Celecoxib compared with sustained-release paracetamol for osteoarthritis: A series of n-of-1 trials

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Published in:
Rheumatology

DOI:
10.1093/rheumatology/kel195

Title

Do n-of-1 trials of celecoxib compared to sustained-release paracetamol change patient use of drugs for osteoarthritis?

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Statement of competing interests

GlaxoSmithKline provided medication and placebos, and funding participated in initial planning discussions; and viewed th manuscript prior to publication, but had no involvement in th collection, analysis or interpretation of data, writing the report or th decision to submit the final manuscript for publication. The provided funding that supported the salaries of Jane Nikles an Norma McNairn on the project.

Acknowledgements

Thanks to the Australian Health Ministers Advisory Council for funding; GlaxoSmithKline Consumer Healthcare for supply of medication, placebos, and funding and for their invaluable support; Donna-Marie Preston, Robyn Brown and Grace McBride for collecting the data; and the doctors and patients who took part in this study.

ABSTRACT

Objective: To assess the use of n-of-1 trials for short-term choice of drugs for osteoarthritis.

Design and setting: Evaluation of community-based patients undergoing n-of-1 trials (double-blind, cross-over comparison of celecoxib 200 or 400 mg daily vs sustained-release paracetamol 1330 mg three times daily in three pairs of two-week treatment periods with randomization of medication within pairs, with the outcomes of pain and stiffness in sites nominated by the patient, functional limitation scores, preferred medication, and side effects).

Participants: Patients with osteoarthritis (with pain for ≥1 month) severe enough to warrant consideration of long-term use of celecoxib but for whom there was doubt about its efficacy.

Main outcome measures: Changes in drug use after an n-of-1 trial.

Results: 41/59 n-of-1 trials were completed, in which for 33 (80%) the overall symptom relief by celecoxib and paracetamol was equivalent. Management after the n-of-1 trial was concordant with its result for 19 of these (13 generally using paracetamol, six celecoxib). Symptom relief for celecoxib and paracetamol was not equivalent for the remaining eight patients: celecoxib provided better relief for seven.

Conclusions: N-of-1 trials provide a rational and effective method to best choose drugs for individual with osteoarthritis. Sustained–release paracetamol is useful for most patients whose management is uncertain.

Introduction

Osteoarthritis (OA) is one of the ten most disabling diseases in the developed world,[1] inflicting joint pain and stiffness among 10% of men and 20% of women aged 45–60 years in the west.[2] This morbidity presents a significant healthcare burden and comes at enormous cost, mostly for analgesic and anti-inflammatory drugs. Paracetamol, relatively cheap and safe, is the agent of first choice of advisory guidelines based on good evidence from trials.[3-5] But NSAIDs are better for some individuals, especially for moderate to severe OA pain[4] or where the pain is unresponsive to paracetamol.[3]

One solution for the safety issue seemed to be COX-2 specific NSAIDs, which were increasingly used until 2004 when reports of elevated risk of cardiovascular events changed this perception.[6;7]

Paracetamol has the disadvantage of requiring 4 doses per day to maintain therapeutic serum levels. The recent introduction of sustained-release paracetamol has reduced this requirement to 3 doses per day.[8;9]

There are three published randomised controlled trials comparing paracetamol and celecoxib,[10-12] but no n-of-1 trials. These provide empirical data of individual responses to treatment. These are within-patient randomized, double-blind, cross-over comparisons, in which patients act as their own controls, and provide the most rigorous information available for any individual patient.[13-17]

We investigated how the results of n-of-1 trials influenced drug use in the short-term for patients with OA.

Methods

We offered an n-of-1 service for celecoxib/sustained-release paracetamol throughout Australia between December 2003 and December 2004 communicating (as we have previously described[13;18;19]) by post, telephone, fax and email. The process was similar to requesting a pathology test: we sent packs of test medications by post to patients' family physicians on request; patients completed a daily symptom diary; and we followed up

patients by telephone, while the clinician continued to provide usual clinical care. At the end of the n-of-1 trial diaries were analysed, and a report sent to the doctor within two weeks. When the patient next consulted their doctor, the results were available to inform management decisions.

