Paracetamol for the Management of Pain in Inflammatory Arthritis: A Systematic Literature Review

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ABSTRACT. ***Objective***. To systematically review the literature on the efficacy and safety of paracetamol (acetaminophen) in the management of pain in inflammatory arthritis.

Methods. A systematic search was performed in Medline, Embase, the Cochrane Library, and 2008/2009 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conference abstracts for clinical trials and observational studies of paracetamol in patients with inflammatory arthritis. Included trials were appraised for risk of bias, and relevant study details were abstracted. Efficacy was assessed from clinical trials using improvement in pain as the outcome measure, and safety was assessed using total adverse events and withdrawals due to adverse events as outcome measures. Safety data from observational studies were assessed separately.

Results. Eleven articles containing 12 clinical trials and 1 observational study were identified, all in patients with rheumatoid arthritis. The trials were of short duration, used atypical doses of paracetamol, and all had a high risk of bias. Overall, there was weak evidence of a benefit of paracetamol over placebo and an additive benefit of paracetamol in combination with nonsteroidal antiinflammatory drugs (NSAID). The benefit of paracetamol to NSAID alone was uncertain. No significant differences in safety were seen in the limited clinical trial data. One cohort study showed an increased rate of serious gastrointestinal events with paracetamol over NSAID when used concurrently with corticosteroids and other analgesics, but had significant methodological limitations.

Conclusion. There is weak evidence for the efficacy of paracetamol in patients with inflammatory arthritis, and insufficient disease-specific safety data to draw conclusions. (J Rheumatol Suppl. 2012 Sept;90:11–16; doi:10.3899/jrheum.120336)

Key Indexing Terms:
SYSTEMATIC REVIEW
RHEUMATOID ARTHRITIS
PARACETAMOL
INFLAMMATORY ARTHRITIS

This report is part of the 3e (Evidence, Expertise, Exchange) Initiative on pain management by pharmacotherapy in inflammatory arthritis[1]. Our objective was to systematically review the available literature concerning one of 10 questions selected as an evidence base for generating recommendations: What is the effectiveness, safety, and role of paracetamol (acetaminophen) in pain management in patients with inflammatory arthritis (i.e., interval, formulation, and route)?

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Dr. Bombardier holds a Pfizer Chair and Canada Research Chair in Knowledge Transfer for Musculoskeletal Care. Dr. Hazlewood is supported by a UCB/Canadian Rheumatology Association (CRA)/The Arthritis Society (TAS) Post-Graduate Rheumatology Fellowship, and an Alberta Innovates Health Solutions Clinical Fellowship.

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METHODS

Rephrasing the research question. The clinical question formed by the expert panel was first translated into epidemiologic terms, using the PICO (Population, Intervention, Comparator, Outcome) format[2]. The population was any adult (age ≥ 18 yrs) with inflammatory arthritis, which included patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and spondyloarthritis (SpA). The intervention was paracetamol and the comparator was placebo or any other analgesic, alone or in combination. For the efficacy analysis, the outcome was improvement in pain, and trials were limited to systematic literature reviews (SLR), randomized controlled trials (RCT), and controlled clinical trials. Safety data were derived from the clinical trials using total adverse events and withdrawals due to adverse events as the outcome measures. For the safety analysis we also included cohort studies, case-control studies, and case series (n > 30).

Systematic literature search. A systematic database search was performed to May 2010 in Medline (1950-), Embase (1980-), and the Cochrane Library using comprehensive keyword and major subject headings for inflammatory arthritis (including RA, PsA, AS, and SpA) and paracetamol. The search strategy was developed in collaboration with an experienced librarian (for a detailed search strategy see the online Appendix: www.3epain.com). Hand searches were performed of conference abstracts from the 2008 and 2009 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conferences and of the reference lists from retrieved articles.

Selection of articles. One reviewer (GH) screened the articles for inclusion, first by title and abstract and then by review of full text. Studies were included if they met inclusion criteria, as defined by the PICO terms, above. We excluded studies published with no English abstract and written in languages other than English, Dutch, German, French, and Portuguese (translation from these languages to English was available if required). Studies with a mixed population of patients were included only if data on the inflammatory arthritis population could be extracted separately.

Data extraction and quality appraisal. One reviewer (GH) graded the quality of the studies and abstracted relevant study details. Study quality of the clinical trials identified was graded according to the Cochrane Collaboration's tool for assessing risk of bias[3]. Studies were grouped according to the comparator used. A metaanalysis of clinical trials was planned if the articles identified through the search allowed for meaningful pooling of results. Safety data from the observational studies identified were analyzed separately.

