EXTENDED REPORT

Paracetamol in osteoarthritis of the knee

C Miceli-Richard, M Le Bars, N Schmidely, M Dougados

See end of article for authors' affiliations
....

Correspondence to:
Professor M Dougados, Cochin Hospital, AP-HP, René Descartes University, Paris, France; maxime. dougados@cch.ap-hop-paris.fr

Accepted
24 February 2004
....

Background: Paracetamol is a recommended symptomatic treatment of osteoarthritis (OA), but in clinical trials sample sizes have been relatively small and variable daily doses of paracetamol have been used.
Objectives: To determine the therapeutic efficacy of paracetamol in OA of the knee and identify predictive factors of clinical response to treatment.
Methods: A double blind, parallel group, placebo controlled trial of analgesic efficacy and safety of paracetamol versus placebo including 779 patients with OA of the knee. Patients were randomly assigned to receive paracetamol 4 g/day (n = 405) or placebo (n = 374) for 6 weeks. Symptomatic OA of the knee was required at inclusion with global pain intensity of the knee during physical activities for the past 24 hours of $\geqslant$30 mm on a 100 mm visual analogue scale. The primary end point was a 30% decrease of global pain intensity of the knee. Intention to treat analyses were performed.
Results: The percentage of responders did not differ significantly between groups: 52.6% and 51.9% in paracetamol and placebo groups, respectively (p = 0.840). In a subgroup of patients with chronic mechanical knee pain without signs of inflammation (n = 123), the mean change in pain intensity from baseline was 25.2 mm *v* 15.2 mm, in the paracetamol (n = 63) and placebo (n = 60) groups, respectively—mean difference 10.0 mm; 95% CI 1.0 to 19.0; p = 0.0294. No serious adverse events were attributable to treatment.
Conclusion: A statistically significant symptomatic effect of oral paracetamol 4 g/day over placebo was not found, suggesting that paracetamol use in symptomatic OA of the knee should be further explored. The tolerability and safety of paracetamol, at the recommended maximum dose of 4 g/day, was confirmed over 6 weeks.

Paracetamol, as a symptomatic treatment of osteoarthritis (OA) is recommended as first line treatment by scientific societies: EULAR,[1][2] American College of Rheumatology,[3][4] North of England,[5] owing to its good efficacy/safety/cost ratio. These recommendations are based on daily practice and therapeutic trials. Nevertheless, for paracetamol the related controlled trials versus placebo or comparative trials versus non-steroidal anti-inflammatory drugs (NSAIDs) show variable results, probably owing to the low sample sizes and also to the variable daily doses used (2.6–4 g/day). Predictive factors of response are not yet clearly defined for patients with OA and there is some controversy about whether the presence of "inflammation" (flare up) is a predictive factor for analgesic response with NSAIDs. Pure analgesics seem to be more suitable for chronic OA related pain than for an acute phase flare up.

The primary objective of this trial was to determine whether differences in possible therapeutic efficacy might be seen between paracetamol and placebo in outpatients with OA of the knee, in a 6 week, double blind, controlled study. The secondary objective was to assess, after 1 week or 6 weeks of treatment, respectively, the predictive factors of clinical response, and to identify patient profiles in which treatments might be more effective. Safety and tolerability of paracetamol were also assessed in this trial.

PATIENTS AND METHODS
Patients
All enrolled patients gave informed written consent before enrolment. Diagnosis of knee OA was made according to the Lequesne criteria.[6] Symptomatic OA of the knee for at least 3 months was required for inclusion, with a global pain intensity of the knee during physical activities for the past 24 hours of at least 30 mm on a 100 mm visual analogue scale (VAS).

Patients were excluded from the study if they had a prosthesis or recent (less than 1 year) surgery of the studied knee; history of allergy to paracetamol; history of hepatitis; severe hepatic or kidney failure; steroids during the past 4 weeks; current treatment with enzymatic inductors or inhibitors; any prior history of asthma or allergy potentially requiring concomitant treatment during the study; pregnancy, lactation, or inefficacious contraception; a history of drug abuse or alcoholism.

The study was approved by the ethics committee of the coordinating site (Hôpital Cochin, Paris, France) and was conducted in accordance with good clinical practice.

Study design
The study was designed as a double blind, two parallel group, placebo controlled, multicentre trial of 6 weeks' duration, determining the analgesic efficacy of oral paracetamol 1 g, at a daily dose of 4 g, in patients with knee OA. Patients were included at visit 1 after a washout period of 24–48 hours (see below). Enrolled patients were randomly assigned to paracetamol or placebo groups. Early efficacy and safety data were collected at visit 2 at the end of the first week (day 8). At the end of the sixth week (day 42 or within the 24 hours after the study discontinuation), patients attended the study end visit (visit 3). If a patient had dropped out before the end of the study, the reason was recorded (non-compliance, voluntary withdrawal, adverse drug reaction, treatment failure, etc).

....

