

Patient Preference for Sustained-release versus Standard Paracetamol (Acetaminophen): a Multicentre, Randomized, Open-label, Two-way Crossover Study in Subjects with Knee Osteoarthritis

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Guidelines for osteoarthritis (OA) management recommend paracetamol (acetaminophen) as the most appropriate first-line analgesic for mild to moderate pain. Standard paracetamol requires four times daily dosing. Drug compliance and convenience are inversely related to daily dose frequency. Compliance is a pivotal component of the successful management of OA pain and is influenced by patient preferences or beliefs. The added convenience of three times daily dosing may enhance compliance and, therefore, pain relief. This multicentre, randomized,

open-label, two-way crossover, phase IV study is the first to evaluate patient preference with a sustained-release paracetamol tablet formulation designed for three times daily dosing. Compared with standard paracetamol tablets dosed four times daily, the sustained-release formulation was preferred in a 2:1 ratio, provided better overall joint pain relief, resulted in higher levels of satisfaction in subjects with OA of the knee and has the potential to improve patient compliance and, therefore, pain control.

KEY WORDS: PARACETAMOL; OSTEOARTHRITIS; SUSTAINED-RELEASE; PREFERENCE; CONVENIENCE; SATISFACTION; COMPLIANCE; THREE TIMES DAILY DOSING

Introduction

Osteoarthritis (OA) is a common degenerative joint condition, characterized by loss of articular cartilage, new bone

formation and thickening of the capsule.¹ The clinical consequences of OA are joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable

degrees of local inflammation.¹ The knee is the principal large joint involved in OA, and OA of the knee is a major cause of impaired mobility, particularly among women.¹

In the elderly, OA is a leading cause of pain and disability.² The prevalence of painful, disabling OA of the knee in people > 55 years of age is 10%, of whom one quarter are severely disabled.³ Recent research in the USA suggests that the lifetime risk of symptomatic OA of the knee is close to 50%, being highest among obese persons.⁴ In Australia, 7% of the population has physician-diagnosed OA and 40% use prescription medications to manage their condition.⁵ By 2050, it is predicted that OA will affect 10.7% of Australians; however, if obesity continues to grow at the levels witnessed over the last decade, then OA could affect up to 11.2% of men and 14.5% of women in Australia.⁶

Individuals living with osteoarthritis suffer from increased pain and physical disability. These are the two main factors known to contribute to a reduced quality of life.⁷ OA related disability has a substantial impact on the daily life of the patient both at home and in the workplace.⁸ Furthermore, quality of life is more adversely affected by OA-related pain than by the symptoms of other chronic conditions, such as respiratory and cardiovascular diseases.⁹

Management of OA includes non-pharmacological modalities (e.g. physical therapy, exercise, weight management, orthotics), medication and surgery. Although non-pharmacological interventions provide the cornerstone for the management of OA, relieving pain is a key objective of therapy as it enables patients to regain their mobility. Guidelines for OA management recommend paracetamol (acetaminophen) as the most appropriate first-line analgesic for mild-to-moderate pain.^{10 - 12} Despite reports that

paracetamol may be slightly less efficacious than non-steroidal anti-inflammatory drugs (NSAIDs),¹³ its first-line position remains firm and is further strengthened by its overall safety and suitability for use by most people.^{14,15} Paracetamol, when effective, is the preferred long-term treatment for OA, to which additional treatment modalities, including NSAIDs, can be added if and when necessary.^{2,16}

Compliance refers to the extent to which patients follow advice (e.g. information on taking medications) given to them by healthcare providers. Compliance may be viewed as an obedience-based approach in which the healthcare provider dictates behaviour that the patient is supposed to follow. The term adherence is often preferred as this indicates that treatment goals have been negotiated between the patient and healthcare provider. Persistence is a measure of whether a patient continues to use the prescribed (usually chronic) medication. It follows, therefore, that a patient may be persistent but not adherent or compliant, i.e. a patient may be taking the medication on a continuous basis but not in the way that it should be taken.

In the clinical setting, an individual's acceptance or rejection of prescribed medications is often the single greatest determinant of treatment effectiveness. Adherence is a pivotal component of the successful management of OA pain with paracetamol. Analgesic medications have in the past been associated with variable rates of patient adherence. For example, Pahor *et al.*¹⁷ assessed the use and dosage of analgesic medications in relation to severity of OA pain in 1002 elderly disabled women. Almost half (48.5%) of these women reported that they had severe pain and 78.8% reported the use of analgesic medications. Among those who had severe pain, however,

41.2% were using < 20% of the maximum analgesic dose.

