Letters to the Editor

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Co-proxamol: where have all the patients gone?

SIR, The Committee on Safety of Medicines (CSM) advised withdrawal of co-proxamol in January 2005 as it was judged that the risk of accidental death by overdose and the drug's frequent use in suicide outweighed its benefits as a painkiller. We were struck by the number of patients who seemed to be coming to the clinic complaining that they were unable to find an effective alternative. A typical complaint would be that they had been on co-proxamol for 20 yrs and found it very satisfactory. They had been tried on co-codamol and tramadol without nearly as good a benefit and wanted their co-proxamol back. We felt that an audit of what had happened to all the patients on co-proxamol was necessary to see if the impression that they were dissatisfied with the alternatives was true.

The aim of this audit was to assess if patients had transferred to an alternative painkiller, how satisfied they were with their change in medication as compared with co-proxamol and whether they would like their co-proxamol back. The standard that we chose to audit against was that all subjects should have found an alternative that they were happy with or they should be allowed to continue their co-proxamol.

The department database was searched for all patients who were current users of co-proxamol in January 2005. A postal questionnaire was sent out in February 2006 to all patients, seeking information on whether they were indeed taking co-proxamol in January 2005 and which drugs they had tried and were currently taking. We asked how effective and tolerable they rated their co-proxamol and whatever drug they were currently taking on visual analogue scales (VAS). We also asked about how they had heard of the imminent withdrawal of co-proxamol and sought information relating to suicide risk using standard questions.

Eighty-one patients were identified from the database and 60 replies were received (response rate $60/81 = 74\%$). Thirteen males (21.6%) and 42 females (70%) responded, with an average age of 59.1 yrs. Five respondents (8.3%) did not indicate sex or age. Rheumatoid arthritis was the commonest indication for taking co-proxamol with 34 patients (56.6%), followed by osteoarthritits with 21 patients (35%). The remaining 13 patients (8.4%) were taking co-proxamol for psoriatic arthritis, systemic lupus erythematosus, enthesitis, spondyloarthropathy, ankylosing spondylitis and tenosynovitis.

Fifty-six of these confirmed that they were taking co-proxamol in January 2005 (93.3%). Seventeen (30.4%) were still taking co-proxamol at follow-up. Of these, only six had tried alternative analgesics since the announcement (most commonly co-codamol and tramadol). Of those patients who had changed from co-proxamol (39), 27 would choose to return to co-proxamol, given the chance (current drug: co-codamol 15; paracetamol 7; co-dydramol 2; codeine 4; tramadol 3; DF118 1; MST 1). There were 12 patients who were content on a new analgesic (current drug: paracetamol 4; codeine/paracetamol 4; DF118 2; co-dydramol 1; tramadol 1). Of the patients who had changed from co-proxamol to an alternative painkiller, a significantly higher level of effectiveness ($P < 0.01$) and satisfaction ($P < 0.01$) on the VAS was found for co-proxamol compared with the current drug. Twenty-seven of the 39 people no longer on co-proxamol (69%) would choose to return to co-proxamol if they had the choice.

General practitioners were most likely to have communicated the withdrawal of co-proxamol (58.9%). The population was at very low risk for suicidal intent 4/60 (6.6%) and thoughts of overdose 2/60 (3.3%).

In total, of the 56 patients confirmed as taking co-proxamol in January 2005, 17 (30%) were still taking it; 27 (48%) were unhappily off it and 12 (21%) were content on a new drug. Forty-eight per cent therefore fail our standard that they should have found a suitable alternative.

Previous work has suggested that up to 65% of people who die from co-proxamol overdose have a chronic physical disease, with approximately half of these being due to a skeletal or muscular disorder, often widespread chronic pain [1]. This case series also found a history of depression in 55% and an undefined mental illness in a further 21%. Chronic alcohol abuse was also a significant factor, being found in up to a third of co-proxamol deaths. We would argue that our patients are at low risk of overdose as they have a well-defined rheumatological condition, and we found little evidence of depression, suicidal intent or ideation in this population.