Recruitment was through a network of participating doctors and a print media and radio publicity campaign. Potential patients were able to contact our service directly, and information packs which we sent out could be taken to the doctor for them to request an n-of-1 trial. Eligibility was restricted to adults providing written informed consent with a clinical diagnosis of OA pain for at least one month of sufficient severity to consider long-term use of anti-inflammatory drugs or paracetamol. Contra-indications to either of these, or sulphas; concomitant disease (such as peptic ulcer, hepatic or renal dysfunction) which increases the risk of side-effects; and depot corticosteroid injection in the last two months, were exclusions.

Patients took either sustained-release paracetamol (1.33 g 3-times daily) or celecoxib (200 mg daily, or 200 mg twice daily for those who were already using this dose), and a placebo encapsulated to be identical to the alternative drug. There were three comparisons with paired 2-week treatment periods, (a total of 12 weeks), each of which was randomly assigned using a computer-generated schedule. Patients, doctors and the research assistant were blinded to medication order. We sent the drugs to participants fortnightly in pre-prepared blister packs. We recommended tramadol to the doctors for 'escape' analgesia for uncontrolled pain.

Ethics approval for this study was provided by the University of Queensland Human Research Ethics Committee.

At commencement, patients provided demographic information and a drug history; and recorded side effects weekly. At the end of each treatment period they guessed which treatment they had received. After the n-of-1 trial, patients were interviewed by telephone about subsequent management decisions.

We assessed pain and stiffness scores daily with visual analog scales marked 0 to 10, omitting the first week of data from each period to negate any

carry-over effects. We assessed the patient specific functional scale[20] using up to 5 patient-nominated functions to assess functional limitation on a 0 to 10 visual analog scale. Differences in mean scores between measurements within pairs of periods were analyzed using hierarchical Bayesian random effects models.[21] Assuming a minimum detectable difference in pain and stiffness scores of 1.0,[22] a definite response was defined as an adjusted mean absolute difference ≥1.0, a probable response as a difference of ≥0.5 but <1.0, and all other responses as no difference. Assuming a minimum detectable difference in functional limitation scores of 2.0,[23] a definite response was defined as an adjusted mean absolute difference ≥2.0, a probable response as a difference of ≥1.0 but <2.0 and all other responses as no different.

At the end of each comparison, we assessed medication preference. A definite response was defined as a preference for one medication in all 3 comparisons, a probable response as a preference in 2 comparisons and no response as a preference in 0 or 1 comparison. We assessed adverse events weekly in each treatment period. Here, a definite response was defined as fewer events on one medication in all 3 comparisons, a probable response as fewer events in 2 comparisons and no response as fewer events in no comparisons or 1 comparison.

To describe the overall response, we created an aggregate response variable, composed from an equally weighted linear combination of the five variables (each defined on a 5-point scale from -2 favouring celecoxib to +2 favouring paracetamol). An individual with aggregate response absolute value ≥6 was considered a definite responder, a value ≥3 but <6 was considered a probable responder, and a value <3 was considered a non-responder.

Results

Recruitment was stopped prematurely in December 2004 because the Australian Therapeutic Goods Administration (TGA) directed all research involving celecoxib to stop in view of newly learned increased risk of cardiovascular events from it.

We enrolled 79 patients: 20 did not start their n-of-1 trials; (13 because of the

TGA directive; two because of a prior recall of rofecoxib (a COX-2 inhibitor in the same class); and five for other reasons, mainly sulpha allergies); 18 completed only one or two comparisons (one because of adverse reactions to celecoxib; six severe pain; five the TGA directive; three the large number of tablets; and one each because of concern relating to side-effects of celecoxib; failure to complete diaries; and impending admission for surgery). The mean age of those who withdrew from this study was 61 years, older than most.

