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### Key questions concerning paracetamol and NSAIDs for OA

The recent leader by Dr Courtney and Professor Doherty provides an excellent evidence based perspective on the treatment of the pain of osteoarthritis (OA) with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) and on the issues related to the appropriate use and positioning of these agents within the therapeutic armamentarium.<sup>1</sup>

Clearly, age is a risk factor for NSAID associated serious upper gastrointestinal (GI) adverse events. Because age is also the most powerful risk factor for OA, a disease for which NSAIDs are widely employed as symptomatic treatment, this presents a particular problem for the clinician. It is important to recognise, therefore, that, as pointed out by Courtney and Doherty, a variety of measures can be employed to permit a reduction in NSAID dose or withdrawal of NSAIDs in the elderly.

Courtney and Doherty raise the possibility that the absence of an antiplatelet effect of coxibs might be disadvantageous and that the antiplatelet effect of non-selective NSAIDs "...might be advantageous in patients with OA who predominantly are elderly with frequent comorbidity such as obesity and thus often at higher risk of cerebrovascular or ischaemic heart disease." They note the increased incidence of myocardial infarction (MI) in the rofecoxib treatment arm of the VIGOR trial,<sup>2</sup> relative to the naproxen arm. However, the published evidence does not permit the conclusion that any NSAID, other than aspirin, which has been shown to decrease the risk of MI by about 30%, will protect against MI.<sup>3,4</sup> With respect to the VIGOR study, if one accepts the proposition promoted by the manufacturer—that is, that rofecoxib treatment did not increase the risk of MI but that naproxen decreased that risk, the effect size of naproxen would have been nearly twice as large as that seen in aspirin prevention trials.

Despite the contention that treatment with coxibs may increase the risk of thrombotic disease, neither of the two large GI safety studies of coxibs (VIGOR,<sup>2</sup> CLASS<sup>5</sup>) had

sufficient statistical power to discern a significant difference in the incidence of MI between treatment groups. Furthermore, the VIGOR trial was conducted exclusively in patients with rheumatoid arthritis, a disease in which the risk of MI is about twice as great as that in OA, and no information was presented to assure that the prevalence of underlying risk factors for MI (for example, obesity, hypercholesterolaemia, diabetes mellitus, smoking) was comparable in the two treatment groups.

The point is this: in patients with OA who are at risk for MI and are, therefore, candidates for low dose aspirin treatment, there are no data to support the suggestion that any other non-selective NSAID can serve as an alternative to aspirin and hence do "double duty" (aiding both the heart and the joint). There is no basis for the potentially risky recommendation that low dose aspirin prophylaxis is not needed in such patients. It should be recognised, however, that the results of the CLASS study suggest that the gastroprotective effect of celecoxib is mitigated by low dose aspirin use.<sup>7</sup> Whether the gastroprotective effect of rofecoxib is similarly abrogated by aspirin use is unknown because patients taking aspirin were excluded from the VIGOR trial.

Furthermore, the recent study by Catella-Lawson *et al* suggests that the non-selective NSAID, ibuprofen, may inhibit the antiplatelet effect of aspirin.<sup>6</sup> Maximal inhibition of serum thromboxane B<sub>2</sub> levels (an index of COX-1 activity in the platelet) and of platelet aggregation produced by a low dose of aspirin were blocked by a single daily dose of ibuprofen (400 mg) given two hours earlier. Similar results were obtained with multiple doses of ibuprofen, 400 mg three times a day, as commonly used in the treatment of OA pain. In contrast, concomitant administration of single doses of rofecoxib, a slow release formulation of diclofenac or paracetamol, 1000 mg, had no effect on aspirin pharmacodynamics. The inhibitory effects of multiple daily doses of ibuprofen were apparent even when subjects received aspirin before their morning dose of ibuprofen. This would suggest that for patients taking low dose aspirin who need an over the counter analgesic for their OA pain, paracetamol might be a better choice than ibuprofen.

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#### Authors' reply

We are grateful to Dr Brandt for expanding on the issue of possible cardioprotection by certain NSAIDs and the interaction between aspirin and coxibs/NSAIDs. We fully concur with the argument that he presents.

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### Reduction of jaw opening in giant cell arteritis

In the September issue of the journal, Nir-Paz *et al* described six patients who developed reduction in jaw opening in association with giant cell arteritis.<sup>1</sup> These authors found that patients with such a complaint seem to have a more severe disease with a higher prevalence of eye involvement.

Although the precise pathological mechanism underlying reduction in jaw opening is unknown, this symptom probably results, like jaw claudication, from partial failure in blood supply to masseter muscles. However, the value of jaw claudication as a harbinger of visual loss has been debated.<sup>2,3</sup> We sought to determine, in a large series of patients with temporal (giant cell) arteritis, the prevalence and clinical associations of reduction in jaw opening.