It has been demonstrated that compliance is inversely related to the daily dose frequency.¹⁸ Regular dosing of standard paracetamol is necessary because of its short half-life and it can sometimes be perceived as being ineffective when insufficient doses or irregular dosing schedules are used.^{19,20} It is possible that the inconvenience of needing to take two tablets four times daily for standard paracetamol formulations may contribute to the failure of individuals to take the maximum recommended dose. Altman *et al.*,²¹ drawing on their clinical experience, have recently surmised that OA patients are not always compliant with paracetamol dosed four times daily and it is this under-dosing that may lead to an inadequate therapeutic response. These authors go on to suggest sustained-release paracetamol as a solution to this problem, as it is specifically designed to improve convenience and reduce the number of daily doses required to achieve lasting therapeutic levels of paracetamol.

Patient preferences and/or beliefs influence adherence to chronic treatment.²² Such preferences are shaped by a number of factors, such as demographics, past experiences, attitudes, diagnosis, health status and relationship with their provider.²³ Importantly, patients' treatment preferences evolve over time²³ and may be different from those of their healthcare providers.²⁴ In the case of OA, despite guidelines advocating paracetamol as the first-line pharmacological option, studies of patient preferences usually favour NSAIDs.² This may reflect lack of informed choice regarding safety profiles. Risk of side-effects is one of the primary deciding factors in OA treatment preference; people prefer treatments associated with fewer risks.²⁵

This study compared a sustained-release paracetamol tablet formulation designed to be dosed three times daily with standard paracetamol tablets dosed four times daily in patients with OA, and measured patient preference, efficacy of pain relief, patient satisfaction and safety.

Patients and methods

PATIENT POPULATION

Eligible patients were aged 40 – 80 years, with symptoms and a documented clinical diagnosis of OA in at least one knee and without other co-morbidities that may have affected pain assessments. If OA affected both knees, the symptoms should have been noticeably and consistently worse in one knee than the other. Current knee pain must have occurred daily or on at least half of the days out of the 3 months prior to the screening visit, been suitable for treatment with a simple analgesic, and exacerbated by movement or weight bearing. Knee pain must also have been at least mild (≥ 2.5 cm) in intensity as recorded on a 10 cm visual analogue scale (VAS): 0 cm, no pain; 10 cm, extreme pain.

Patients were excluded if they had a history or current evidence of secondary causes of OA, or if they had any other medical condition that would affect their ability to rate pain, any other illness likely to prevent completion of the study, or any contraindication or intolerance to paracetamol or ibuprofen. Patients who were pregnant, had received an intra-articular corticosteroid injection to the knees within the last 2 weeks, or were taking intra-articular hyaluronan, oral corticosteroids or glucosamine (for ≥ 3 or ≤ 6 months) were also excluded.

This study was conducted at 12 Australian sites between January and June 2008. Ethics approval was provided for each individual

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study site, details of which are included in the Appendix. Patients' written consent was obtained according to the Declaration of Helsinki and the study was conducted under the guidance of Good Clinical Practice.

STUDY DESIGN

This multicentre, randomized, open-label, two-way crossover, phase IV study compared the effect of a sustained-release paracetamol formulation versus standard paracetamol on patient preference and other endpoints in subjects with OA pain affecting the knee. There was a 7-day run-in with standard paracetamol 500 mg tablets (one to two tablets, orally every 4 – 6 h up to four times daily) prior to the start of the study. Patients at each study site were then randomly assigned (according to a computer-generated randomization schedule) to receive either sustained-release or standard paracetamol tablets for 2 weeks and were then switched to the other treatment for another 2 weeks. They were assessed after each treatment period.

All study products were supplied by the Clinical Supply Department, GlaxoSmithKline Australia, Boronia, Australia, and were obtained as commercially marketed packs with a study label applied. The sustained-release paracetamol test product was Panadol

Osteo[®] tablets (paracetamol 665 mg); patients were instructed to take two tablets orally every 6 – 8 h (three times daily dosing). The reference product was Panamax[®] tablets (standard paracetamol 500 mg); patients were instructed to take two tablets orally every 4 – 6 h (four times daily dosing). Patients used each of the two products for 14 days (\pm 2 days) (Fig. 1).