Doctors proposed nine n-of-1 trials to patients; patients initiated 50 (45 after approaching us having heard of the service by advertisements; four heard about them from other patients; and one worked in our research building). Demographic and clinical characteristics of the 59 enrolled patients were unremarkable, Table 1.

Blinding

The dose of celecoxib used during the celecoxib periods was 200 mg, once daily for 32 patients and twice daily for nine patients. Only one of the 41 patients guessed which medication they were using in 6/6 treatment periods correctly; one 5/6; four 4/4; and the remainder 0/6, 1/6 or 2/6 correctly, no difference from what could be expected from chance alone.

Pain, stiffness and functional limitation scores

Of the 41 completers, 12 had detectable differences in pain scores, (10 in favour of celecoxib); 14 in stiffness scores, (12 in favour of celecoxib); two in functional limitation scores, (both in favour of celecoxib). The number of patients with no detectable differences between medications for these scores was 24, 22 and 26 respectively (Table 2).

With meta-analysis of all 41 trials, the mean (SD) scores for the group were lower for celecoxib by ---( ) for pain, ---( ) for stiffness and ---( ) for functional limitation.

~~*Aggregate response* ***Should this appear here or after the 'adverse effect results – given that is uses these results too?***~~

~~Looking at the whole group, 33 (80%) patients showed no difference in their response to the two medications; 5 had responses that were probably better~~

~~from celecoxib than paracetamol and; one had a response that was probably better to paracetamol than to celecoxib. Two patients' responses were definitely better to celecoxib than paracetamol.~~

Medication preference

Three patients preferred celecoxib over paracetamol in all three comparisons: and five in two of three comparisons. The remaining 33 had no obvious preference.

Adverse events

Only one adverse event—severe foot/ankle swelling on celecoxib—resulted in withdrawal. Nine patients reported more adverse events while on paracetamol than on celecoxib, and five reported more while on celecoxib than on paracetamol. In the other 25 patients there was no difference in the prevalence of adverse events reported.

The most common adverse events on celecoxib were headache and loss of energy (54%), indigestion (36%) and constipation (32%); on paracetamol they were loss of energy (51%), headache (49%) and constipation and indigestion (44%) (Table 4).

Adverse events were mild or moderate in 32 patients. The other nine had between 1 and 3 severe symptoms, and one had 6 severe symptoms. One patient had tinnitus through the trial on both drugs. Two other patients had this with celecoxib only. Other severe events on celecoxib were trembles, upper body rash, loss of energy and indigestion/heartburn.

Two patients had severe loss of energy on paracetamol extend. Other severe events on paracetamol extend were dizziness, diarrhoea, restless leg and poor concentration.

Aggregate response

The aggregate response showed no difference in the response to the two medications in 33 (80%) patients; five had responses that were probably better to celecoxib than paracetamol and; one had a response that was probably better to paracetamol than to celecoxib. Two patients' responses

were definitely better to celecoxib than paracetamol. Agreement between all pair-wise comparisons of the 5 outcome variables contributing to the aggregate response was poor (κ<0.40), except for that between pain and stiffness (κ=0.80).

Change in drug use after the n-of-1 trial

Following the n-of-1 trials there was no change in management in 15/41 (37%) patients; 12/41 (29%) discontinued NSAID/COX-2 inhibitors afterwards; paracetamol was added or substituted for 7/41 (17%) patients; and paracetamol was discontinued in 6/41 (15%) patients.

Consistency of drug management with the result of the n-of-1 trial

Among the 33 patients for whom there was no difference between medications, 13 were subsequently managed with paracetamol mainly and six with COX-2 inhibitors mainly; three switched to NSAIDs, two ceased drugs, and the management was unknown for nine. Of the other eight patients whose results favoured one or the other drug, six were managed consistently with their IMET result. Altogether, in 25/41 (61%) management was consistent with their IMET results.