Table 1 Patients' characteristics at baseline

Characteristics	Paracetamol (n = 405)	Placebo (n = 374)	All (n = 779)
Female, No (%)	292 (72)	291 (78)	583 (75)
Age (years), mean (SD)*	69 (12)	70 (11)	70 (11)
Body mass index (BMI), mean (SD)	29 (5)	29 (5)	29 (5)
Disease duration (months),† mean (SD)	46 (45)	45 (48)	46 (47)
Kellgren and Lawrence radiological score‡			
• 2≤MTF<4 and LTF<4 and PF<4	266 (66)	243 (65)	509 (65)
• MTF≥2 and LTF<2 and PF<2	98 (24)	97 (26)	195 (25)
• 2≤MTF<4 and LTF<2 and PF<2	90 (22)	88 (24)	178 (23)
• LTF≥2 and MTF<2 and PF<2	17 (4)	13 (3)	30 (4)
• PF≥2 and MTF<2 and LTF<2	28 (7)	14 (4)	42 (5)
Clinical symptoms at baseline			
Sudden increase of pain within the 2 weeks before D0, No (%)	269 (66)	240 (64)	509 (65)
Pain at night, No (%)	214 (53)	212 (57)	426 (55)
Morning stiffness (>20 minutes), No (%)	342 (84)	307 (82)	649 (83)
Knee effusion (at least moderate), No (%)	34 (8)	34 (9)	68 (9)
Global pain intensity mm, mean (SD)	66.7 (18)	69.0 (17)	67.8 (18)
Patient's global assessment of knee OA (0–100 mm), mean (SD)	66.0 (17)	66.7 (18)	66.4 (18)
WOMAC Function subscale (0–100), mean (SD)	54 (15	54 (15	54 (15
Prior OA treatments, No (%)			
NSAIDs only	12 (3)	11 (3)	23 (3)
Paracetamol only	36 (9)	36 (10)	72 (9)
Both	10 (2)	4 (1)	14 (2)
None	347 (86)	323 (86)	670 (86)

*SD, standard deviation; †duration of the disease is the interval between the first symptom probably due to knee OA and the selection visit; ‡MTF, medial tibiofemoral compartment; LTF, lateral tibiofemoral compartment; PF, patellofemoral compartment—data are presented as number (percentage).

Study drug and concomitant treatments

The study drug was 1 g of oral paracetamol or matched placebo, given four times a day, with 4–6 hours between intakes. Patients had to continue treatment for 6 weeks. Compliance was assessed by blister examination and pill count at each study visit. Compliance with treatment was defined as an effective intake of at least 85% of the theoretical dose (based on the pill count). Patients were washed out of paracetamol or NSAIDs for at least 24 hours (or 48 hours for long half life treatments such as oxicams) before starting the study drug (washout period). Patients who had had an intra-articular injection in the previous 4 weeks were excluded from the study. Concomitant treatments, such as long acting OA drugs, psychotropic or myorelaxing drugs, vitamins or minerals, had to be given at stable doses for at least 3 weeks before inclusion and during the study.

Rescue drugs for OA, such as oral or injectable analgesics (including acetaminophen), NSAIDs, intra-articular drugs, were prohibited during the whole study and patients were interviewed at each visit about their concomitant OA drug treatment.

End points

Patients were evaluated at week 1 (day 8) and week 6 (day 42). The global pain intensity of the studied knee during physical activities for the past 24 hours (100 mm VAS), the patient's global assessment of knee OA for the past 24 hours (100 mm VAS), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for physical function (17 item subscale—100 mm VAS)[7] were assessed. Signs and symptoms suggestive of ''inflammation'' were also recorded: nocturnal pain interfering with sleep, duration of morning stiffness, joint effusion, and a sudden increase of pain during the previous 2 weeks.

The primary end point was a 30% decrease of the global pain intensity during physical activities for the past 24 hours.

Secondary end points were responses to treatment, with the minimal decrease in global pain intensity set at 20% and

50%; differences in scores from baseline for global pain intensity and patient's global assessment of knee OA severity (absolute and relative values); normalised WOMAC score and OARSI's combined response criteria based on changes from baseline in pain, function, and patient's global assessment of knee OA.[8] According to OARSI A criteria, a patient was defined as a responder when they had a 45% decrease of pain intensity and 20 mm decrease on VAS or two of the three following criteria:

- 15% decrease of pain intensity and 10 mm decrease on VAS
- 35% decrease of OA severity and 10 mm on VAS
- 30% decrease of the WOMAC (functional subscore) score and 15 mm on VAS

According to OARSI B criteria, a patient was defined as responder when they had a 50% decrease of pain intensity and 20 mm on VAS or

- 60% decrease of the WOMAC score and 20 mm on VAS

or

- 30% decrease of pain intensity and 15 mm decrease on VAS.
- 20% decrease of OA severity and 20 mm on VAS
- 25% decrease of the WOMAC score (functional subscore) and 10 mm on VAS.