All patients attended an initial screening visit at each study site. After 7 – 14 days they reported back to the site for a run-in visit and, 7 days later, returned to the site again for their baseline visit. Patients then had one assessment visit after 14 (\pm 2) days of treatment with each of the two study drugs. A diary was used by the patients to record study product usage and adverse events. The patients were provided with rescue medication (8 \times 200 mg ibuprofen tablets) at the start of each treatment period.

OUTCOME MEASURES

The primary efficacy endpoint was the proportion of subjects preferring sustained-release versus standard paracetamol tablets for the management of OA pain at the end of the study. Secondary efficacy endpoints included: treatment regimen preference (sustained-release paracetamol three times daily versus standard paracetamol four times daily); convenience (the treatment

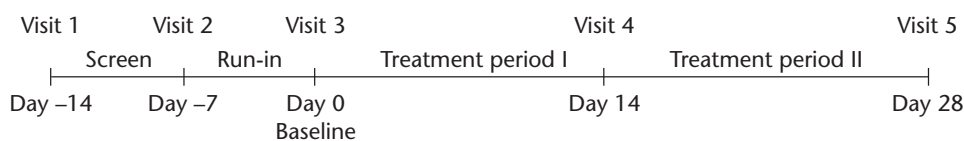


FIGURE 1: Study protocol: this was an open-label, two-way crossover design in which patients with osteoarthritis of the knee were randomized to receive a sustained-release paracetamol tablet formulation three times daily for 14 ± 2 days, followed immediately by standard paracetamol tablets four times daily for 14 ± 2 days, or *vice versa*. There was a 7-day run-in period with standard paracetamol tablets (one to two tablets, orally every 4 – 6 h up to four times daily) prior to the start of the study

routine that would fit more easily into daily life, three times daily versus four times daily); attitude toward convenience (based on the question, "If given the choice, will you use sustained-release paracetamol over standard paracetamol?"); attitude towards compliance (proportion of patients choosing a treatment routine that would be easier to comply with if it needed to be taken regularly: sustained-release paracetamol three times daily, standard paracetamol four times daily, or no difference); patient global assessment of response to treatment (PGART) at the end of treatment with each of the products; satisfaction after treatment with each product; measures of pain control at the end of the study treatment with each product (overall knee pain, knee pain on waking, knee pain at rest, knee pain when walking on flat); and impact on sleep quality (knee pain interfered with sleep at night and number of times woken during night due to knee pain after treatment with each product). Patients assessed how much their knee joint pain had interfered with their sleep at night using a 10 cm VAS: 0 cm, no effect (slept well); 10 cm, completely interrupted (unable to sleep).

A verbal rating score (VRS) was used to assess patient satisfaction with each treatment and PGART (0, none; 1, poor; 2, fair; 3, good; 4, excellent). Pain assessments were made on a 10-cm VAS (0 cm, no pain; 10 cm, extreme pain). Assessment of safety was based on the number of adverse events reported by all patients following dosing with the study medications. The safety population included all randomized subjects in the study independent of whether or not they were included in the efficacy analysis.

STATISTICAL ANALYSES

Sample size calculations were based on the primary endpoint. A minimum of 200

patients were required in order to achieve an 80% power of detecting a preference ratio between treatments of 60% versus 40% at the 5% level of significance. To allow for patient withdrawals and for those patients who expressed 'no preference', approximately 260 patients were to be screened in the run-in period.

Analyses were performed on the intent-to-treat (ITT) population, which was defined as all those patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. The primary endpoint was analysed using a binomial approach and a hypothetical value (value under H_0) $P = 0.6$ for the proportion of subjects preferring the sustained-release formulation, in order to detect a preference ratio of 2:1 (sustained-release:standard paracetamol). For other preference endpoints, i.e. treatment regimen preference, convenience, attitude toward convenience and attitude toward compliance, the default hypothetical value of $P = 0.5$ was used to test if the proportion of patients preferring sustained-release paracetamol was higher than that of standard paracetamol. Analyses were performed using Proc Freq in SAS version 8.2 2007 (SAS Institute Inc., Cary, NC, USA), based on the binomial approach specified by the hypothetical values. All analyses of preference results are based on those patients who participated in both treatment periods and, therefore, were able to provide preference data. VRS scores for PGART and satisfaction, and VAS joint pain relief scores were analysed based on a mixed model approach using analysis of covariance with fixed effects for baseline and treatment, and random effects for site, sequence and patient. These analyses were performed using Proc Mixed in SAS version 8.2 2007. The number of night-time disturbances due to knee pain were

summarized by treatment, using Proc Freq in SAS version 8.2 2007. A χ^2 test was used to test differences between groups across treatments. Compliance was estimated by the ratio of the number of tablets taken over the total number of tablets that could have been taken. A χ^2 test was also used to compare compliant and non-compliant groups between the two treatments.