RESULTS

A total of 2351 abstracts were identified from the available databases (Figure 1). After title/abstract screening, 60 articles remained, of which 12 were included after full-text review. One additional article, which had not been indexed properly, was identified through a hand search of the references from the retrieved articles, for a total of 13 articles. No articles were identified through the ACR/EULAR conference abstracts.

Summary of included studies. We identified 1 SLR[4], 11 articles containing 12 clinical trials[5,6,7,8,9,10,11,12,13,14,15], and 1 cohort study[16] (Table 1). All the articles described patients with RA. Eight studies were in patients with active RA[5,6,7,8,10,11,12,13]; the remaining 4 studies provided no details on baseline disease activity[9,14,15,16]. The SLR evaluated RCT of paracetamol versus nonsteroidal antiinflammatory drugs (NSAID) for pain management in RA, a more narrow focus than our evaluation[2]. There were also some differences in the selection of studies; we did not limit trial duration, thus we included 2 studies that they excluded[7,8], and they did not limit outcomes to pain; thus they included one trial that we excluded[17].

The clinical trials identified compared paracetamol to placebo, NSAID, or weak opioids; 2 compared paracetamol + NSAID to placebo + NSAID. Several studies included multiple arms using different comparators and were therefore included in the analysis for more than 1 comparator group. Eight articles, with a total of 9 separate trials, included pain as an outcome measure and were included in the efficacy analysis[7,8,9,10,12,13,14,15]. Three articles included safety data but did not include pain as an outcome measure and were therefore included only in the safety analysis[5,6,11]. Two trials were parallel-group design[10,11] and the remaining were crossover. The included studies were older (1959–1993), had small sample sizes (range 12–143), short trial duration (range 6 h–13 wks), and often used atypical doses of paracetamol (range 650 mg/day–7.5 g/day).

Quality appraisal. All trials had a high risk of bias. Common reasons for the high risk of bias were incomplete reporting of details surrounding sequence generation, allocation concealment, and blinding; incomplete outcome data with high dropout rates and lack of intention-to-treat analysis; crossover trial design; and termination of trial through sequential analysis. For full details of the risk of bias assessment, see the online Appendix, available from www.3epain.com.

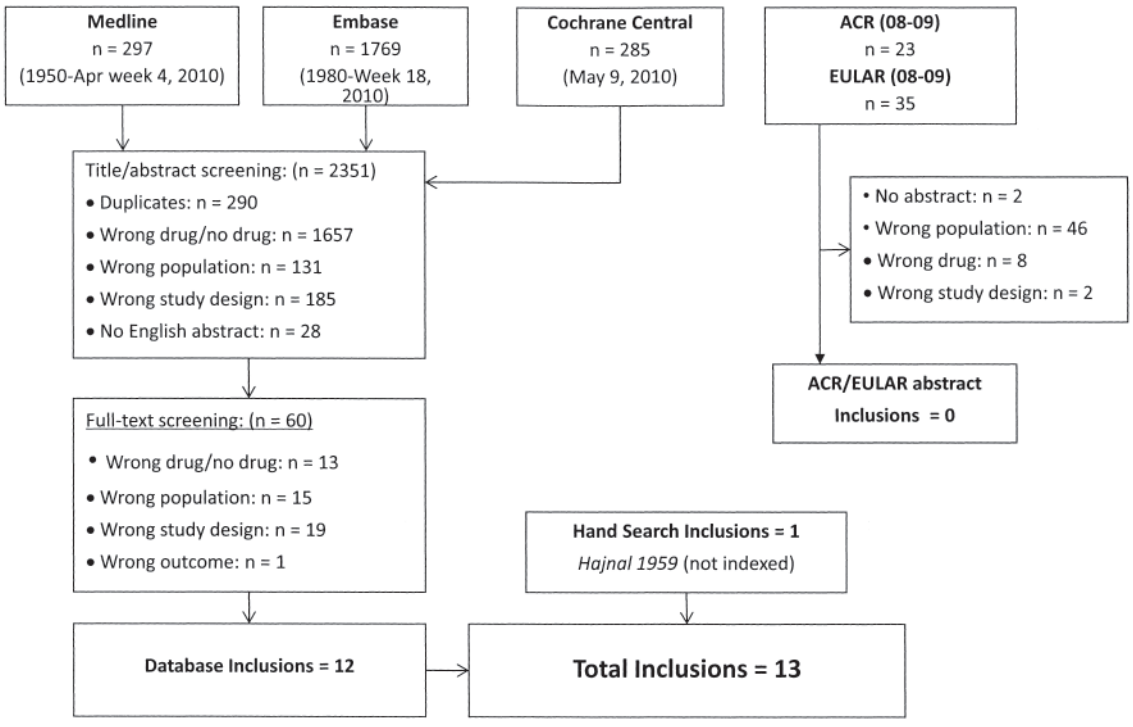

Figure 1. Literature search from which 61 articles were selected for detailed review. Thirteen articles met inclusion criteria.

