*. Antibody against hepatitis A in European countries. I. Comparison of prevalence data in different age groups. *Am J Epidemiol* 1979;110:63-9.
- 5 Lecour H, Ribeiro AT, Amaral I, Rodrigues MA. Prevalence of viral hepatitis markers in the population of Portugal. *Bull WHO* 1984;62:743-7.
- 6 Ramia S. Antibody against hepatitis A in Saudi Arabians and in expatriates from various parts of the world working in Saudi Arabia. *J Infect* 1986;12:153-5.

Out of hours investigations are no longer used exclusively for diagnosis leading to urgent treatment. Deleting tests that do not meet traditional criteria of urgency might thus lead to additional costs—for example, by delaying discharge of a patient at the weekend or necessitating earlier admission so that preoperative tests could be done during normal working hours.

Although the need to reduce costs is obvious, the reductions must be both financially worthwhile and not affect patient care. Reducing laboratory work done out of hours probably does not meet these criteria. The cost and effectiveness of laboratory investigations need to be improved by day as well as by night, using a strategy that will influence the requesting practices of doctors.¹¹ Reducing laboratory costs should not be the primary motivation for doing this.

P M G BROUGHTON

Deputy Director,
Wolfson Research Laboratories,
Department of Clinical Chemistry,
Queen Elizabeth Medical Centre,
Birmingham B15 2TH

- 1 Sandler G. Costs of unnecessary tests. *Br Med J* 1979;ii:21-4.
- 2 Sandler G. Do emergency tests help in the management of acute medical admissions? *Br Med J* 1984;289:973-7.
- 3 Broughton PMG, Woodford FP. Benefits of costing in the clinical laboratory. *J Clin Pathol* 1983;36:1028-35.
- 4 Winkel P, Statland BE. Assessing cost savings when unnecessary utilisation of laboratory tests can be abolished. *Am J Clin Pathol* 1984;82:418-23.
- 5 Winkelman JW. Less utilisation of the clinical laboratory produces disproportionately small true cost reductions. *Hum Pathol* 1984;15:499-501.
- 6 Gray TA, McLeod AJ, Bignell AHC. Future of the pathologist in an era of technological change and cost containment. *Br Med J* 1987;294:902-3.
- 7 Gunn IR, Little AJ, Payne RB. Effects of workload and analysis time on the cost of out-of-hours investigations. *Ann Clin Biochem* 1986;23:502-3.
- 8 Smith ADS, Shenkin A, Dryburgh FJ, Morgan HG. Emergency biochemistry services—are they abused? *Ann Clin Biochem* 1982;19:325-8.
- 9 Lester E. A new strategy for out-of-hours laboratory investigations. *Ann Clin Biochem* 1986;23:497-500.
- 10 Payne RB, Young RM. Out-of-hours chemical pathology. *Lancet* 1985;ii:103.
- 11 Fraser GC, Woodford FP. Strategies to modify the test-requesting patterns of clinicians. *Ann Clin Biochem* 1987;24:223-31.

Use and abuse of allopurinol

Allopurinol was first synthesised as an adjunct to anticancer treatment with mercaptopurine in 1960 but was found to have powerful hypouricaemic effects.¹ It has caused severe tophaceous gout to all but vanish, and renal complications of gout are now rare.² Recently a controlled trial has confirmed that allopurinol can inhibit the formation of calcium oxalate stones in the 15-20% of patients who form stones and who are hyperuricosuric.³ More than 5 million patient years of treatment have now accumulated, and more than 70 tonnes of what is in general a safe and effective agent are ingested each year. Minor reactions to the drug do occur—probably 2% of patients will develop itching and rashes.⁴ More severe reactions, including exfoliative dermatitis or toxic epidermolysis, eosinophilia with interstitial nephritis or vasculitis, hepatic granulomas, and bone marrow depression have been described in about 350 patients,⁵⁻²³ with a further 250 unpublished cases (G Lovett, personal communication). Many of those suffering severe reactions had reduced renal function and often the dose of allopurinol used was either not stated or was too high for the degree of renal function.⁷⁻²² We believe that these toxic effects could mostly have been avoided by better understanding of the metabolism and renal handling of the drug.

About 60-70% of allopurinol is metabolised to its active

principle, oxipurinol, which is excreted through the kidney together with allopurinol itself and allopurinol riboside, the second main metabolite.²⁴ Unlike allopurinol and its riboside, which are rapidly cleared, oxipurinol undergoes net reabsorption in the renal tubule,^{25 26} just like urate itself. Oxipurinol may thus accumulate easily in patients with renal failure, in patients with gout or in patients being treated with thiazides because their fractional excretion of urate and oxipurinol is low. A single dose of allopurinol may achieve therapeutic concentrations of oxipurinol (40-60 $\mu\text{mol/l}$) in the plasma for a week or longer;^{23 25 26} we have found plasma oxipurinol concentrations as high as 300 $\mu\text{mol/l}$.²³ In addition, as with urate transport, the net reabsorption of oxipurinol is greatly increased in states of volume contraction and hypovolaemia,²⁷ including those induced by diuretics; net reabsorption is decreased in states of volume expansion. Clearance of oxipurinol is also altered by changes in the glomerular filtration rate,^{6 24} including the transient changes induced by differences in protein ingestion.²⁸

Suggested maintenance dose of allopurinol for patients with diminished renal function

Creatinine clearance (ml/min)	Allopurinol dose
0	100 mg thrice weekly
10	100 mg on alternate days
20	100 mg daily
40	150 mg daily
60	200 mg daily
≥ 100	300 mg daily

Despite the fact that this information has long been available many patients with renal impairment are still given too high a dose of allopurinol. Most of these treated with the drug are middle aged and elderly, and even in those without cardiac or renal disease renal function diminishes steadily with age, although plasma creatinine or urea concentrations do not rise to signal this decline.²⁹ Plasma oxipurinol assays are not readily available, and our own and other workers' data lead to the suggestions shown in the table for maintenance doses of allopurinol in patients with diminished renal function.^{7 23 26 30 31} If only the plasma creatinine concentration is available then a formula that takes account of age as well as body size (based on that of Cockcroft and Gault³²) may be used to calculate the clearance:

$$\text{creatinine clearance (ml/min)} = \frac{140 - \text{age in years} \times \text{weight in kilograms}}{7.6 \times \text{plasma creatinine concentration in } \mu\text{mol/l}}$$

If the urate clearance is known to be reduced the dose should be reduced even further. In patients with normal renal function the dose should not exceed 300 mg/24h initially and rarely needs to exceed it thereafter except in the unusual case of resistance to the drug.³³ Side effects can usually be prevented, even on rechallenge, by starting the dose at 5-10 mg/24h and then increasing it gradually.⁶

A further problem arises when allopurinol is used to redistribute the excreted purine load away from just urate in patients with gross purine overproduction—that is, those being treated for malignancies of the bone marrow or lymphomas^{23 34} and those with inherited deficiencies of the enzyme hypoxanthine-guanine phosphoribosyltransferase.^{34 35} Complete deficiency of this enzyme leads to the Lesch-Nyhan syndrome and incomplete deficiency to sex linked familial gout. During treatment with allopurinol the purine end products are a much reduced amount of urate,