Results

PATIENTS

In total, 250 patients were screened, of whom 210 met the clinical inclusion criteria and were randomized to treatment; five patients did not receive the allocated intervention (Fig. 2). The ITT population, therefore, comprised 205 patients. Of the 210 randomized patients, 91 (43.3%) were male, 203 (96.7%) were Caucasian and the mean \pm SD age was 61.7 ± 8.68 years (Table 1). At baseline, joint (knee) pain intensity was moderate (mean VAS score \pm SD, 5.2 ± 1.8 cm).

TABLE 1:
Demographic and baseline characteristics of the osteoarthritis patients randomized for the study

Characteristic	Randomized patients (<i>n</i> = 210)
Gender, <i>n</i> (%)	
Male	91 (43.3)
Female	119 (56.7)
Age (years), mean \pm SD	61.7 (8.68)
Race, <i>n</i> (%)	
Asian	3 (1.4)
Black	1 (0.5)
Caucasian	203 (96.7)
Hispanic	0 (0.0)
Other	3 (1.4)
Joint pain (VAS), mean \pm SD	5.2 \pm 1.8

VAS, visual analogue score.

EFFICACY

Preference, convenience and compliance

Results of efficacy analyses for preference endpoints are presented in Table 2. Only 199 of the patients in the ITT population

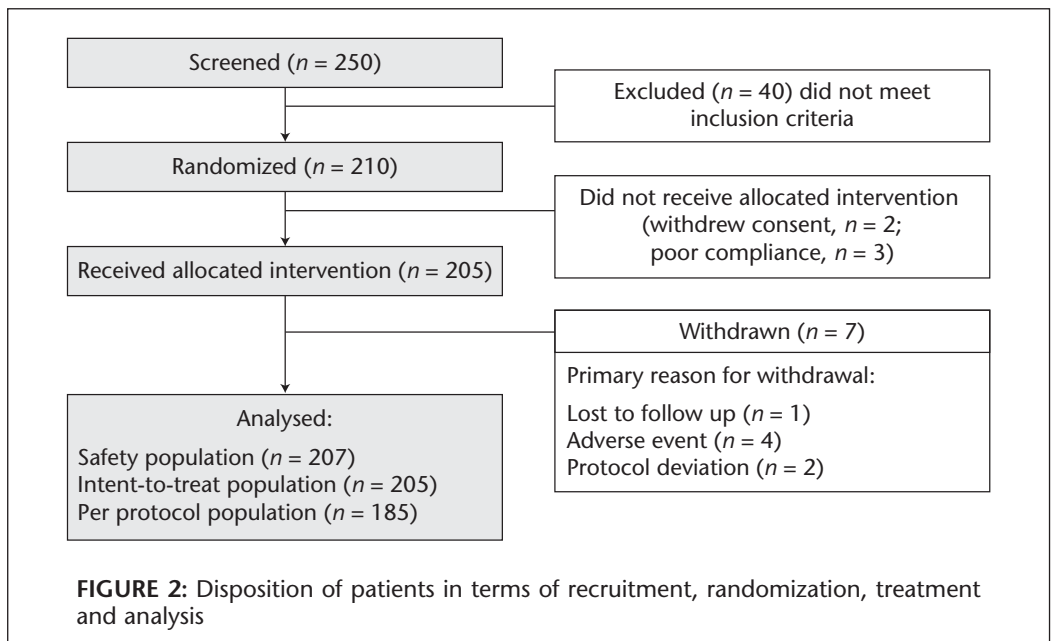


TABLE 2: Preference endpoint comparisons between the sustained-release paracetamol and standard paracetamol ($n = 199$)^a

Endpoint	Paracetamol preference			95% CI	Statistical significance
	Sustained-release, $\times 3$ daily n (%)	Standard, $\times 4$ daily n (%)	No preference, n (%)		
Treatment preference	114 (57.3)	54 (27.1)	31 (15.6)	0.6080, 0.7492 ^b	$P = 0.0188$
Treatment regimen preference $\times 3$ daily vs $\times 4$ daily	151 (75.9)	34 (17.1)	14 (7.0)	0.7604, 0.8720 ^c	$P < 0.0001$
Attitude toward convenience "If given the choice, will you use sustained-release over standard paracetamol?"	137 (69)	62 (31)	0	0.6241, 0.7528 ^c	$P < 0.0001$
Convenience Treatment routine that would fit easier into daily life	164 (82)	10 (6)	25 (12)	0.7712, 0.8770 ^c	$P < 0.0001$
Attitude toward compliance Treatment routine that would be easier to comply with if to be taken regularly	157 (79)	18 (9)	24 (12)	0.7322, 0.8456 ^c	$P < 0.0001$
Compliance No. of tablets taken/total number of tablets	> 99%	> 99%	–	–	NS

