Drug interactions in arthritic patients

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Abstract

The drug treatment of 100 consecutive new patients admitted to a regional rheumatology centre was reviewed. Potential drug interactions were sought according to appendix one of the *British National Formulary* (September 1989) and identified in 55 of 100 patients. The clinical and laboratory features of these patients were then reviewed, showing that only 11 displayed clinical manifestations of a drug interaction. Five patients had drug induced drowsiness, which was easily corrected, five a raised serum creatinine, which was less easily corrected, and one both.

Although there is considerable potential for drug interaction in patients with severe arthritis, the proportion of patients who display clinical manifestations of this is small.

Patients with arthritis often require several drugs to control their symptoms. Many take an analgesic for pain and an anti-inflammatory drug for stiffness. Patients with rheumatoid arthritis are likely to need a disease modifying drug added to this regimen. Many patients are elderly, requiring concomitant drugs for other diseases, so the potential for drug interaction is considerable.¹

As a guide to practice in the United Kingdom the *British National Formulary* contains an appendix with a comprehensive list of potential drug interactions.² Although these interactions are proved in pharmacokinetic terms, their clinical relevance is not always clear, particularly when patients have a multitude of diseases.

To measure the extent of this problem we surveyed drug interactions and their clinical relevance in a series of 100 consecutive subjects selected for their relatively severe arthritis by referral from many health authorities for admission to a regional rheumatology centre.

Methods

One hundred consecutive subjects admitted to the Royal Bath Hospital, Harrogate were studied over a four week period in November 1989. Demographic data and details of drugs taken on admission, before any changes in treatment, were recorded. Drug interactions were then sought, defined as those listed in appendix one of the *British National Formulary*, September 1989.² Patients identified as having treatment which included drugs for which there was a risk of interaction were then questioned further and examined to determine whether the interaction was of clinical significance. When it

was significant an attempt was made to correct the drug treatment to avoid the interaction and the patient was followed up during the remainder of the admission (average duration three weeks) to determine whether the patient was able to tolerate this change without loss of therapeutic control. In the light of this, recommendations on future drug treatment were made to the family practitioner in the discharge summary.

Results

Of 100 consecutive admissions studied, 70 were female and 30 were male. Their mean age was 59.6 years (range 20-84), and the principal rheumatic diagnosis on admission was rheumatoid arthritis (43), osteoarthritis (29), non-articular rheumatism (seven), psoriatic arthritis (six), ankylosing spondylitis (five), polymyalgia rheumatica (three), other arthritis (seven). The mean plasma urea for the group was 6.56 mmol/l (range 2.1-18.4 mmol/l) and the mean serum creatinine for the group was 81.7 µmol/l (range 30-205 µmol/l).

Eighty seven of the 100 patients were receiving three or more drugs. Thirty nine were receiving six or more drugs, 19 patients 10 or more drugs, and three were receiving 13 or more drugs. Non-arthritic conditions commonly present and requiring drug treatment included congestive cardiac failure, sleeplessness, iron deficiency, thyroid disorders and vitamin deficiencies, including folic acid and vitamin B-12.

At least one potential interaction was found in 55 of the 100 patients (mean 1.25 interactions per patient). Eight patients were at risk of three interactions, six patients at risk of four, one patient at risk of five, two patients at risk of six, and one patient at risk of 10.

As a result of full clinical history and examination it was judged that the drug interactions were only of clinical relevance in 11 of these 55 patients (table 1). Table 2 shows the drug combinations taken by these 11 patients and the clinical effects produced. Six of these patients were female and five male with a mean age of 72 years (range 57-84 years). Seven of these patients had rheumatoid arthritis, three osteoarthritis, and one polymyalgia rheumatica as their main rheumatic diagnosis. Mean urea concentration for the group was 9.7 mmol/l (range 4.5-16.4 mmol/l) and mean creatinine 111 µmol/l (range 39-168 µmol/l).

