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

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Objective. To assess the use of n-of-1 trials for short-term choice of drugs for osteoarthritis, with particular reference to comparing the efficacy of sustained-release [SR] paracetamol with celecoxib in individual patients.

Methods. Evaluation of community-based patients undergoing n-of-1 trials which consisted of double-blind, crossover comparisons of celecoxib 200 or $400 \, \text{mg/day}$ with sustained-release paracetamol 1330 mg three times a day in three pairs of 2 week treatment periods per drug with random order of the drugs within pairs. Outcomes evaluated were pain and stiffness in sites nominated by the patient, functional limitation scores, preferred medication, side effects and changes in drug use after an n-of-1 trial. Participants were 59 patients with osteoarthritis in multiple sites (hip 6, knee 24, hand 6, shoulder/neck 8, back 14, foot 5), 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. Forty-one n-of-1 trials were completed.

Results. Although on average, celecoxib showed better scores than SR paracetamol [0.2 (0.1) for pain, 0.3 (0.1) for stiffness and 0.3 (0.1) for functional limitation], 33 of the 41 individual patients (80%) failed to identify the differences between SR paracetamol and celecoxib in terms of overall symptom relief. Of the eight patients who were able to identify the differences, seven had better relief with celecoxib and one with SR paracetamol. In 25 out of 41 [61%] patients, subsequent management was consistent with their trial results.

Conclusions. N-of-1 trials may provide a rational and effective method to best choose drugs for individuals with osteoarthritis. SR paracetamol is more useful than celecoxib for most patients of whom management is uncertain.

KEY WORDS: n-of-1 trials, osteoarthritis, celecoxib, SR paracetamol.

Introduction

Osteoarthritis (OA) is one of the 10 most disabling diseases in the developed world [1], inflicting joint pain and stiffness among 10% of men and 20% of women aged 45–60 yrs 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 inexpensive and safe, is the agent of first choice of advisory guidelines based on good evidence from trials [3–5]. But non-steroidal anti-inflammatory drugs (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 cyclooxygenase enzyme, subtype 2 (COX-2) specific NSAIDs, which were increasingly used until 2004 when the reports of elevated risk of cardiovascular events changed this perception [6, 7].

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

N-of-1 trials provide empirical data of individual responses to the treatment. These are within-patient randomized, double-blind, crossover trials, in which patients act as their own controls, and provide the most rigorous information available for any individual patient [10–14]. In the n-of-1 trial, the unit of randomization is the treatment sequence for an individual patient, and a single n-of-1 treatment cycle includes an exposure to each therapy. Data are usually analysed for individual patients. In contrast, in randomized crossover trials, where the individual is randomized to one group or another, each participant receives each intervention at different time frames of the study, and the data are analysed for each group as a whole. The question answered by an n-of-1 trial is 'which therapy is better for this patient?' and in classic crossover designs, 'in population x, which drug is better?'

There are no n-of-1 trials comparing paracetamol and celecoxib, and only three published reports of randomized controlled trials comparing paracetamol and celecoxib. For knee or hip OA, celecoxib was more efficacious than paracetamol [15]. For knee OA, celecoxib showed significantly greater efficacy [16] and faster onset of efficacy [17] than paracetamol.

Our main hypothesis was that for each individual patient there was no difference between the two medications. We also hypothesized that the results of n-of-1 trials influenced drug use in the short-term for patients with OA, with particular reference to the efficacy of SR paracetamol compared with celecoxib in individual patients.

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Methods

We offered an n-of-1 trial service for celecoxib (Pfizer, PO Box 57, West Ryde NSW, Australia 2114) [10–12] compared with SR paracetamol [GlaxoSmithKline, 82 Hughes Avenue, Locked Bag 3, Ermington, NSW 2115] throughout Australia between December 2003 and December 2004, communicating as we have previously described [13,18,19] by post, telephone, fax and e-mail. The process was similar to requesting a pathology test: we sent packs of test medications by post to patients on request from their family physicians; 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 2 weeks. When the patient next consulted their doctor, the results were available to inform management decisions.

Recruitment

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.

Subjects

Eligibility was restricted to adults providing written informed consent with a clinical diagnosis of OA pain for at least 1 month (in the opinion of their attending general practitioner) of sufficient severity to consider long-term use of anti-inflammatory drugs or SR 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. Subjects did not need to have radiographic OA.