^aOnly 199 of the patients in the intent-to-treat population answered the preference questions and, therefore, are included in these analyses.
^b95% confidence interval (CI) testing proportion of sustained-release paracetamol $P = 0.6$ based on the proportion of patients who expressed a preference.
^c95% CI testing proportion of sustained-release paracetamol $P = 0.5$.
 NS, not statistically significant ($P > 0.05$).

answered the preference questions and, therefore, could be used in these analyses. Of those patients who expressed a preference ($n = 168$), significantly more preferred sustained-release paracetamol over standard paracetamol at a ratio $> 2:1$ (114/168 [68%] versus 54/168 [32%]; $P = 0.0188$; Table 2). A ratio in favour of sustained-release paracetamol was also observed for all other preference endpoints. When patients were asked which treatment regimen they preferred, the proportion preferring sustained-release paracetamol three times daily was significantly higher than the proportion who stated a preference for standard paracetamol four times daily ($P < 0.0001$; Table 2). When patients were asked, "If given the choice, will you use sustained-release paracetamol over standard paracetamol?", a significantly higher proportion answered "Yes" compared with those who answered "No", showing a significantly better attitude toward convenience for sustained-release paracetamol three times daily over standard paracetamol four times daily ($P < 0.0001$; Table 2). To determine the impact of dosing regimen on convenience, patients were asked to specify which treatment routine (three times daily versus four times daily) would fit more easily into their daily life. Significantly more patients (164/199, 82%) chose the three times daily routine than the 10/199 (5%) who chose the four times daily routine ($P < 0.001$) and 25/199 (13%) stated no preference. A similar result was found for the treatment routine that would be easier to comply with if it needed to be taken regularly: significantly more patients chose sustained-release paracetamol three times daily (157/199, 79%) than standard paracetamol four times daily (18/199; 9%) ($P < 0.001$), while 24/199 (12%) stated "no difference". Compliance based on

assessment of tablet counts at the end of each treatment period was high ($> 99\%$) for both treatment regimens (Table 2).

Pain assessments

A summary of results and analyses for the VAS endpoints is presented in Table 3. Improvements in overall knee joint pain and pain on waking up were statistically significantly better for sustained-release compared with standard paracetamol. At the end of the treatment with sustained-release paracetamol, overall joint pain was 12% less than at the end of treatment with standard paracetamol ($P = 0.0019$, Table 3). The most substantial contributor to superior pain relief with sustained-release paracetamol was pain on waking up; VAS scores were 14% less after taking sustained-release paracetamol than after taking standard paracetamol ($P = 0.0126$, Table 3). Assessments of pain at rest and pain on walking on the flat were not significantly different between the two treatments, although VAS scores were numerically lower after taking sustained-release paracetamol compared with standard paracetamol (Table 3). Compared with the level of pain at baseline, both sustained-release paracetamol and standard paracetamol were significantly efficacious in reducing pain when walking on the flat and at rest (Table 4); pain at the end of treatment with sustained-release paracetamol was reduced by 34% and 59%, respectively, and with standard paracetamol by 30% and 54%, respectively ($P < 0.001$).

PGART and satisfaction scores

The sustained-release paracetamol formulation was significantly superior to standard paracetamol for both PGART and satisfaction scores at the end of each treatment period ($P = 0.0116$ and $P = 0.0003$, respectively; Table 5). For PGART the VRS

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TABLE 3:

Comparison of the effect of sustained-release paracetamol and standard paracetamol on pain reduction at the end of each treatment period

Knee joint pain ^a	Mean VAS score			Statistical significance
	Sustained-release paracetamol ^b	Standard paracetamol ^c	Difference ^d (95% CI)	
Overall	3.56	4.05	-0.5 (-0.81, -0.19)	<i>P</i> = 0.0019
Interference with sleep	2.18	2.46	-0.3 (-0.67, 0.06)	NS
On waking up	3.00	3.47	-0.48 (-0.85, -0.09)	<i>P</i> = 0.0126
Walking on the flat	3.45	3.68	-0.23 (-0.55, 0.1)	NS
At rest	2.13	2.39	-0.27 (-0.57, 0.04)	NS

^aAssessments made at the end of each treatment period of 14 ± 2 days using a 10-cm visual analogue scale (VAS) of 0 cm, no pain; 10 cm, extreme pain.

