Polypharmacy in rheumatic diseases

Traditionally polypharmacy is condemned: in reality it is widely practised. Many patients with arthritis receive more than one non-steroidal anti-inflammatory agent simultaneously or else one of these drugs ("for stiffness") with an analgesic ("for pain"). Evidence of the synergistic value of these combinations is often lacking. Claims have been made that synergism between naproxen and aspirin in rheumatoid arthritis, but others have failed to show this synergism. Furthermore, serum indomethacin concentrations may even be lowered by giving salicylates at the same time, though again there are conflicting reports. Nor are serum concentrations of a drug necessarily a guide to clinical improvement. A recent study from New Zealand of the possible clinical and pharmacokinetic interaction between aspirin and ibuprofen in rheumatoid arthritis showed a weak additive clinical effect between 1600 mg ibuprofen and 3600 mg aspirin daily, though not with lower doses of the drugs. Ibuprofen had no effect on serum concentrations of salicylate, but salicylate reduced the serum concentration of ibuprofen without affecting its elimination half-life. Altered absorption of ibuprofen, protein binding, or possibly both may have been responsible for the fall. The patients did not appear to suffer clinically.

While a plethora of new non-steroidal anti-inflammatory agents has been introduced, little attention has been paid to the most efficient use of the old ones. Patients are seldom advised about the relation of dosage to meals, and doctors forget that half lives of drugs tend to be longer in older patients, so that less frequent administration may be reasonable in rheumatic diseases of the elderly. Monitoring of serum concentrations, useful as a test of compliance as well as drug availability, is becoming more easily available to rheumatologists. Few practitioners realise, for example, that phenylbutazone with a half life of around 70 hours needs to be tried for at least two weeks before being discarded as "ineffective." Equally, pharmacokinetics should not override the clinical picture as testified by the rapid response of patients with gout to phenylbutazone in spite of its long half life. In rheumatic diseases, drug concentrations in synovial fluid and the tissues are likely to be more relevant than those in the serum.

The non-steroidal anti-inflammatory agents may be grouped generically by their clinical structure into a few families, yet few studies have attempted to correlate clinical improvement with plasma profiles when drugs from two different families are given simultaneously—the rational approach to polypharmacy. The treatment of epilepsy has been revolutionised by neurologists learning to replace multiple drug treatment with closely monitored use of a single drug, and all rheumatologists would agree that the difficulty is matching the right drug to the right disease in the right patient.

While polypharmacy among non-steroidal anti-inflammatory agents might be usefully trimmed, the concept of polypharmacy in the specific long-term treatment of rheumatoid arthritis is more exciting. Traditionally, drugs such as d-penicillamine and gold are given in isolation. Analogy with diseases such as ulcerative colitis and lymphomas, both chronic diseases with autoimmune aspects, suggests there may be a case for initiating a remission with one agent and subsequent maintenance treatment with a second. So far, however, the similarity of the side effects of gold and d-penicillamine has prevented these drugs being used in rapid succession—and, indeed, studies in patients where the drugs have been given with a respectable interval between them suggest that there may still be some accumulation of adverse reactions.

Some patients with rheumatoid arthritis are started on steroids pending subsequent transfer to a "steroid-sparing agent" such as d-penicillamine in order to gain rapid improvement when immediate relief of symptoms is required, though many rheumatologists believe the possible side effects of prednisolone do not justify its dramatic results. Prednisolone does, however, reduce the amount of cyclophosphamide required to produce remission and regression of radiological erosions in rheumatoid arthritis. Whether it "potentiates" other drugs in this manner is not yet known. Old drugs recently claimed to have specific antirheumatoid properties include sulphasalazine, oral gold, dapsone.
and zinc compounds\textsuperscript{12} among the less toxic front runners. These do not share the side effects of existing antirheumatoid drugs, which suggests that combination treatment or successive use of a series of these compounds may be worth trying—and might even lead to earlier and more convincing remission.

\textsuperscript{1} Wilkins RF, Segre EJ. Combination therapy with naproxen and aspirin in rheumatoid arthritis. \textit{Arthritis Rheum} 1976;19:677-82.
\textsuperscript{7} Webster M, Coomes EN. An assessment of penicillamine therapy in rheumatoid arthritis and the influence of previous gold therapy. \textit{J Rheumatol} 1979;6:20-4.
\textsuperscript{10} Gottlieb NL. Gold compounds in rheumatoid arthritis: clinical-pharmacokinetic correlates. \textit{J Rheumatol} 1979;suppl 5:51-5.