This selected group of patients experience significantly better pain relief with co-proxamol than with alternative analgesics. We would suggest that more note should be taken of what are effectively *n* of 1 studies and that more patients should be allowed to continue to take what is the best drug for them.

Rheumatology key message

- Many patients have not found a satisfactory alternative to co-proxamol.

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L. OTTEWELL, D. J. WALKER

Musculoskeletal Unit, The Freeman Hospital, Newcastle-upon-Tyne, Tyne and Wear, UK
Accepted 10 September 2007
Correspondence to: D. J. Walker.
E-mail: d.walker@ncl.ac.uk; david.walker@nuth.nhs.uk

1 Dywer PS, Jones IF. Fatal self-poisoning in the UK and the paracetamol/dextropropoxyphene combination. Hum Toxicol 1984;3(Suppl.):145–74S.

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RF latex and anti-CCP antibodies: a combined strategy for diagnosing RA in primary care?

SIR, Deborah Symmons makes a strong case in your recent editorial that RF testing should not be abandoned but used in conjunction with anti-cyclic citrullinated peptide (CCP) antibodies in the diagnosis of early RA in secondary care [1]. Whilst combining RF with anti-CCP antibodies may add some additional diagnostic and prognostic information, there is a consensus view that measuring anti-CCP antibodies in patients who are already known to have clinically diagnosed RA adds little additional

information in the presence of high-titre RF [2]. However, serological testing for RF is not diagnostic, being predictive of more severe disease in those with known RA. In secondary care, where the pre-test probability of a diagnosis of inflammatory arthritis in patients is high, one may argue that there is a need for CCP antibody testing only for those in whom the diagnosis of RA is not yet clear. However, in primary care, where currently patients are tested inappropriately for RF with a lower pre-test probability, there are many false positives, leading to inappropriate referrals to specialist clinics. The use of anti-CCP antibody testing in this setting may reduce false positive results, inappropriate referral and ultimately prove cost-saving to the health economy.

We undertook a prospective study to examine a new serological approach for the diagnosis of RA in primary care. We hypothesized that a rheumatoid latex test could be used as an initial screening tool, given its relatively high sensitivity and low specificity. Samples from primary care were screened by RF latex testing, and if positive, tested for anti-CCP antibodies. We compared this strategy with the conventional RF latex plus particle agglutination assay (RAPA) currently used for diagnosis of RA in primary care.

We collected 112 new referrals to the rheumatology outpatient department with joint pain who had previously been subjected to RF testing in primary care. Serum samples were tested for RF using a latex test (RF latex at a screening dilution of 1:120), particle agglutination assay (RAPA-positive if titre >1:80) and anti-CCP antibody (Diasorin, Reading, UK). Clinical diagnoses were recorded blindly by an experienced rheumatologist.

Out of 112 patients referred, 31 (27.6%) had a diagnosis of inflammatory arthritis, of whom 13 were diagnosed with definite RA. Fifteen patients were RF latex/RAPA positive of whom nine (60%) had inflammatory arthritis and eight (53%) definite RA. In contrast, nine patients were RF latex and anti-CCP positive, all of whom had inflammatory arthritis and eight out of nine (89%) had definite RA. One patient with an undifferentiated inflammatory arthritis had a negative RF latex and was positive for anti-CCP antibody. Ninety patients were negative for RF and anti-CCP, of whom five were diagnosed with RA (5.6%). Furthermore, of the 80 patients with non-inflammatory joint pain, 5 (6.25%) were latex/RAPA positive and 12 (15%) were latex-positive/CCP-negative, and referred to out patients on this basis; no patient was CCP antibody positive in this group.

This pilot study suggests that using RF latex as a screening test together with anti-CCP antibody (if the latex test is positive) is an effective strategy for screening for RA in primary care. The combination of RF latex testing and CCP antibody testing provides a highly specific screening test for RA, with comparable sensitivity to latex/RAPA. This approach will not pick up those RA patients who are latex negative and CCP antibody positive, although only one such patient was identified in this study. However, such patients would not be picked up anyway with the conventional approach to screening (latex/RAPA).