Predictive factors of response

The following patient characteristics were collected at baseline, because they were expected to be predictive factors of response to treatment: demographics (age, weight, height, sex), residence (rural or town dwelling), occupation (sedentary, physical, sporting or other), details of the condition (OA location on the studied knee and involvement of other articular locations), signs and symptoms suggestive of ''inflammation'' on physical examination. Local or systemic
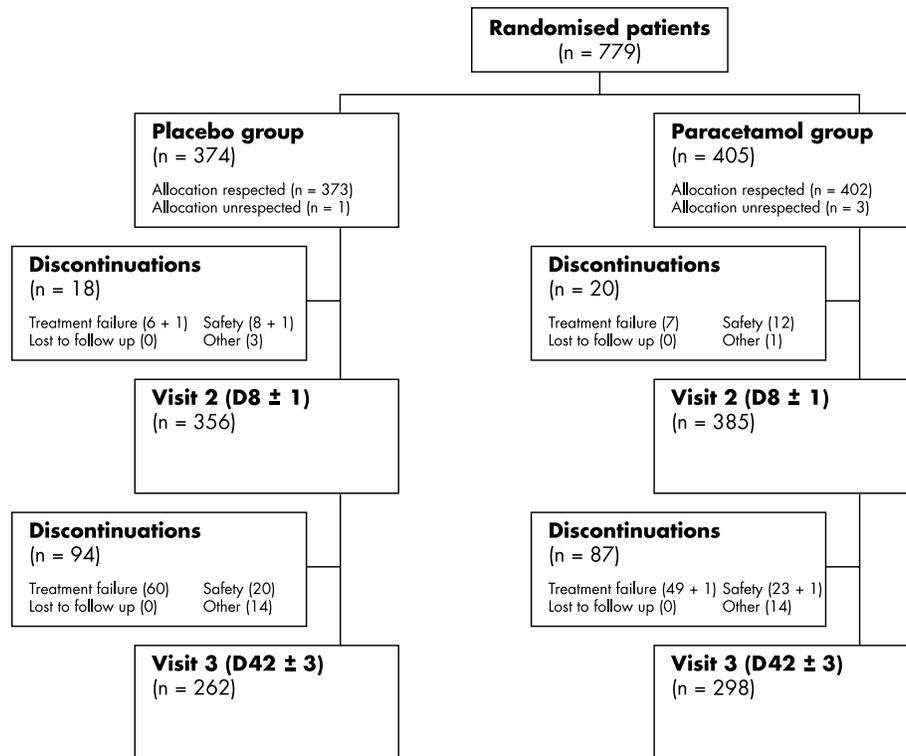
Figure 1 Patients' disposition.

aetiological factors were collected in order to classify OA as primary or secondary, according to the GREES criteria.[9] Assessment of the radiographic severity of OA was by the Kellgren and Lawrence grading scale.[10]

Sample size determination

Sample size calculation was based on the primary end point—that is, the percentage of patients responding to treatment after 6 weeks (30% pain intensity decrease). In the placebo group the estimated percentage of responders was 30–40%; in the paracetamol group the expected percentage was 50–60%. At a two sided α level of 5%, to achieve 80% power, the minimal required sample size was 387 patients in each group. Initially, it was planned to include 450 patients in each group, allowing for a 10–15% loss at follow up. Because the loss of follow up was insignificant, the recruitment was stopped when a total of 779 patients had been enrolled. The sample size required for the primary objective was considered adequate to identify potential predictive factors of response to treatment.

Statistical analysis

Patient disposition and deviations from protocol were studied to determine the analysis populations. Owing to a low rate of major protocol deviations (3.2% and 1.9% in the paracetamol

and placebo groups, respectively), only an intention to treat (ITT) analysis was conducted, using the last observation carried forward procedure (including baseline) to manage missing data from patients withdrawn from study (irrespective of reasons).

The percentage of responders (30% decrease in pain intensity) and binary secondary criteria were analysed using a χ^2 test. Quantitative measures were analysed using analysis of covariance including treatment group as fixed effect and corresponding baseline as covariate.

Predictive factors of response to treatment were identified by various methodologies. Firstly, a logistic regression analysis was conducted to predict the probability of being a responder to treatment. Significance of dependent variables was tested using Wald's test considered at an α level of 10%. Owing to the large number of potential predictive factors, a forward regression method was used to select the dependent variables. This analysis was conducted independently in the two treatment groups to identify factors that were potentially related to a placebo response and by comparison to determine predictive factors that were specific to paracetamol. To explore possible non-linear relationships between predictive factors and response to treatment and to identify cut off points for quantitative baseline characteristics without a priori determination, a decision tree analysis was conducted

Table 2 Changes during the 6 weeks of the study in the three main symptomatic outcome variables by treatment group

Outcome variable	Changes at week 1			Changes at week 6		
	Paracetamol (n = 405)	Placebo (n = 374)	p Values	Paracetamol (n = 405)	Placebo (n = 374)	p Values
Pain VAS (0–100 mm)	16 (21)	15 (21)	0.398	23 (27)	23 (26)	0.660
WOMAC function subscale (0–100)	8 (12)	7 (12)	0.499	12 (17)	12 (16)	0.580
Patient's global assessment (0–100 mm)	14 (21)	12 (22)	0.063	22 (26)	20 (27)	0.229

Results are shown as mean (SD).