### Primary aldosteronism

The possibility of "curing" hypertension is attractive to doctors, who are in general averse to prescribing lifelong medication, and to many patients, who are averse to receiving it. Hence it is always worth while for a doctor to consider whether there is any remediable cause of a raised blood pressure in a newly diagnosed hypertensive patient. Primary aldosteronism is one such cause, though the initial belief\textsuperscript{1} that it accounted for a fifth of patients with "essential hypertension" proved too optimistic. Nevertheless, it is an important diagnosis to make, both because of the possibility of operative treatment and because it causes symptoms in addition to those due to the hypertension.

In most patients primary aldosteronism is due to an adrenal adenoma; some have apparent hyperactivity of the adrenal zona glomerulosa (micronodular hyperplasia); and a few have histologically normal adrenal glands. The physiological changes are most clear cut when an adrenal adenoma secretes excessive quantities of aldosterone. This stimulates activity in the distal renal tubules, increasing the reabsorption of sodium and the excretion of potassium. Retention of sodium suppresses the secretion of renin, but it is not necessarily responsible for raising the blood pressure—mineralocorticoid hormones may possibly produce changes in the responsiveness of the blood vessels by a mechanism which is independent of sodium retention.\textsuperscript{2} Whatever the mechanism of hypertension in primary aldosteronism, characteristic biochemical abnormalities are low serum concentrations of potassium and renin and a raised urinary output of aldosterone. Usually the hypokalaemia raises the first clinical suspicion, since it may give rise to muscle weakness, cramps, tetany, and polyuria. Hypokalaemia is not, however, always present: in one study 22\% of patients with primary aldosteronism had a serum potassium concentration above 3.5 mmol/l.\textsuperscript{13} Repeated measurement of serum potassium concentrations should reduce the incidence of such "normokalaemic" aldosteronism. Patients with aldosteronism due to bilateral hyperplasia usually have less florid biochemical changes, and no expansion of the exchangeable sodium.\textsuperscript{4}

Between 50 and 60\% of patients with an adenoma show a good response to its surgical removal, but hyperplasia demands subtotal or bilateral adrenalectomy and even then the effect on the blood pressure is disappointing. The treatment of choice for this group is probably medical, using either spironolactone or amiloride.\textsuperscript{5,6}

The main requirements for adequate management of primary aldosteronism, therefore, are, firstly, to make the diagnosis and, secondly, to establish whether the syndrome is due to an adenoma. Finding a serum potassium concentration at or below the lower limit of normal should raise the possibility of primary aldosteronism. Unfortunately hypokalaemia is all too common in hypertensive patients treated with potassium-losing diuretics and in patients with poorly controlled severe hypertension—secondary aldosteronism. Only where the hypokalaemia persists despite withdrawal of the diuretics and the use of effective hypotensive treatment does the diagnosis of primary aldosteronism become likely. One diagnostic clue is provided by the serum sodium concentration, which tends to be higher or in the upper part of the normal range in primary aldosteronism and lower in secondary aldosteronism. There is, however, a substantial overlap between the two groups. The serum concentration of renin is low in primary aldosteronism and raised in secondary aldosteronism. More refined testing includes showing that the secretion of aldosterone cannot be suppressed normally by saline infusion and that the concentration of renin does not rise normally after frusemide.\textsuperscript{7}

Distinguishing those patients who have an aldosterone-secreting adenoma, in whom surgery is the treatment of choice, is primarily a matter of biochemical investigation by appropriate weighting of the changes in potassium, renin, and aldosterone using quadric\textsuperscript{8} or multiple logistic\textsuperscript{9} analysis. Adrenal scanning after the injection of iodine- or technetium-labelled cholesterol has been useful in some hands.\textsuperscript{10,11} The biochemical techniques demand rigorously standardised procedures based on experience with large numbers of patients: they are not suitable where experience is more limited.

Another discriminatory test is based on changes in the serum concentration of aldosterone with posture. The normal rise with the upright posture is reversed in many patients with aldosterone-secreting adenomas, who show a postural reduction. In adrenal hyperplasia, in contrast, the aldosterone concentration rises though the rise may be subnormal.\textsuperscript{5} This abnormality has been used in preoperative classification of patients,\textsuperscript{5} but the results may be misleading in patients with unilateral lesions,\textsuperscript{3} and ideally the aldosterone concentration should be compared in the adrenal venous effluent from the two sides.\textsuperscript{3} The diagnosis may be supported by adrenal scanning,\textsuperscript{12} though there may be sufficient asymmetry on the two sides for a false diagnosis of adenoma to be made occasionally.\textsuperscript{13}

Screening large populations of hypertensive patients for primary aldosteronism with tests such as these is not a reasonable use of resources. Primary aldosteronism is a rare