^b*n* = 199 for assessment of pain reduction in 'overall' knee joint pain and 'interference with sleep' and *n* = 200 for assessment of pain reduction 'on waking up', 'walking on the flat' and 'at rest'.

^c*n* = 195 for assessment of pain reduction in 'overall' knee joint pain and 'interference with sleep' and *n* = 197 for assessment of pain reduction 'on waking up', 'walking on the flat' and 'at rest'.

^dDifference between adjusted least squares means (sustained-release paracetamol minus standard paracetamol). NS, not statistically significant (*P* > 0.05).

TABLE 4:

Effect of sustained-release paracetamol and standard paracetamol versus baseline on pain reduction at the end of each treatment period (*n* = 200)

Knee joint pain ^a	Sustained-release paracetamol		Standard paracetamol	
	Mean VAS difference ^b (95% CI)	Statistical significance	Mean VAS difference ^b (95% CI)	Statistical significance
Walking on the flat	-1.78 (-2.12, -1.40)	<i>P</i> < 0.0001	-1.54 (-1.89, -1.19)	<i>P</i> < 0.0001
At rest	-3.10 (-3.42, -2.80)	<i>P</i> < 0.0001	-2.84 (-3.17, -2.51)	<i>P</i> < 0.0001

^aAssessments made at the end of each treatment period of 14 ± 2 days using a 10-cm visual analogue scale (VAS) of 0 cm, no pain; 10 cm, extreme pain.

^bMean of differences across patients between active treatment and baseline.

TABLE 5:

Comparison of the effect of sustained-release paracetamol (*n* = 203) and standard paracetamol (*n* = 200) on patient global assessment of response to treatment (PGART) and satisfaction at the end of each treatment period

End point ^a	Mean VRS			Statistical significance
	Sustained-release paracetamol	Standard paracetamol	Difference ^b (95% CI)	
PGART	2.50	2.29	0.21 (0.05, 0.39)	<i>P</i> = 0.0116
Satisfaction	2.60	2.26	0.34 (0.16, 0.53)	<i>P</i> = 0.0003

^aPGART and satisfaction were measured using a verbal rating score (VRS): 0, none; 1, poor; 2, fair; 3, good; 4, excellent.

^bDifference between adjusted least squares means (sustained-release minus standard paracetamol).

measure was 0.21 greater for sustained-release paracetamol than for standard paracetamol, a 10% improvement. Similarly, there was a 15% improvement in the satisfaction score for sustained-release paracetamol versus standard paracetamol.

Sleep quality

The specific effects of three and four times daily dosing on sleep quality were assessed by measuring the extent to which knee joint pain interfered with sleep and the number of times each patient was woken during the night because of knee joint pain at the end of each treatment period. Mean VAS scores for pain interference with sleep were lower for sustained-release paracetamol compared with standard paracetamol (Table 3). Although there was no significant difference between treatments with respect to the number of sleep disturbances due to pain, the number of patients without night-time disturbance was higher for sustained-release paracetamol compared with standard paracetamol (Table 6).

SAFETY

There were no significant differences between the treatments in the percentage of patients who reported adverse events. Twenty-three adverse events were reported by 14 (6.9%) patients during treatment with sustained-release paracetamol and 39 adverse events were reported in 25 patients (12.3%) during treatment with standard

paracetamol. The most frequently reported types of adverse event are categorized in Table 7. None of the adverse events reported was related to sustained-release paracetamol treatment and four were related to standard paracetamol treatment: three gastrointestinal disorders and one general disorder. All treatment-related adverse events were mild or moderate in intensity. No serious adverse events were reported.

Discussion

This study showed that, compared with standard paracetamol dosed four times daily, sustained-release paracetamol dosed three times daily was preferred in a > 2:1 ratio, provided better overall joint pain relief and resulted in higher levels of satisfaction in patients with knee OA.