Table 3　Predictive factors of response to treatment: results of the logistic regression in the two study groups*

Parameter	Paracetamol (n = 396)			Placebo (n = 365)		
	Odds ratio	95% CI†	p Values‡	Odds ratio	95% CI†	p Values‡
Sudden increase of pain within the 2 weeks before inclusion	1.61	1.04 to 2.49	0.0338	1.65	1.05 to 2.58	0.0297
Morning stiffness (>20 minutes)	1.64	1.05 to 2.54	0.0294	NR		
Pain at night	NR¶			1.59	1.03 to 2.45	0.0370
Kellgren and Lawrence radiological score for MTF§	0.78	0.65 to 0.94	0.0081	NR		
Body mass index (unit = 10 kg/cm²)	1.68	1.10 to 2.56	0.0157	NR		
WOMAC function subscale (unit = 10 points)	0.88	0.76 to 1.02	0.0965	NR		
Patient's global assessment of knee OA (unit = 10 mm)	NR			0.88	0.78 to 0.99	0.0385
Aetiology (primary or secondary OA)	NR			0.51	0.22 to 1.15	0.1022

*Response to treatment was defined as a decrease of at least 30% in pain intensity during the 6 weeks of the study (ITT analysis). Patients included in these analyses are all the patients of the ITT population for whom complete data for the independent variables were available; †95% CI, 95% confidence interval; ‡Wald's test; §MTF, medial tibiofemoral compartment; ¶NR, not relevant.

separately in the two treatment groups. Patient subgroups that were identified through these two methods were studied to assess the treatment effect on the primary criterion (percentage of responders) using a χ^2 test, and the mean changes in pain after 6 weeks using covariance analysis including treatment group (fixed effect) and baseline pain intensity (covariate).

Adverse events (AEs) spontaneously reported by patients or observed by general practitioners were listed, detailing intensity, evolution, and relationship to the study drug. Treatment emergent AEs were coded, before unblinding, using the WHO-ART dictionary, by identifying a preferred term and corresponding system organ. The incidence of treatment emergent AEs was compared between the groups using a χ^2 test or Fisher's exact test when appropriate. Analyses were conducted on preferred terms and system organs.

RESULTS
Patients' baseline characteristics
Seven hundred and seventy nine patients, aged 18 years or more, were included from November 1999 to August 2000 through 200 French sites by general practitioners. None of the patients were lost of follow up. Overall, 583 (75%) of the patients were women, with a mean age of 70 years (range 33–100) (table 1); more than 70% of patients had a body mass index equal to or higher than 25; patients were mainly unemployed (73%), and living in urban areas (93%). No significant differences were seen in the demographic characteristics between both groups.

OA characteristics at baseline were also comparable between both groups. OA of the knee was idiopathic in 94% of cases and associated with another location of the disease in 43% of cases. Fifteen per cent of patients did not demonstrate any signs of "inflammation" (acute flare up) (see table 1 for details). Overall, mean duration of the disease was 46 months. Pain and patient's global assessment of the disease scores measured at inclusion were higher than 65 mm and mean functional index (normalised WOMAC score) was 54. Eighty six per cent of patients did not report any analgesic treatment (NSAIDs or paracetamol) at inclusion (table 1).

Compliance
Seventy two per cent of patients in the paracetamol group and 76% in the placebo group were compliant over the 6 week treatment period.
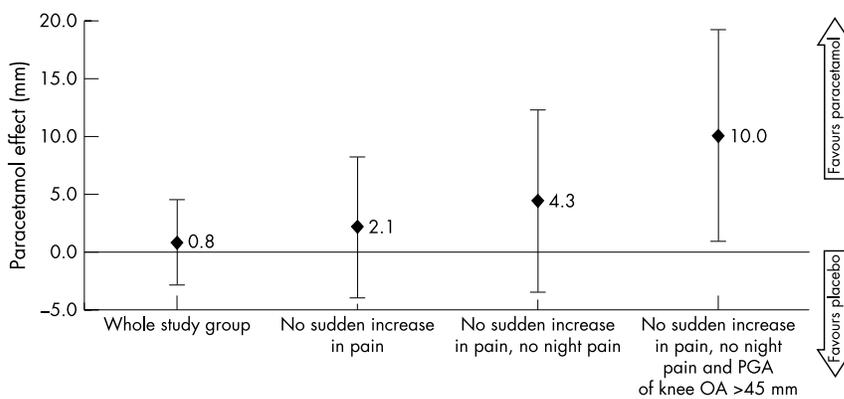

Figure 2　Treatment effect (differences in changes in pain intensity between the two study groups) in different selected subgroups.

	Whole study group		No sudden increase in pain		No sudden increase in pain, no night pain		No sudden increase in pain, no night pain and PGA of knee OA >45 mm	
	n	Mean	n	Mean	n	Mean	n	Mean
Paracetamol	401	23.6	133	19.3	85	20.6	63	25.2
Placebo	373	22.8	134	17.3	74	16.3	60	15.2
Mean effect (95% CI)	0.8 (−2.8 to 4.4) p = 0.660		2.1 (−4.0 to 8.1) p = 0.502		4.3 (−3.5 to 12.1) p = 0.274		10.0 (1.0 to 19.0) p = 0.029	

Withdrawals from the study

Over the 6 week treatment period, a total of 107 (26%) patients in the paracetamol group and 112 (30%) in the placebo group withdrew from the study. Withdrawals due to treatment failure were noted in 14% and 18% in the paracetamol and placebo groups, respectively (fig 1).