Table 1. Characteristics of included trials.

Study	Trial Design	n	Duration, Each Drug	Paracetamol Dose, g/day	Comparator(s), dose/day
Hajnal, 1959[7]	CO	75	7 days	7.5 g	ASA 5 g
Lee, 1975[10]	Par	143	14 days	4 g	ASA 3.9 g, indomethacin 100 mg
Solomon, 1974[14]	CO	35	7 days	6 g	Diclofenac 150 mg
Solomon, 1977[15]	CO	35	7 days	6 g	Bumadizone 660 mg
Hardin, 1979[8]	CO	30	6 h	650 mg	ASA 650 mg, codeine 65 mg, propoxyphene 65 mg, pentazocine 50 mg, placebo
Huskisson, 1974[9] (trial 1)	CO	30	6 h	1 g	Paracetamol/DXP 650/65 mg, pentazocine 50 mg, placebo
Huskisson, 1974[9] (trial 2)	CO	24	6 h	1 g	CIBA 44,328 100 mg, placebo
Seideman, 1988[13]	CO	20	2 wks	4 g + IND 50 mg*	IND 150 mg
Seideman, 1993[12]	CO	20	2 wks	4 g + NAP 500 mg*	NAP 500 mg
				4 g + NAP 1000 mg*	NAP 1000 mg
Boardman, 1967[5]**	CO	18	7 days	6 g	Placebo
di Munno, 1982[6]**	CO	12	4 days	2 g	TLM 1200 mg
Roth, 1975[11]**	Par	51	13 wks	2.6 g + TLM 600 mg*	TLM 600 mg

* Trial compared paracetamol + NSAID to placebo + NSAID; ** Only data on safety available; not included in efficacy analysis; CO: Crossover design; Par: Parallel group design; ASA: acetylsalicylic acid; IND: indomethacin; NAP: naproxen; DXP: dextropropoxyphene; TLM: tolmetin.

Efficacy. A metaanalysis was considered inappropriate for several reasons: the poor study quality may lead to misleading results if pooled; the doses of paracetamol used were often much less or greater than typical therapeutic doses; the outcome measures used varied greatly, with inconsistent reporting of effect sizes and standard error; and the comparators used were too dissimilar. A narrative summary of efficacy results is presented and discussed below (Table 2).

Acetaminophen versus placebo: Two studies containing 3 separate trials were identified that compared paracetamol to placebo[8,9]. All trials were crossover design containing multiple arms. The trials were 6 hours in duration with one dose of medication. Each trial showed a statistical benefit of paracetamol over placebo for mean pain relief over the 6 hour trial period.

Acetaminophen versus NSAID: Four trials were identified that compared paracetamol to NSAID[7,10,14,15]. The NSAID used as comparators were acetylsalicylic acid (ASA) 5 g[7], diclofenac 150 mg[14], bumadizone 660 mg[15], and one trial with 2 separate comparator arms of ASA 3.9 g and indomethacin 100 mg[10]. The trial duration ranged from 7 days to 2 weeks for each drug and the doses of paracetamol ranged from 4 g to 7.5 g. All studies indicated a benefit for NSAID over paracetamol, but it was difficult to draw conclusions. Two studies performed by the same author reported a statistically significant superiority of NSAID over paracetamol but did not report an effect size[14,15]. Another study reported the mean difference in pain between groups, but not the actual pain scores for each group or the statistical significance of the result[7]. The final study showed a benefit of NSAID over paracetamol when using a complex outcome measure, the after-treatment pain rating (ATPR) adjusted for baseline pain[10]. In this trial, pain increased from baseline across all study arms, but when the ATPR were adjusted for baseline pain, there was a difference between groups, favoring NSAID.

Acetaminophen versus weak opioids: The 3 trials that included weak opioids as a comparator are the same as those comparing paracetamol to placebo discussed above[8,9]. No trial showed a difference between paracetamol and any of the weak opioids tested.

Acetaminophen + NSAID versus placebo + NSAID: Two studies were identified[12,13]. Both were crossover design, 2 weeks in duration, and were performed by the same author. One study compared acetaminophen 4 g/day + indomethacin 50 mg to indomethacin 150 mg and showed no difference in mean morning or mean QHS pain and no difference in tolerability[13]. The authors interpreted these results as indicating an added benefit of paracetamol, since a lower dose of indomethacin could be used to achieve the same effect.