DISCUSSION

The aggregate results showed that most (80%) patients completing an n-of-1 trials have a similar response to celecoxib as to paracetamol. Of the remainder celecoxib was probably better in most. These findings are hardly surprising as they are similar to previous ones for OA.[13,14] Caution is warranted in generalising these results the broader population of patients with OA as they are derived from a population of patients characterised by uncertainty about the efficacy of their drugs for them as individuals and so may not represent. Likewise, caution applies to interpreting the post-trial decisions about medications as the highly publicised problem with COX-2 inhibitors that occurred simultaneously may have led more patients to stop celecoxib than would have otherwise.

The main application of n-of-1 trials in clinical practice could be to guide patients in a rational decision about which of a pair of management options best favours their chronic disease. These data might help medical services

decide to adopt this process. We have shown that for one of the most common chronic diseases use of n-of-1 trials is entirely feasible. That they are acceptable to many patients can be attested by the fact that they must commit to completing daily symptom diaries for 12 weeks. The withdrawal rate of 30% is fairly typical of n-of-1 trials (34%, 40% and 37%)[13,14;15] and indeed typical of many conventional randomised controlled trials.[24]

We have shown that use of n-of-1 trials promotes rational management of chronic OA. The impact of this useful clinical tool on long-term management and subsequent economic consequences needs further evaluation before it becomes more widely accepted.

TABLES:

Table 1: Demographic and clinical characteristics of completers, non-completers and total commencers of the chronic pain IMET.

Table 2. Response status for each of the five outcomes and the aggregate response weighting all available outcomes equally (n =41)

Table 3. Global assessment of response based on an aggregate score with equal weightings for pain, stiffness, function, preferred drug and adverse events.

Table 4: Regular drug treatment after the n-of-1 trial compared to before

Table 5. Frequency (%) of adverse events during the total treatment period of up to 6 weeks on each medication during the n-of-1 trial. Events for each medication are counted only once per participant.(n=41)

Table 1: Demographic and clinical characteristics of completers, non-completers and total commencers of the chronic pain IMET.

Variable		**Completers (n = 41)**	**Non-completers (n = 18)**	**Total (n = 59)**
Age	range	47-80	30-82	47-82
	mean (SD)	65.5 (8.29)	61 (12.28)	64 (9.89)
Duration of pain (years)	range	1-46	2-30	1-46
	mean (SD)	11 (10.34)	12 (9.47)	11 (10.16)
Frequency (%)		**n (%)**		
Sex				
Male		15 (37)	6 (33)	21 (36)
Female		26 (63)	12 (67)	38 (64)
Employment status				
Full time employment		6 (15)	1 (6)	7 (12)
Part time/casual employment		3 (7)	2 (11)	5 (8)
Unpaid homemaker/unemployed		3 (7)	2 (11)	5 (8)
Retired		26 (63)	8 (44)	34 (58)
Other		3 (7)	2 (11)	5 (8)
Not applicable/no response		0	3 (17)	3 (5)
Marker joint/area				
Upper limb		8 (20)	2 (11)	8 (14)
Lower limb		21 (51)	9 (50)	30 (51)
Neck/back		8 (20)	7 (39)	15 (25)
Two or more categories		6 (15)	0	6 (10)
Unknown		0	0	0
Pre-IMET regular medication				
Paracetamol alone		1 (2)	0	1 (2)
NSAID/Cox-2 inhibitor alone		23 (56)	11 (61)	34 (58)
Paracetamol plus NSAID/Cox-2 inhibitor		7 (17)	4 (22)	11 (19)
Other		4 (10)	0	4 (7)
No drug		6 (15)	1 (6)	7 (12)
Unknown		0	2 (11)	2 (4)