Global pain intensity of the knee during physical activities

For the primary criterion, the percentage of responders (30% decrease in global pain intensity) observed in the ITT population (n = 779) was sizeable in both groups (52.6% and 51.9% in paracetamol and placebo groups, respectively) and no significant difference was found (p = 0.840). For the percentage of responders when 20% and 50% decrease in global pain intensity and other derived criteria were considered, non-significant results were also noted (61.4% v 59.9% and 36.8% v 38.0% in the paracetamol v placebo at week 1 and week 6, respectively) (data not shown).

In absolute values, the mean difference from baseline after 6 weeks was 23 mm in both the paracetamol and placebo groups (table 2).

Patient's global assessment of knee OA

Table 2 shows the results for patient's global assessment of knee OA. Mean difference from baseline was 22 mm for the paracetamol group and 20 mm for the placebo group. No significant differences were shown between paracetamol and placebo for these criteria.

Normalised WOMAC for physical function

Table 2 shows the results for the normalised WOMAC OA score at each visit and over the study period (absolute and relative differences from baseline). Mean absolute difference from baseline over the study period was 12 for the paracetamol group and 12 for the placebo group. No significant differences were observed between the groups for any of the criteria derived from the WOMAC OA index for physical function.

OARSI response criteria

Results for the percentage of responders to treatment as determined by using OARSI's combined response criteria showed no statistical significant differences between paracetamol and placebo groups. The percentage of responders at week 6 were 51% v 49% and 51% v 51% in the paracetamol v placebo groups according to OARSI: criteria A and criteria B, respectively.

Predictive factors of response to treatment

The first step of this analysis consisted of a logistic regression conducted separately in the two treatments groups to identify factors that were potentially related to a ''spontaneous''-type response and by comparison to determine predictive factors that were specific to paracetamol (table 3). In the placebo group, odds ratios suggest that the response to treatment was greater when signs of ''inflammation'' (that is, a sudden increase of pain within the 2 weeks before inclusion and presence of night pain) were present at inclusion and lower when the disease was more severe (that is patient's global assessment of knee OA). In the paracetamol group, odds ratios suggest that response to treatment was greater when signs of ''inflammation'' were present at inclusion (that is, a sudden increase of pain within the 2 weeks before inclusion, morning stiffness lasting for more than 20 minutes) and for those with a higher body mass index and lower when the disease was more severe (that is the severity of medial knee OA, defined by the Kellgren and Lawrence score).

As the above analyses showed a relationship between ''inflammation'' and response, further analyses were conducted.

The decision tree analyses were first conducted separately in the two treatment groups. Several factors were identified as explaining differences in response rates. In the placebo group the response to treatment was greater when signs of inflammation (that is, a sudden increase of pain within the 2 weeks before inclusion, presence of night pain) were present at inclusion and if the disease was less severe (that is, the severity of medial knee OA, defined by Kellgren and Lawrence score $\leqslant 2$ and patient's global assessment of knee

Table 4 Safety results—treatment emergent adverse events (TEAEs)

	Paracetamol (n = 405)	Placebo (n = 374)	All (n = 779)	p Values*
Patients with at least 1 TEAE, No (%)	85 (21)	86 (23)	171 (22)	0.499
Patients with at least 1 serious AE, No (%)	5 (1)	3 (1)	8 (1)	
Patients withdrawn for safety reasons, No (%)	36 (9)	29 (8)	65 (8)	
Body system involved†				
Gastrointestinal system disorders, No (%)	46 (11)	42 (11)	88 (11)	0.739
Musculoskeletal system disorders, No (%)	10 (2)	16 (4)	26 (3)	0.104
Respiratory system disorders, No (%)	12 (3)	13 (3)	25 (3)	0.955
Body as a whole—general disorders, No (%)	8 (2)	12 (3)	20 (3)	0.161
Central and peripheral nervous system disorders, No (%)	7 (2)	6 (2)	13 (2)	
Skin and appendages disorders, No (%)	6 (1)	4 (1)	10 (1)	
Total number of reported AEs	142	132	274	
Intensity‡				
Mild	42 (30)	30 (23)	72 (26)	
Moderate	77 (54)	69 (52)	146 (53)	
Severe	18 (13)	31 (23)	49 (18)	
Missing data	5 (4)	2 (2)	7 (3)	
Relationship with study drug‡				
Definite	13 (9)	8 (6)	21 (8)	
Probable	38 (27)	36 (27)	74 (27)	
Possible	28 (20)	23 (17)	51 (19)	
Improbable	63 (44)	65 (49)	128 (47)	

*p Values for χ^2 test; †percentages based on total number of patients; ‡percentages based on total number of reported AEs.

