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. Reducing laboratory costs should not be the primary motivation for doing this.

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Use and abuse of allopurinol

Allopurinol was first used as an adjunct to anticancer treatment with mercaptopurine in 1960 but was found to have powerful hypouricaemic effects. It has caused severe tophaceous gout to all but vanish, and renal complications of gout are now rare. 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. More than 5 million patients year 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. More severe reactions, including exfoliative dermatitis or toxic epidermolyis, eosinophilia with interstitial nephritis or vasculitis, hepatic granulomas, and bone marrow depression have been described in about 350 patients, with a further 250 unpublished cases (G Lovett, personal communication).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. 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. Unlike allopurinol and its riboside, which are rapidly cleared, oxipurinol undergoes net reabsorption in the renal tubule, 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 μmol/l) in the plasma for a week or longer, we have found plasma oxipurinol concentrations as high as 300 μmol/l. In addition, as with urate transport, the net reabsorption of oxipurinol is greatly increased in states of volume contraction and hypovolaemia, 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, excluding the transient changes induced by differences in protein ingestion.

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. 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. 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 Gault) may be used to calculate the clearance:

\[
\text{creatinine clearance (ml/min)} = \frac{140 - \text{age in years × weight in kilograms}}{7.86 \times \text{plasma creatinine concentration in μmol/l}}
\]

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. Side effects can usually be prevented, even on rechallenge, by starting the dose at 5-10 mg/24h and then increasing it gradually. 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 and those with inherited deficiencies of the enzyme hypoxanthine-guanine phosphoribosyltransferase. 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,
accompanied by a considerable increase in the excretion of xanthine, and a lesser amount of hypoxanthine. Hypoxanthine is soluble, but xanthine is about as insoluble as urate—but, unlike urate, its solubility does not increase when the urine is alkalised. Thus when allopurinol is used in states of gross urate overproduction xanthine may precipitate in the kidney and urinary tract. Allopurinol must thus be used with care and given only when there is clear evidence of therapeutic benefit. Its use in gout is established, and as well as controlling symptoms it may protect renal function, especially in familial cases. Its use for moderate symptomless hyperuricaemia has so far not found support either for protecting renal function or reducing cardiovascular risk. Because of the very occasional disastrous reaction the use of allopurinol is not recommended in the many people with mild symptomless hyperuricaemia.

In any patient presenting with gout or hyperuricaemia potential causes such as diet and drugs, particularly diuretics, should be sought and eliminated. In men under 30 and women not taking diuretics specialist advice should be sought to exclude metabolic defects before beginning treatment with allopurinol.

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