Previous studies have established the efficacy and safety of sustained-release paracetamol in managing OA pain. For example, a 12-week, multicentre, randomized, double-blind, parallel-group, placebo-controlled study established that sustained-release paracetamol (1300 mg) given three times daily for the treatment of moderate to moderately severe OA of the hip or knee was significantly superior to placebo.²¹ A small ($n = 30$) 4-week, open-label study has also been conducted in Malaysia to assess the efficacy and tolerability of sustained-release paracetamol in patients with mild to moderate pain associated with knee OA.²⁶ Patients received

TABLE 6: Comparison of the effect of sustained-release paracetamol and standard paracetamol on night-time disturbances due to knee pain

No. of night-time disturbances	Sustained-release paracetamol <i>n</i> (%)	Standard paracetamol <i>n</i> (%)
None	97/185 (52.4)	86/184 (46.7)
One or more	88/185 (47.6)	98/184 (53.3)

TABLE 7:
Comparison of treatment-emergent adverse events reported by patients following administration of sustained-release paracetamol or standard paracetamol for 14 ± 2 days^a

Treatment-emergent adverse event	Sustained-release paracetamol (n = 203)	Standard paracetamol (n = 203)	Overall (n = 207) ^a
Any treatment-emergent adverse event	23	39	62
Any serious treatment-emergent adverse event	0	0	0
Musculoskeletal and connective tissue disorders	14	22	36
Nervous system disorders	3	4	7
Gastrointestinal disorders	1	3	4
Infections and infestations	2	2	4
General disorders ^b	0	3	3
Skin disorders	1	2	3
Ear disorders	1	0	1
Respiratory disorders	1	0	1
Injury, poisoning and procedural complications	0	3	3

^aThe 'overall' safety analysis included four patients in whom non-treatment-emergent adverse events were observed during the run-in period of the study, prior to treatment; accordingly no data are recorded for these four patients because this table only shows treatment-emergent adverse events.

^bGeneral disorders and administration site conditions, including chest pain, ill-defined disorders and influenza-like symptoms.

sustained-release paracetamol three times daily and were also taught knee exercises. Overall there was a statistically significant improvement in all parameters of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at week 4 versus baseline, with mean reduction in aggregate WOMAC scores of 98, 29 and 420 for pain, stiffness and performing activities, respectively. In an individual medication effectiveness test (*n*-of-1 trial), aggregate results showed that most (33/41, 80%) of the subjects had a similar response in terms of overall symptom relief to both celecoxib and sustained-release paracetamol.²⁷

Subject preference studies provide a global evaluation of the clinical profile of a product including efficacy (e.g. onset and duration of action), tolerability, ease of use and impact on daily life. Such studies complement traditional clinical safety and efficacy studies, and can provide evidence that a particular product is more aligned to patient

needs. For the present preference study, a crossover design was selected as appropriate; it offers the advantage that each subject provides information for both treatment arms, allowing within subject comparisons of treatment. Patients received standard paracetamol during the 7-day run-in period and this ensured that only patients who could manage their pain with paracetamol were allowed to continue to the randomized part of the study. There was no washout between the two treatment arms as both were provided with similar daily doses of paracetamol (approximately 4 g/day). The study design was restricted to 2 weeks for each treatment arm to ensure optimal recall of treatment effects by the patients at the end of each treatment period.

It has previously been suggested that the added convenience of three times daily dosing may enhance compliance with paracetamol and, therefore, pain relief, especially for chronic pain conditions or those that require

repeated doses of analgesics.^{21,28} The present study demonstrated, for the first time, the benefits that can be derived from three times daily sustained-release paracetamol dosing. Not only did significantly more patients prefer it, they felt it would be easier to comply with if they had to take the product on a regular basis and that it would be easier to fit into their daily routine. Patients' global assessment of response to treatment and satisfaction with treatment both significantly favoured sustained-release over standard paracetamol.

Patients' attitude towards compliance in the present study significantly favoured sustained-release paracetamol. While the short treatment duration may have aided collection of the primary endpoint data, it may, however, have limited the true assessment of compliance (based on pill counts), accounting for the very high compliance rates observed in both treatment arms of the study. Such high rates of adherence are not unexpected in clinical trials; for example, a 12-month trial of standard paracetamol with a four times daily dosing regimen amongst patients with OA had a median dose adherence of 95.5% – 98.6% during the study.²⁹ Equally high rates of adherence in both treatment arms do not, however, explain the significant differences in favour of sustained-release paracetamol that were observed in the present study in terms of overall knee joint pain and pain when waking up. Given that both treatment regimens provided a total paracetamol dose of approximately 4 g/day, no significant differences were expected in terms of the analgesic effects of the two products. The observed efficacy differences may, therefore, be related to differences in the pharmacokinetic profiles of the two products. In a steady-state pharmacokinetic study with sustained-release paracetamol (1330 mg three times daily), mean plasma paracetamol