OA score ≤45 mm) (data not shown). Similarly, in the paracetamol group, the response to treatment was greater when at least one sign of inflammation was present at inclusion, and if the disease was less severe (that is, severity of medial knee OA and of the femoropatellar knee OA defined by Kellgren and Lawrence score ≤2 and WOMAC ≤71) (data not shown). These results were very close to those obtained by the multivariate logistic regression models.

Both sets of results suggest that patients presenting signs of "inflammation" or with low severity of OA will probably show an important reduction of pain intensity after treatment, whatever the treatment received. The pain intensity reduction may have been spontaneous, related to the disease "evolution".

Based on these obtained results, we finally performed a decision tree analysis in the subgroup of patients for whom the parameters identified as "spontaneous"-type response (that is, sudden increase in pain, night pain, and patient's global assessment of knee OA ≤45 mm) were absent. Such selection led to 123 "unspontaneous"-type responders. In such a subgroup, the first dependent variable that spontaneously entered the decision tree (that is, which best explained differences in response to treatment) was the treatment group. The calculations showed that 55.6% of patients were responders to treatment in the paracetamol group v 38.3% of responders in the placebo group (χ^2 test, p = 0.056).

To visualise such results we also calculated the treatment effect (defined as the difference in the changes in pain intensity over 6 weeks between the two study groups, in the differently selected subgroup (fig 2)). In the subgroup of patients with no sudden increase in pain, no night pain, and with patient's global assessment of knee OA >45 mm (n = 123), the mean change in pain intensity from baseline was 25.2 mm v 15.2 mm in the paracetamol (n = 63) and placebo (n = 60) groups, respectively—that is, a significant paracetamol effect The mean difference between the groups was 10.0 mm (95% confidence interval 1.0 to 19.0; p = 0.0294).

Safety results

The analysis of clinical AEs was conducted on the whole population of patients (n = 779). No significant difference in the incidence of AEs was found between the two groups. Overall, 274 AEs were reported during the trial (142 in the paracetamol group and 132 in the placebo group). Thirty six patients (9%) withdrew from the treatment for safety reasons in the paracetamol group and 29 (8%) in the placebo group. These frequencies were comparable between groups (1%). Eight serious AEs were reported (three in the placebo group and five in the paracetamol group). None of them were attributable to the treatment (table 4).

DISCUSSION

This study failed to demonstrate a statistically significant symptomatic effect of oral paracetamol 4 g/day over placebo in symptomatic OA of the knee, although the percentage of paracetamol responders was as high as expected (52.6%) before the start of the study. An unusually high percentage of placebo responders was found in patients with OA of the knee (51.9%). Nevertheless, complementary analyses suggested that the symptomatic effect might be observed in a subgroup of patients with chronic mechanical knee pain without signs of inflammation (flare up). Moreover, the excellent tolerance and safety profile of paracetamol, even given at the recommended maximum dose of 4 g/day over a relatively long period of 6 weeks, has been confirmed here.

The failure to demonstrate a symptomatic effect of paracetamol on the whole population of patients evaluated

seems in contradiction with some previously published data in clinical trials. The analgesic effect of oral paracetamol has been clearly demonstrated with single (up to 1 g/intake) or repeated doses (up to 4 g/day) in acute pain, such as headache,[11] post partum,[12] or postoperative pain.[13–16] Studies evaluating paracetamol in OA are limited, often short lasting, and rarely placebo controlled. Two previous placebo controlled trials (one using a crossover design and the other one a parallel group design), have demonstrated the superiority of oral paracetamol 3–4 g/day.[17 18] Another placebo controlled trial using parallel groups' design, failed to demonstrate any superiority of paracetamol v placebo for treating symptomatic OA of the knee.[19] However, more recently, Pincus et al in two different placebo controlled trials, using a crossover design, reported a superiority of paracetamol v placebo in pain and WOMAC scores, in patients with symptomatic OA of the knee, but the results were variable and seemed to be period dependent.[20] Finally, in a recent meta-analysis, Zhang et al clearly demonstrated that paracetamol was effective in relieving pain due to OA (effect size) on pain intensity v placebo was 0.21, 95% CI 0.02 to 0.41).[21] Note that the effect size on pain intensity of NSAIDs v placebo was 0.34, 95% CI 0.14 to 0.54.

Based on results of placebo controlled studies[17 18] and also on comparative studies v NSAIDs,[22 23] emphasising the good efficacy/safety ratio of paracetamol, emerging guidelines issued from scientific societies have recommended paracetamol as first line symptomatic treatment of OA.[1–4 24]

A lack of power of the study does not explain the failure to demonstrate differences between active treatment and placebo, because more than 350 patients in each arm were included to detect a treatment effect of 20%. In line with published data, we have chosen as primary end point a response to treatment defined as an improvement of pain of at least 30%. The percentage of responders in both arms was very high (52.6% of responders in the paracetamol group (expected) v 51.9% in the placebo group (unusual), corresponding to a very small treatment effect (0.7%). This observation is similar to that of a systematic review including 29 clinical OA trials using suitable statistical approaches and evaluating the percentage of patients showing at least 50% of pain relief with different treatments.[25] The therapeutic effect of paracetamol (3 g/day) with or without codeine (180 mg/day) but also that of NSAIDs such as ibuprofen (1200 mg/day or less) or piroxicam (20 mg/day) was close to that of placebo (around 20–40% of responders).