Intervention

Patients took either SR paracetamol [as $2 \times 665 \,\mathrm{mg}$ tablets (i.e. $1.33 \,\mathrm{g}$) 3 times a day] or celecoxib [200 mg daily, or 200 mg twice a day for those who were already using this dose], and a placebo identical to the alternative drug. The celecoxib and its placebo were encapsulated; the paracetamol placebo was manufactured. There were three cycles of paired treatment periods (2 weeks for each treatment and a total of 12 weeks). The order of the drugs in each pair was randomly assigned using a computergenerated 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 that they request tramadol (the dose was prescribed by their general practitioner) for additional analgesia as required.

Ethics approval for this study was provided by The University of Queensland Human Research Ethics Committee. The subjects' written consent was obtained according to the Declaration of Helsinki [20].

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.

Outcome measures

There were five primary outcomes to which we decide to give equal weight: pain, stiffness and functional limitation scores, medication preference and adverse effects.

We used pain/stiffness intensity rating scales to assess pain and stiffness scores daily with visual analogue scales marked 0–10 [21, 22]. We omitted the first week of data from each period to negate any carry-over effects [the effects of celecoxib wear off after

multiple dosing within 5 days (10 half-lives)]. To assess functional limitation, we used the patient-specific functional scale [23] with up to five patient-nominated functions on a 0–10 visual analogue scale. Differences in mean scores between treatments were analysed using hierarchical Bayesian random effects models [24]. The Bayesian method which we employed allows for individual assessment and group meta-analysis. Assuming a minimum detectable difference in pain and stiffness scores of 1.0 [25], a definite response was defined as an adjusted mean absolute difference \geq 1.0, a probable response as a difference. Assuming a minimum detectable difference in functional limitation scores of 2.0 [26], a definite response was defined as an adjusted mean absolute difference \geq 2.0, a probable response as a difference of \geq 1.0 but <2.0, and all other responses as no difference.

At the end of each cycle, we assessed the medication preference. A definite response was defined as a preference for one medication in all three cycles, a probable response as a preference in two cycles and no response as a preference in no cycle or one cycle. We assessed adverse events weekly in each treatment period. Here, a 'definite response' was defined as fewer events on one medication in all three cycles, a 'probable response' as fewer events in two cycles and 'no response' as fewer events in no cycles or one cycle. All patients who completed the trial took at least 96% of their tablets.

Statistical analysis

To describe the overall response, we created an aggregate response variable, composed from an equally weighted linear combination of the five variables (each arbitrarily defined on a 5-point scale from -2 favouring celecoxib to +2 favouring SR paracetamol). An individual with an 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.

The Kappa statistic was used to measure the agreement between matched categorical outcome variables.

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 discovered increased risk of cardiovascular events.

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 cycles (one because of adverse reactions to celecoxib; six due to severe pain; five due to the TGA directive; three due to 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). Marker joints were knee 24, back 14, shoulder/neck 8, hand 6, hip 6, foot 5 (some had multiple sites). 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 a day for 32 patients and 200 mg twice a day for nine patients. Only one of the 41 patients guessed which medication they were using in 6/6 treatment periods correctly, one guessed 5/6, four 4/4 and the remainder 0/6, 1/6 or 2/6 correctly, no different from what could be expected from chance alone. All patients who completed the trial took at least 96% of their tablets.

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

Variable	Completers $(n=41)$	Non-completers $(n = 18)$	Total $(n = 59)$
Age (min-max)	47–80	30–82	47–82
mean (s.D.)	65 (8)	61 (12)	64 (10)
Duration of pain	. ,	• •	` '
Range (yrs)	1–46	2–30	1-46
Mean (s.D.)	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-trial regular medication			
SR paracetamol alone	1 (2)	0	1 (2)
NSÂID/Cox-2 inhibitor alone	23 (56)	11 (61)	34 (58)
SR 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	O	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 SR 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	

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) and 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).

Using hierarchical Bayesian random effects models to metaanalyse differences in mean scores within pairs for all 41 trials, the mean (s.d.) scores for the group were lower for celecoxib: 0.2 (0.1) for pain, 0.3 (0.1) for stiffness and 0.3 (0.1) for functional limitation.

Medication preference

Three patients preferred celecoxib over SR paracetamol in all three cycles and five in two of three cycles. 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 SR paracetamol than on celecoxib, and five reported more while on celecoxib than on SR 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 (54%), loss of energy (54%), indigestion (36%) and constipation (32%); and on SR paracetamol were loss of energy (51%), headache (49%) and constipation and indigestion (44%) (Table 5). There were differences between the two drugs in terms of stomach pain (15% for celecoxib vs 27% for SR paracetamol) and vomiting (2% for celebrex vs 7% for SR paracetamol). This may be due to the small sample size, rather than a real difference in response to the two drugs.