For six patients the adverse clinical effect was drowsiness and in each case it proved possible to relieve symptoms by simple changes in drugs.

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Table 1 Clinical details of 11 patients in whom drug interactions occurred

Case No	Age	Sex	Main rheumatic diagnosis	Urea (mmol/l)	Creatinine (μ mol/l)
1	63	F	RA*	13.8	107
2	57	F	RA	4.5	39
3	72	M	RA	7.2	95
4	82	F	PMR*	6.8	68
5	68	M	RA	7.1	126
6	81	F	OA*	10.6	123
7	69	F	RA	16.4	168
8	79	M	OA	10.8	131
9	84	M	OA	9.8	111
10	65	M	RA	7.6	149
11	73	F	RA	12.2	110

*RA=rheumatoid arthritis; PMR=polymyalgia rheumatica; OA=osteoarthritis.

admission, either at the level of the general practitioner or at the local district general hospital. The group was therefore biased in favour of patients who would need many drugs and who might be at particular risk of drug interaction.

It was reassuring that despite identifying drug combinations with the potential for interaction in 55 out of 100 patients, in only 11 of these patients was the interaction judged to be of clinical significance. Moreover, only two clinical interactions were noted. The first, drowsiness, could normally be alleviated by simple adjustment of treatment, the second, a raised creatinine concentration, not noted symptomatically by the patient, was less easily correctable and in several patients a compromise had to be reached, leaving the patient with raised creatinine in deference to realistic control of arthritis and peripheral oedema. Patients with rheumatic diseases may have abnormalities of renal function,³ and the way in which non-steroidal anti-inflammatory drugs may cause a reversible impairment of renal function as measured by creatinine clearance is now recognised.⁴ It may even be untrue to imply that the impaired renal function in these patients resulted from drug interaction alone. It remains reassuring that, as judged by this group of predominantly elderly patients with severe disease, the considerable potential for drug interaction is unlikely to have major clinical consequences and those that are found are often easily correctable.

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Table 2 Drug combinations and their effects in 11 arthritic patients

Case No	Drug combination	Effect
1	Co-proxamol/lorazepam/temazepam	Drowsiness
2	Nitrazepam/dihydrocodeine/amitriptyline	Drowsiness
3	Nitrazepam/co-proxamol/metoprolol	Drowsiness
4	Chlorpheniramine/propranolol/dihydrocodeine	Drowsiness
5	Co-proxamol/diazepam/cimetidine/buprenorphine/dihydrocodeine/nifedipine	Drowsiness
6	Indomethacin/chlorothiazide/nefopam/terodiline	Drowsiness/raised creatinine
7	Bendrofluzide/indomethacin	Raised creatinine
8	Amiloride/ibuprofen	Raised creatinine
9	Ibuprofen/thiazide/triamterene	Raised creatinine
10	Naproxen/thiazide/triamterene	Raised creatinine
11	Mefenamic acid/bendrofluzide	Raised creatinine

Although renal impairment was seen in patients 1 and 5 of this group, this was not thought to be drug induced. For the six patients who displayed a raised creatinine (mean 132 μ mol/l) that might have been exacerbated by drug reaction, recommendations were made to alter drug treatment, but these proved harder to enforce because they either induced exacerbation of arthritis or caused a worsening of cardiac failure.

Discussion

Selected by hospital referral to a regional centre, all these patients presented complex therapeutic problems that had proved insoluble without

- 1 Bird H A, Wright V. Polypharmacy. In: *Applied drug therapy of the rheumatic diseases*. Bristol: Wright, 1982: 89-102.
- 2 Appendix 1: Interactions. *British national formulary*. Vol 18. Great Britain: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1989: 440-57.
- 3 Bird H A, Yu H, Cooper E H. Renal proximal tubular dysfunction in patients with rheumatic diseases. *BMJ* 1984; **288**: 1044-5.
- 4 Bird H A. The kidney in rheumatic diseases. *Ann Rheum Dis* 1989; **48**: 1029-30.