Whilst there is a cost implication to this screening strategy, we calculate that within a catchment population of around 400 000 people, we need to reduce inappropriate outpatient referrals by only 20 patients/yr to make this strategy cost-effective for the health economy, based on current outpatient tariffs. We believe this approach to serological testing for RA in primary care merits further study [3].

Rheumatology key message

- A combination of RF latex plus anti-CCP antibody is an effective screening strategy for RA in primary care.

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A. Steuer[1], J. Watkins[1], F. Smith[2], L. Day[2], F. Demetriadi[1] H. Chapel[2]

[1]*Department of Rheumatology and* [2]*Department of Immunology, Wexham Park Hospital, Slough, Berks SL2 4HL, UK*
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Correspondence to: A. Steuer, Department of Rheumatology, Wexham Park Hospital, Slough, Berks SL2 4HL, UK. E-mail: alan.steuer@hwph-tr.nhs.uk

1 Symmons DPM. Classification criteria for rheumatoid arthritis – time to abandon rheumatoid factor? Rheumatology 2007;46:725–6.
2 Nell VP, Machold KP, Stamm TA *et al.* Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. Ann Rheum Dis 2005;64:1731–6.
3 Watkins JA, Smith F, Day L, Demetriadi F, Steuer A, Chapel H. The end of rheumatoid factor in primary care? Rheumatology 2006;45:i90.

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Three significant cases of neutropenia with etanercept

Sir, Current BSR guidelines do not recommend regular blood count monitoring for anti-TNF therapy [1] as studies have suggested no increase in adverse haematological events [2–4]. We have noted a minority (14.3%) of our patients becoming neutropenic ($<2.0 \times 10^9$/l) on anti-TNF [5], predominantly asymptomatically [5]. However, not all episodes have been without concern. Here we describe three cases of significant neutropenia on etanercept.

A 57-yr-old lady with aggressive seropositive RA since 1984 was intolerant of multiple DMARDs. She was on methotrexate and prednisolone (<10 mg), but with persistent synovitis. An isolated episode of asymptomatic neutropenia of 1.26 during methotrexate therapy was documented. She started etanercept 25 mg twice weekly, with excellent response. She became neutropenic 7 weeks after first dose (1.76×10^9/l) and persisted throughout treatment, the lowest being 0.84×10^9/l. These episodes responded to increased prednisolone up to 5 mg. Bone marrow examination showed active haemopoiesis and white cell production with increased immature granulocyte production, suggesting peripheral neutrophil consumption. Because of the persisting neutropenia, she was changed to adalimumab 40 mg fortnightly. She was intermittently mildly neutropenic during the first 6 months, (lowest value 1.95×10^9/l) but with a higher average neutrophil count. She currently has a normal neutrophil count and good response to adalimumab.

A 50-yr-old lady with seropositive RA requiring maintenance prednisolone (10–20 mg) was intolerant of methotrexate, cyclosporin and azathioprine. She had previously documented asymptomatic neutropenia (0.42×10^9/l) prior to commencing DMARDs, and an asymptomatic neutropenia (0.35×10^9/l) was noted during cyclosporin treatment, rapidly responding to 10 mg prednisolone. Etanercept was started and she became neutropenic (0.17×10^9/l) 17 days after the first dose, with symptoms of sore throat, mouth ulcers and pyrexia. She was admitted for urgent intravenous tazocin and gentamicin. All cultures were negative. She required two doses of G-CSF to bring her neutrophil count over 1.0×10^9/l. Three months later, she had a persistent neutropenia (0.61×10^9/l), and has been maintained on 10 mg prednisolone since. A bone marrow examination showed normal cellularity with active white cell production and normal granulocyte precursors.

A 61-yr-old male diagnosed in 1998 with psoriatic arthritis was intolerant of sulphasalazine. He was found to be persistently