Adverse events were mild or moderate in 32 patients. The other nine had between one and three severe symptoms, and one had six 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 SR paracetamol. Other severe events on SR paracetamol were dizziness, diarrhoea, restless leg and poor concentration.

M. J. Yelland et al.

TABLE 3. Regular drug treatment after the n-of-1 trial compared with treatment before the trial

	Treatment after the n-of-1 trial						
Treatment before the n-of-1 trial	No change	NSAID/Cox-2 inhibitor added or substituted	SR paracetamol added or substituted	NSAID/Cox-2 inhibitor discontinued	SR paracetamol discontinued	Other/ unknown	
SR paracetamol alone [1]	1	0	0	0	0	0	
NSÂID/Cox-2 inhibitor alone [23]	9	1	5 ^a	11	0	1	
SR paracetamol plus NSAID/Cox-2 inhibitor [7]	1	0	0	1 ^b	6	0	
Other [4] ^c	1	2	0	0	0	1	
No drug [6]	3	1	2	0	0	0	
Total [41]	15	4	7	12	6	2	

^a4 patients switched from NSAID/cox-2 inhibitor to SR paracetamol and are also counted in the following column.

Table 4. Global assessment of response based on an aggregate score with equal weightings for pain, stiffness, function, preferred drug and adverse events

	Celecoxib			Long-acting SR paracetamol		
	Definitely better	Probably better	No difference	Probably better	Definitely better	Total
Management consistent with result	1	4	19 ^a	1	0	25
Management inconsistent with result	1 ^b	0	3 ^c	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 categorized according to the consistency of post-n-of-1 trial management decisions with this global assessment.

Aggregate scores

The aggregate scores showed no difference between the two medications in 33 (80%) patients; five had scores that showed a probable advantage of celecoxib over SR paracetamol and one had a score that showed a probable advantage of SR paracetamol over celecoxib. Two patients' scores showed a definite advantage of celecoxib over SR paracetamol. Agreement between all pairwise comparisons of the five outcome variables contributing to the aggregate score was poor ($\kappa < 0.40$), except for that between pain and stiffness ($\kappa = 0.80$). Of the nine patients who were taking celecoxib 200 mg b.i.d., in one patient SR paracetamol was probably better, in three celecoxib was probably better and in the rest there was no difference.

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; SR paracetamol was added or substituted for 7/41 (17%) patients and SR paracetamol was discontinued in 6/41 (15%) patients (Table 3).

Consistency of drug management immediately after the trial 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 SR 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 trial result (i.e. the favoured drug was prescribed). Altogether, in 25/41 (61%) patients, management was consistent with their results, meaning that a logical decision was made based on the results

(Table 4); for example, for those with no difference between medications, either medication could be logically prescribed.

Discussion

This is the first study to report n-of-1 trials of SR paracetamol vs celecoxib, and one of the few to use Bayesian methods to conduct statistical analysis of n-of-1 trials. It is the first in the pharmacological OA literature to apply Bayesian methods to n-of-1 trial analysis.

The aggregate results showed that most (80%) patients completing an n-of-1 trial had a similar response to celecoxib as to SR 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 generalizing these results to the broader population of patients with OA, as they are derived from a population of patients characterized by uncertainty about the efficacy of their drugs for them as individuals and so may not be representative. Such a population may be less likely to show differences between the drugs as their response rates to both drugs may be lower than in the broader population of patients with OA. Likewise, caution applies to interpreting the post-trial decisions about medications, as the highly publicized problems 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 suits 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, the use of n-of-1 trials is entirely feasible. That they are acceptable to many patients can be attested by the fact that they commit to completing the daily-symptom diaries for 12 weeks.

^bThis patient ceased SR paracetamol in addition and is also counted in the following column.

^cAropax, glucosamine, tramadol.

^a13 patients mainly using SR paracetamol.

^bSwitched to simple analgesics.

^cSwitched to NSAIDs.

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	SR paracetamo			
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)			

The withdrawal rate of 30% is fairly typical of n-of-1 trials [13–15] and indeed typical of many conventional randomized controlled trials [27].

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

Key messages Sustained-release [SR] paracetamol was as effective as celecoxib for most [80%] patients with osteoarthritis whose management is uncertain. N-of-1 trials may provide a rational and effective method to best choose drugs for individuals with osteoarthritis.

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