concentrations (C_{mean}) remained consistently above the estimated minimum effective therapeutic concentration (3 – 5 µg/ml) throughout the 24-h evaluation period.³⁰ Compared with standard paracetamol (2 × 500 mg tablets four times daily), sustained-release paracetamol provided a lower mean maximum plasma concentration (C_{max} 10.71 versus 14.08 g/ml respectively, $P < 0.001$), a slightly higher mean minimum plasma concentration (C_{min} 3.74 versus 3.66 µg/ml, respectively) and a lower mean fluctuation index ($(C_{\text{max}} - C_{\text{min}})/C_{\text{mean}}$) (0.957 versus 1.388, respectively, $P < 0.001$).³⁰ The steadier plasma paracetamol concentrations achievable with the sustained-release formulation, mean that it may be particularly appropriate for patients who require repeat doses. Furthermore, since these pharmacokinetic data show that the steady-state conditions were achieved within 24 h, it can be inferred that maximum therapeutic efficacy from sustained-release paracetamol is likely to develop within this time-frame. Despite the daily doses of sustained-release paracetamol and standard paracetamol being almost the same (3.99 vs 4.00 g, respectively), breakthrough pain may occur with standard paracetamol given four times daily. Thus, as has previously been observed in other studies with sustained-release paracetamol,^{28,31} it is possible that the improved control of overall knee joint pain and pain on waking up observed with the sustained-release paracetamol in the present study was related to a more consistent therapeutic plasma paracetamol concentration.

There were several limitations to the present study. An open-label design was used due to differences in the dosing regimens. The aim was to observe patient preferences between three and four times daily dosing, hence a double-dummy design would not have been practicable. The assessments used to assess

sleep quality may not have been optimal. They included two questions on sleep (VAS rating of how much pain had interfered with sleep and number of times woken at night due to pain). Whilst this is usual practice in studies of OA patients, the use of other assessment tools such as the Epworth Sleepiness Scale and a sleep quality questionnaire (number of hours of sleep, overall quality of sleep) or all-night polysomnography (for objective measurement), as have been used by Rosenthal *et al.*,³² may have provided more specific insights into the impact of three versus four times daily dosing on sleep quality.

Bannwarth² previously compiled a narrative review of preference data amongst OA patients, reporting that 40% find paracetamol four times daily better than or equally satisfactory to NSAIDs. The studies from which these preference data were derived compared various NSAID dosing regimens with paracetamol dosed four times daily.^{33–36} The present study, however, is the first to evaluate patient preference with a sustained-release paracetamol formulation designed for three times daily dosing. The OA patients studied preferred sustained-release paracetamol dosed three times daily, over that of standard paracetamol dosed four times daily, and the three times daily formulation provided higher patient satisfaction and improvements in the control of overall knee joint pain and pain on waking up. Patients specified that the three times daily dosing would enhance compliance and convenience if they had to take it regularly. Paracetamol is the first-line pharmacological treatment of choice in mild-to-moderate OA, hence optimizing long-term patient compliance and improving pain control through the use of sustained-release paracetamol has the potential to reduce the number of OA patients who may progress to second-line

therapies that have a less favourable benefit/risk profile.

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Conflicts of interest

Dr Michael Benson is an employee of Captain Stirling Medical Centre. Captain Stirling Medical Centre was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare, USA, in respect of the work undertaken in this research. Dr Andrew Marangou is the Director of Swan Valley Primary Care and Research Centre. He was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare, USA, in respect of the work undertaken in this research. Dr Marc A. Russo is the Director of Hunter Clinical Research. He was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare, USA, in respect of the work undertaken in this research. Mr John Durocher is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position within the company is Project Manager Clinical Operations. Dr Argon Collaku is a biostatistician and is an employee of GlaxoSmithKline Consumer Healthcare, USA. Dr Yan-Yan Starkey is an employee of GlaxoSmithKline Consumer Healthcare, USA. Her current position within the company is Medical Director.

Appendix

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Ethics approval for this study was provided by the following institutions: Bellberry Human Research Ethics Committee (Drs Benson, Cooke, DeLooze, Karrasch, Marangou, Nixon, Proudman and Russo), The Medical Research Ethics Committee of the University of Queensland (Dr McKeirnan), The Prince Charles Hospital Human Research Ethics Committee (Dr Crawford), Uniting Care Health Human Research Ethics Committee (Dr Todhunter) and Princess Alexandra Hospital Human Research Ethics Committee (Dr Vecchio).

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