Between January 1977 and August 2002, 222 consecutive patients were diagnosed as having temporal arteritis in the Department of Internal Medicine. Clinical, laboratory, and pathological data were recorded prospectively before treatment at the time of diagnosis in 217 patients (178 biopsy proven), using a specifically designed, comprehensive questionnaire. The following items pertaining to jaw-mouth-throat problems were included in the questionnaire: jaw claudication, reduction or difficulty in jaw opening, maxillary or tooth pain, lingual discomfort or ischaemia, sore throat, dysphagia, hoarseness, and dry cough. Various jaw-mouth-throat complaints were present in 126 patients, including typical jaw claudication in 80 (63%), reduction or difficulty in jaw opening in 45 (36%), maxillary pain in 28 (22%), sore throat in 27 (21%), dysphagia in 22 (17%), dry cough in 14 (11%), hoarseness in 11 (9%), lingual discomfort in 7 (6%), and multiple complaints in 60 (48%).

Table 1 shows that reduction or pain in jaw opening was associated with pain over temples, occipitalgia, jaw claudication, and other

**Table 1** Prevalence and clinical associations of reduction in jaw opening. Results are shown as No (%) unless indicated otherwise

	Patients with pain and/or reduction in jaw opening (n=45)	Patients without this problem (n=171)
Mean age (years)	75.6	75.1
Men	13 (29)	60 (35)
Acute onset of symptoms	22 (49)	60 (36)‡
Delay in diagnosis (days)	58 (10–350)	78 (4–360)
Headache (temple)	43 (96)	127 (74)*
Occipitalgia	29 (64)	73 (43)*
Temporal artery clinically abnormal	34 (77)†	81 (47)**
Jaw claudication	27 (60)	52 (30)**
Multiple jaw-mouth-throat symptoms	31 (69)	29 (17)**
Permanent visual loss	7 (16)	22 (13)
Rheumatic symptoms	14 (31)	68 (40)
Large artery involvement	5 (11)	31 (18)
Constitutional symptoms	29 (66)†	127 (74)
Positive result of temporal artery biopsy	38 (84)	138 (81)
Mean (SD) erythrocyte sedimentation rate (mm/1st h)	88.8 (29.2)	90.7 (27.5)
Mean (SD) C reactive protein (mg/l)	99 (62)	94 (59)
Mean (SD) haemoglobin (g/l)	115 (23)	113 (16)
Mean (SD) platelet value (g/l)	444 (148)	426 (146)

\* $p < 0.05$ ; \*\* $p < 0.001$ . ( $\chi^2$  test, exact Fisher's test, or Mann-Whitney U test, as needed); † results not available for one patient; ‡ results not available for two patients.

jaw-mouth-throat complaints but not with other pretreatment variables, including the delay in diagnosis, permanent visual loss, extracephalic signs, constitutional symptoms, and inflammatory response. Finally, reduction or pain in jaw opening was the only jaw-mouth-throat complaint in 13 patients and the sole cephalic symptom in one patient.

Thus, our study only partially confirms the findings of Nir-Paz *et al.* Reduction in jaw opening seems to delineate, along with jaw claudication and other jaw-mouth-throat symptoms, a subset of giant cell arteritis characterised by a constellation of symptoms or signs indicating the involvement of multiple branches of the external carotid artery. Of importance is our finding of no association between reduction in jaw opening and visual symptoms, contrary to the Israeli study. This result is not surprising, because reduction in jaw opening involves vasculitis lesions in the external carotid artery system, whereas visual loss is due to vasculitis in distal branches of the ophthalmic artery—that is, in the internal carotid artery system.<sup>8</sup> In our opinion, the observed differences between our results and those presented by Nir-Paz *et al.* may be related to different study designs. Furthermore, we did not separate patients with true reduction in jaw opening and those with pain upon jaw opening but without obvious trismus, which may account for further discrepancies. Finally, we agree with Nir-Paz *et al.* that jaw-mouth-throat complaints, including reduction of jaw opening, should be better known to doctors because such symptoms may speed up the diagnosis of giant cell arteritis. In our experience, jaw-mouth-throat complaints represented, along with laboratory abnormalities, the keystone of diagnosis in five patients with biopsy-proven disease—that is, 2.3% of the series.

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## Authors' reply

We thank Liozon *et al.* for their interest in our article.<sup>1</sup> The data they present show that the reduction in jaw opening and pain upon jaw opening is probably more prevalent in patients with giant cell arteritis (GCA) than the 6.8% trismus we observed in our series.<sup>1</sup> One reason for the higher prevalence may be the prospective questionnaire specifically inquiring about reduction or difficulty in jaw opening. Nevertheless, it might be that the French patients with GCA they describe have different manifestations of the disease, as evidenced by a higher prevalence of jaw involvement (36% of the overall patients with GCA compared with 21% in cohorts reported from our country, Israel, and 24% from Spain.<sup>2,3</sup>

In the series presented by Liozon *et al.* (as in our series) the delay in diagnosis was shorter for patients with pain and/or reduction in jaw opening than in those without this problem (8.2 weeks *v* 11 weeks). This fact might imply that patients with GCA with trismus symptoms had a more aggressive and extensive form of GCA. Furthermore, Gonzalez-Gay *et al.* have reported that one of the predictors for permanent visual loss in a series of 239 patients with biopsy proven GCA is jaw claudication.<sup>4</sup>

We agree with Liozon *et al.* that jaw and throat signs (trismus among them) are very important to the diagnosis of GCA and should not be overlooked. Prevalence of the signs and measurements of jaw opening in series of patients with GCA from other geographical areas may further illuminate its prevalence, aetiology, and association with the severity of the disease.

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