The quality of the study does not seem to explain the failure to demonstrate the symptomatic effect of paracetamol because the study was performed according to good clinical practice, with careful monitoring by a clinical research assistant, and an a posteriori control of the data showed that they were concordant with those expected. Thus, demographic data (sex ratio, age, body mass index) as well as symptomatic severity criteria (pain and functional impairment) at baseline were similar to those seen in other studies.[26–28] Moreover, the level of correlation between data (pain on VAS v functional impairment on a WOMAC scale) corresponded with that reported in previous studies, which were used to elaborate OARSI criteria[29] (data not shown).

During the study, all rescue analgesics were prohibited and patients were asked at each visit to report the intake of such drugs. However, because this was a community based study (outpatients only), one could not exclude the possibility of self treatment with rescue analgesics, which might have had an impact on the results.

It is usual to differentiate between mechanical pain (occurring after physical activities) and "inflammatory" pain (resting pain interfering with sleep in the second part of the night and associated with morning stiffness). In fact, it has

been suggested that paracetamol should be proposed for mechanical pain, whereas NSAIDs should be reserved for ''inflammatory'' flares of the disease. The failure to demonstrate the symptomatic effect of paracetamol in our study may be partly explained by the high proportion of patients with inflammatory pain, because more than 55% of patients had two or more signs or symptoms suggestive of a flare at the entry visit (data not shown).

Moreover, this study did not exclusively include patients with chronic and mechanical knee pain. Numerous studies define chronic pain as pain lasting for at least 6 months (as defined herein) associated with a daily intake of a symptomatic treatment (NSAIDs or paracetamol) within the month before inclusion. The patients are asked to discontinue the symptomatic treatment at screening. Only patients demonstrating pain increase between screening and enrolment (responders to a symptomatic treatment) are effectively included in the study.[27][28] This method named ''flare design'' has been usually applied in recently published studies reporting the symptomatic effect of NSAIDs in OA.[26][30] This approach takes advantage of an exclusion of patients with mild OA symptoms, which would probably disappear in few weeks, with or without treatment. The clinical characteristics of the patients enrolled in this study might explain the failure to demonstrate the symptomatic effect of paracetamol. In fact, up to 85% of the enrolled patients did not receive any symptomatic treatment within the week before inclusion and about 65% of the patients reported a sudden increase of pain within the 2 weeks before inclusion (table 1). Thus, the marked placebo response seen in our study (51.9% of responders at the end of the study in the placebo group v a 30% expected rate) might be explained by an OA ''flare'' (justifying a medical visit and the study enrolment) with a spontaneous improvement within the 6 weeks after inclusion. Such an interpretation is supported by the different analyses conducted in order to assess the predictive factors of therapeutic response. In particular, a significant difference ($p = 0.0294$) was found in the mean changes in pain between the two study groups in favour of paracetamol when such analysis was conducted in the subgroup without signs of inflammation (fig 2).

Moreover, this study has confirmed the excellent tolerability and safety profile of paracetamol when given at a daily dose of 4 g for 6 weeks. There was no increase in AEs related to the study drug as compared with placebo. This is in agreement with the excellent safety record of paracetamol.[21][31–34]

In conclusion, this study conducted in a large number of patients did not confirm the expected symptomatic effect of paracetamol over placebo, at a daily dose of 4 g, on the whole population of outpatients included, suggesting that the use of paracetamol in symptomatic OA of the knee might be further explored. However, complementary analyses suggest that a significant symptomatic effect might be observed in cases of chronic non-inflammatory mechanical knee pain. Further trials are thus necessary to document and confirm this trend.

ACKNOWLEDGEMENTS

. . . .

Authors' affiliations

C Miceli-Richard, M Dougados, Cochin Hospital, AP-HP, René Descartes University, Paris, France

M Le Bars, International Medical Organisation/Europe, Bristol-Myers Squibb-UPSA

N Schmidely, Biostatistics and Data Management Unit, France, Bristol-Myers Squibb-UPSA

REFERENCES

1 **Pendleton A**, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, et al. EULAR recommendations for the management of knee osteoarthritis. Report of a task force of the Standing Committee of Clinical trials and Epidemiological Studies. Ann Rheum Dis 2000;**59**:936–44.

2 **Jordan K**, Arden N, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) Ann Rheum Dis 2003;**62**:1145–55.

3 **Hochberg MC**, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. I. OA of the hip American College of Rheumatology. Arthritis Rheum. 1995;38: 1535–40, II.OA of the knee American College of Rheumatology.Arthritis Rheum, 1995;**38**:1541–6.

4 **ACR**. ACR subcommitttee on osteoarthritis guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;**43**:1905–15.