Table 2. Response status for each of the five outcomes and the aggregate response weighting all available outcomes equally (n =41)

	celecoxib			long acting paracetamol		
	definitely better	probably better	No difference	probably better	definitely better	Incomplete data
Lower pain scores	2	8	24	0	2	5
Lower stiffness scores	3	9	22	1	1	5
Lower functional limitation scores	0	2	26	0	0	13
Preferred medication	4	5	28	0	0	5
Fewer adverse events	7	2	25	4	1	7
Overall response	2	5	33	1	0	

Table 3. Global assessment of response based on an aggregate score with equal weightings for pain, stiffness, function, preferred drug and adverse events.

	celecoxib			paracetamol		
	definitely better	probably better	No difference	probably better	definitely better	TOTAL
Management consistent with result	1	4	19#	1	0	25
Management inconsistent with result	1*	0	3**	0	0	4
Unknown	0	1	9	0	0	10
Nil	0	0	2	0		2
Total	**2**	**5**	**33**	**1**	**0**	**41**

Response status is further categorised according to the consistency of post n-of-1 trial management decisions with this global assessment.

*switched to simple analgesics
**switched to NSAIDs
#13 patients mainly using paracetamol

Table 4: Regular drug treatment after the n-of-1 trial compared to before

Treatment *before* the n-of-1 trial	Treatment *after* the n-of-1 trial: No change	NSAID/Cox-2 inhibitor added or substituted	Paracetamol added or substituted	NSAID/Cox-2 inhibitor discontinued	Paracetamol discontinued	Other/unknown
Paracetamol alone (1)	1	0	0	0	0	0
NSAID/Cox-2 inhibitor alone (23)	9	1	5*	11	0	1
Paracetamol plus NSAID/Cox-2 inhibitor (7)	1	0	0	1**	6	0
Other (4) #	1	2	0	0	0	1
No drug (6)	3	1	2	0	0	0
Total (41)	15	4	7	12	6	2

* 4 patients switched from NSAID/cox-2 inhibitor to paracetamol and are also counted in the following column

** This patient ceased paracetamol in addition and is also counted in the following column

Aropax, glucosamine, tramadol

Table 5. Frequency (%) of adverse events during the total treatment period of up to 6 weeks on each medication during the n-of-1 trial. Events for each medication are counted only once per participant.(n=41)

		n (%)
Adverse event	**Celecoxib**	**ER paracetamol**
Drowsiness	9 (22)	9 (22)
Dizziness	6 (15)	6 (15)
Indigestion	15 (36)	18 (44)
Heartburn	11 (27)	12 (29)
Nausea	7 (17)	9 (22)
Constipation	13 (32)	18 (44)
Diarrhoea	10 (24)	6 (15)
Stomach pains	6 (15)	11 (27)
Vomiting	1 (2)	3 (7)
Headache	22 (54)	20 (49)
Loss of energy	22 (54)	21 (51)
Poor concentration	13 (32)	14 (34)
Ringing in ears/tinnitus	12 (29)	10 (24)
Swelling	4 (10)	6 (15)
Belching	1 (2)	1 (2)
Trembles	1 (2)	1 (2)
Aching legs/knees/feet	1 (2)	1 (2)
Sore oral mucosa	1 (2)	1 (2)
Skin rash	1 (2)	0
Sore throat/ears/mouth	1 (2)	0
Allergic reaction	1 (2)	0
Bloating	1 (2)	0
Flatulence	1 (2)	1 (2)
Tiredness	0	2 (5)
Teeth grinding	0	1 (2)
Hand tremor	0	1 (2)
Restless legs	0	1 (2)
Poor circulation	0	1 (2)

References

(1) World Health Organization. Chronic rheumatic conditions. http://www who int/chp/topics/rheumatic/en/ [2005 [cited 5 A.D. Aug. 23]; Available from: URL:http://www.who.int/chp/topics/rheumatic/en/

(2) March LM, Schwarz JM, Carfrae BH, Bagge E. Clinical validation of self-reported osteoarthritis. Osteoarthritis Cartilage 1998; 6(2):87-93.