The second trial compared paracetamol + naproxen to

Table 2. Efficacy outcomes, grouped by comparator class.

Study	Comparator	Outcome	Results		Significance
			Paracetamol	Comparator	
Placebo					
Hardin, 1979[8]	Placebo	Mean % maximum pain relief	50.7%	35.8%	$p < 0.05$
Huskisson, 1974 [9] (trial 1)	Placebo	Mean pain relief Q1h x 6. (0-3: 0=none, 3=complete)	1.2	0.8	$p < 0.02$ at all time points
Huskisson, 1974 [9](trial 2)	Placebo		1.2	0.8	$p < 0.05$, except at h 1.4 (NS)
NSAID					
Hajnal, 1959[7]	ASA 5g	Mean pain difference between groups (0-3: 0=no pain, 3=very severe pain)		-0.18 (SE 0.06)	NR
Solomon, 1974[14]	DICL 150 mg	"Pain on a linear scale"	NR	NR	DICL superior ($p < 0.025$)
Solomon, 1977[15]	BDZ 660 mg	"Pain on a linear scale"	NR	NR	BDZ superior (p = NR)
Lee, 1975[10]	ASA 3.9 g	After treatment pain rating, adjusted for initial pain rating (1-5: 1=nil, 5=very severe)	3.5 (SE 0.1)	3.3 (SE 0.1)	NS
	IND 100 mg			2.9 (SE 0.1)	$p < 0.01$
Weak opioid					
Hardin, 1979[8]	Codeine 65 mg	Mean % maximum pain relief	50.7%	53.2%	NS
	PROP 65 mg			39.5%	NS
	PENT 50 mg			43.0%	NS
Huskisson, 1974 [9](trial 1)	Paracetamol/DXP 650/65 mg	Mean pain relief Q1h x 6. (0-3: 0=none, 3=complete)	1.2 (est.)*	1.5 (est.)*	$p < 0.05$ h 3-5; NS h 1-2, 6
	PENT 50 mg			1.2 (est.)*	NS
Huskisson, 1974[9] (trial 2)	CIBA 100 mg		1.2 (est.)*	1.2 (est.)*	NS
Paracetamol + NSAID vs NSAID					
Seideman, 1988[13]	Paracetamol + IND 50 mg vs IND 150 mg	Mean morning pain during week 2 (100 mm VAS)	29.9 (SD 26.4)	29.2 (SD 26.4)	NS
		Mean QHS pain during week 2 (100 mm VAS)	33.9 (SD 26.1)	30.5 (SD 24.9)	NS
Seideman, 1993[12]	Paracetamol + NAP 500 mg vs. NAP 500 mg	Mean rest pain (100 mm VAS)	45.7 (SD 14.6)	61.5 (SD 15.9)	$p < 0.001$
		Mean pain with movement (100 mm VAS)	46.2 (SD 14.3)	62.1 (SD 15.3)	$p < 0.001$
	Paracetamol + NAP 1 g vs NAP 1 g	Mean rest pain (100 mm VAS)	31.7 (SD 9.6)	46.5 (SD 14.6)	$p < 0.05$
		Mean pain with movement (100 mm VAS)	32.6 (SD 9.7)	47.1 (SD 14.4)	$p < 0.05$

* Data presented in graphic format, outcomes shown are estimates extrapolated from graphs. ASA: acetylsalicylic acid; DICL: diclofenac; BDZ: bumadizone; IND: indomethacin; PROP: propoxyphene; PENT: pentazocine; DXP: dextropropoxyphene; CIBA: CIBA 44,328; NAP: naproxen; NR: not reported; NS: not significant; VAS: visual analog scale.

placebo + naproxen, with naproxen doses of 500 mg and 1000 mg[12]. Mean rest pain (100 mm visual analog scale) was less with the combination of paracetamol and naproxen than with naproxen alone for both 500 mg and 1000 mg doses of naproxen (500 mg: 45.7 ± 14.6 vs 61.5 ± 15.9, $p < 0.001$; 1000 mg: 31.7 ± 9.6 vs 46.5 ± 14.6, $p < 0.05$). Similar effect sizes

were seen for mean pain with movement. There was no difference in tolerability.