5 **Eccles M**, Freemantle N, Mason J, for the North of England NSAIDs drug guideline development group. North of England evidence based guideline development project: summary guideline for NSAIDs versus basic analgesic in treating the pain of degenerative arthritis. BMJ 1998;**317**:526–30.

6 **Lequesne M**. Arthrose de la hanche et du genou, critères de diagnostic. Indices de mesure de la douleur, de la fonction et du résultat thérapeutique. In: Peyron JG, L'arthrose, problèmes cliniques et fondamentaux actuels, Paris :Ciba-Geigy, 1985.

7 **Bellamy N**, Buchanan WW, Goldsmith CH, Campbell J, Stitt LWJ. Validation of WOMAC - a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1995;**15**:1833–40.

8 **Dougados M**, Le Claire P, Van Der Heijde D, Bloch D, Bellamy N, Altman R. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative. Osteoarthritis Cartilage 2000;**8**:395–403.

9 **GREES: Osteoarthritis section**. Recommendations for the registration of drugs used in the treatment of osteoarthritis. Ann Rheum Dis 1996;**55**:552–7.

10 **Kellgren JH**, Lawrence JS. Radiologic assessment of osteoarthritis. Ann Rheum Dis 1957;**16**:494–501.

11 **Steiner TJ**, Lange R. Ketoprofen (25 mg) in the symptomatic treatment of episodic tension type headache double-blind placebo-controlled comparison with acetaminophen (1 g). Cephalgia 1998;**18**:38–43.

12 **Skovlund E**, Fyllingen G, Landre H, Nesheim BI. Comparison of post-partum pain treatments using a sequential trial design: II. Naproxen versus acetaminophen. Eur J Clin Pharmacol 1991;**40**:539–42.

13 **Seymour RA**, Kelly PJ, Hawkesford JE. The efficacy of ketoprofen and acetaminophen (in post-operative pain after third molar surgery. Br J Pharmacol 1996;**41**:581–5.

14 **MacQuay HJ**, Poppleton B, Carroll D, Summerfield RJ, Bullingham RE, Moore RA. Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 1986;**39**:89–93.

15 **Skoglund LA**, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen1 g, acetaminophen 2000 mg and the combination of acetaminophen 1 g and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy 1991;**11**:364–9.

16 **Schug SA**, Sidebotham DA, McGuinnety M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesth Analg 1998;**87**:368–72.

17 **Amadio P**, Cummings DM. Evaluation of Acetaminophen in the management of osteoarthritis of the knee. Curr Ther Res 1983;**34**:59–66.

18 **Zoppi M**, Peretti G, Boccard E. Placebo-controlled study of the analgesic efficacy of an effervescent formulation of 500 mg acetaminophen in arthritis of the knee or the hip. Eur J Pain 1996;**16**:42–8.

19 **Case JP**, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis. A randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. Arch Inernt Med 2003;**163**:169–78.

20 **Pincus T**, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;**63**:931–9.

21 **Zhang W**, Jones A, Doherty M. Does paracetamol work for osteoarthritis? A meta-analysis of randomised controlled trials [abstract]. Osteoarthritis Cartilage 2003;**11**(suppl A):S41.

22 **Bradley JD**, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Treatment of knee osteoarthritis: relationship of clinical features of joint inflammation to the response to a nonsteroidal anti-inflammatory drug or pure analgesic. J Rheumatol 1992;**19**:1950–4.

23 **Williams HJ**, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;**36**:1196–206.

24 **American Geriatic Society**. Panel on chronic pain in older persons. The management of chronic pain in older persons. J Am Geriatr Soc 1998;**46**:635–51.

25 http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Chronrev/OARA/ OANSAID.html (accessed 31 May 2004).
26 **Geba GP**, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;**287**:64–71.
27 **Ehrich EW**, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, for the rofecoxib osteoarthritis pilot study group, *et al.* Effect of specific Cox-2 inhibition in osteoarthritis of the knee: a 6-week double-blind, placebo controlled pilot study of rofecoxib. *J Rheumatol* 1999;**26**:2438–47.
28 **Bensen WG**, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999;**74**:1095–105.
29 **Dougados M**, Le Claire P, van der Heijde D, Bloch D, Bellamy N, Altman R. Response criteria for clinical trials on osteoarthritis of knee and hip: a report of the Osteoarthritis research Society International Standing Committee for clinical trials response criteria initiative. *Osteoart Cartilage* 2000;**8**:395–403.
30 **Pincus T**, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, *et al.* A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;**44**:1587–98.
31 **Prescott LF**. Therapeutic misadventure with acetaminophen: fact or fiction. *Am J Ther* 2000;**7**:99–114.
32 **Graham GG**, Graham RI, Day RO. Comparative analgesia, cardiovascular and renal effects of celecoxib, rofecoxib and acetaminophen (paracetamol). *Curr Pharm Des* 2002;**8**:1063–75.
33 **Fored CM**, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, *et al.* Acetaminophen, aspirin and chronic renal failure. *N Engl J Med* 2001;**345**:1801–8.
34 **Singh G**. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. *Am J Ther* 2000;**7**:115–21.