(3) Jordan KM, Arden NK, 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(12):1145-1155.

(4) American College of Rheumatology Subcommittee on Osteoarthritis. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis and Rheumatism 2000; 43(9):1905-1915.

(5) Koes BW, Sanders RJ, Tuut MK. [The Dutch Institute for Health Care Improvement (CBO) guideline for the diagnosis and treatment of aspecific acute and chronic low back complaints]. Ned Tijdschr Geneeskd 2004; 148(7):310-314.

(6) FDA MedWatch. **COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**. http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#NSAID . 15-6-2005.
Ref Type: Internet Communication

(7) Day RO GGG. The vascular effects of COX-2 selective inhibitors. Australian Prescriber . 2005.
Ref Type: Journal (Full)

(8) Bacon TH, Hole JG, North M, Burnett I. Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee. Br J Clin Pharmacol 2002; 53(6):629-636.

(9) Coulthard P, Hill CM, Frame JW, Barry H, Ridge BD, Bacon TH. Pain control with paracetamol from a sustained release formulation and a standard release formulation after third molar surgery: a randomised controlled trial. BDJ 2001; 191(6):319-324.

(10) Pincus T, Fort JF, Mangal B, Kock G, Wolfe F, Moskowitz R. Patient preference for placebo, acetaminophen (paracetamol), or Celebrex effectiveness study (PACES-1): a double-blinded, randomized, cross-over clinical trial in patients with osteoarthritis of the hip or knee. Ann

Rheum.Dis. 62[Suppl 1], 73. 2003.
Ref Type: Abstract

(11) Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R et al. Patient preference for Placebo, Acetaminophen or Celecoxib Efficacy Studies (PACES): Two randomized placebo-controlled cross-over clinical trials in patients with osteoarthritis of the knee or hip. Ann Rheum Dis 2004.

(12) 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(1):64-71.

(13) Nikles CJ, Yelland M, Glasziou PP, Del MC. Do individualized medication effectiveness tests (n-of-1 trials) change clinical decisions about which drugs to use for osteoarthritis and chronic pain? Am J Ther 2005; 12(1):92-97.

(14) March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. N of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. BMJ 1994; 309(6961):1041-1045.

(15) Sheather-Reid RB, Cohen M. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. J Pain Symptom Manage 1998; 15(4):244-252.

(16) Larson EB. N-of-1 clinical trials. A technique for improving medical therapeutics. West J Med 1990; 152(1):52-56.

(17) Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience. Ann Intern Med 1990; 112(4):293-299.

(18) Coxeter PD, Schluter PJ, Eastwood HL, Nikles CJ, Glasziou PP. Valerian does not appear to reduce symptoms for patients with chronic insomnia in general practice using a series of randomised n-of-1 trials. Complement Ther Med 2003; 11(4):215-222.

(19) Nikles CJ, Clavarino AM, Del Mar CB. Using n-of-1 trials as a clinical tool to improve prescribing. Br J Gen Pract 2005; 55(512):175-180.

(20) Stratford PW, Gill C. Assessing disability and change in individual patients: a report of a patient-specific measure. Physiotherapy Canada 1995;47:258-63.**)**

(21) Zucker DR, Schmid CH, McIntosh MW, D'Agostino RB, Selker HP, Lau J. Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. J Clin Epidemiol 1997; 50(4):401-410.

(22) Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire

and global assessments in patients with osteoarthritis. J Rheumatol 2000; 27(11):2635-2641.

(23) Chatman AB, Hyams SP, Neel JM, Binkley JM, Stratford PW, Schomberg A et al. The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction. Phys Ther 1997; 77(8):820-829.

(24) Martin R, Vogtle L, Gilliam F, Faught E. Health-related quality of life in senior adults with epilepsy: what we know from randomized clinical trials and suggestions for future research. Epilepsy Behav 2003; 4(6):626-634.