Safety. There were no differences in total adverse events (AE) or withdrawals due to adverse events between the treatment and comparator arms in 8/10 clinical trials that reported safety data[5,6,7,8,11,12,13,15]. In one trial, there was a higher rate of withdrawals due to adverse events [mainly gastrointestinal (GI) symptoms] in the paracetamol arm (6/32, 19%) than in the diclofenac arm (0/32, 0%), but paracetamol was used at a dose of 6 g/day[14]. Another trial showed fewer withdrawals due to AE with paracetamol 4 g than ASA 3.9 g[10]. There were no serious AE reported in any of the trials.

The only cohort study identified compared the incidence of serious GI events between users of acetaminophen, acetylsalicylic acid (ASA), and ibuprofen in a cohort of 5692 patients with RA[16]. No difference was seen between the analgesic groups in patients using the medication alone. An increased risk was seen for paracetamol versus ASA or ibuprofen when combined with corticosteroids and one of the other 2 study medications (rate per 1000 patient-yrs: paracetamol 15, ASA 8.7, ibuprofen 6.1; $p < 0.05$). However, the significance of this uncertain. The specific medications used in each medication group were not reported, doses were unknown, and the study may have been biased through confounding by indication.

DISCUSSION

Our systematic review summarizes available evidence for paracetamol in the treatment of pain in patients with inflammatory arthritis. Combined with the expert opinion of a broad panel of rheumatologists in the 3e Initiative, the results served as an evidence base for generating one of the 10 clinical recommendations for the use of paracetamol in the management of pain in patients with inflammatory arthritis[1].

Based on 8 trials with high risk of bias we found weak evidence for the following in patients with RA: an increased benefit of paracetamol over placebo, an uncertain benefit of NSAID over paracetamol, no difference between paracetamol and weak opioids, and an additive benefit of paracetamol in combination with NSAID. There was no evidence in patients with other forms of inflammatory arthritis. For the efficacy of paracetamol versus NSAID in patients with RA, the SLR we identified in our search drew a similar conclusion: the trials were of poor quality and it was uncertain whether NSAID were superior to paracetamol[4].

Many of the trials included were old and had significant methodological flaws. Most of the studies were crossover design, which may bias results secondary to a carryover effect from one treatment to the next. Several of these crossed over several times to different medications at 1-day intervals, which may have further compounded a carryover effect. Several of the trials used sequential analysis to determine the stop point[5,7,14,15]. Sequential analysis is a method where the data are analyzed after each study participant and the trial is stopped when a statistical effect is seen. It is prone to an overestimation of treatment effect. Key study details were often omitted, leading to significant uncertainty in the rigor of sequence generation, allocation concealment, and blinding; and reporting of outcome measures was poor.

The design of the studies was not reflective of current practice, leading to difficulties in extrapolating the results to treatment recommendations. The doses of medications used were atypical, the study duration was too short for the treatment of a chronic pain condition, and the comparators included medications not commonly used. Also, the trials were performed in patients with active RA and at a time when effective therapies for controlling the disease process were limited. With effective treatment of the inflammation, analgesic therapy may not be required. The role of paracetamol in the treatment of persistent pain after disease activity has been adequately controlled was not addressed by any of the trials.

The safety data from the trials were too limited to draw conclusions, but no indications of safety issues were seen. The only cohort study identified did show a possible increased risk of paracetamol over ASA or ibuprofen when used with corticosteroids and one of the other study medications, but the interpretation of this was difficult secondary to methodological limitations. No increased risk was seen in patients using paracetamol alone versus ASA or ibuprofen.

Extrapolating these results to treatment recommendations is difficult. When limited disease-specific data are available to guide the therapeutic choice, other disease models may provide insight. When pain medications are tested in chronic pain, osteoarthritis is often the model used. In a recently updated Cochrane Review on the efficacy and safety of paracetamol in osteoarthritis that included 15 RCT with a total of 5986 patients, there was evidence to support the efficacy of paracetamol in comparison to placebo, but with a low overall effect size (SMD –0.13, 95% CI –0.22 to –0.04)[18]. When compared with NSAID, paracetamol was found to be less effective, but had a decreased risk of any GI event when compared with traditional NSAID (number needed to harm 12, 95% CI 6 to 66)[18].

In summary, the results of this systematic review showed that there is limited disease-specific evidence to support the role of paracetamol in the treatment of pain in patients with inflammatory arthritis. The available evidence, all with high risk of bias, suggests that there is a potential benefit of paracetamol, alone or when combined with NSAID in patients with RA. Given the relative paucity of information, recommendations should incorporate expert opinion and may rely on extrapolation from evidence in other chronic pain conditions.

ACKNOWLEDGMENT

The authors thank Louise Falzon for help with the literature search strategy.

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