Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis

A C M Wegman, D A W M van der Windt, M de Haan, W L J M Devillé, C T Chin A Fo, Th P G M de Vries

Objectives: To investigate for individual patients who have been using NSAIDs regularly, whether paracetamol is as effective as non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of pain and disability related to osteoarthritis of the hip or knee.

Methods: A series of n of 1 trials were conducted in general practices in Amsterdam and the surrounding area. Each patient was his or her own control and received five pairs of treatments comprising two weeks of an NSAID and two weeks of paracetamol. For each pair, the order of treatments was randomised. Outcome measures were severity of individual main complaints, intensity of pain, satisfaction with drugs, function test, and side effects.

Results: Thirteen patients were selected. Six patients did not complete the study. For five patients completing the study little or no difference was found between NSAIDs and paracetamol, for one patient the results favoured the NSAID, and for one patient there was no association between outcome and type of drug. It was recommended that six patients changed to paracetamol; the others continued with NSAIDs.

Conclusion: The results of the n of 1 trials varied across patients. n of 1 trials can be used to investigate which treatment is best for any specific person, thus avoiding unnecessary prolonged treatment with NSAIDs. However, practical reasons may cause patients to switch from NSAIDs to paracetamol or not.

Osteoarthritis (OA) is a common musculoskeletal disorder. The prevalence of OA increases with age to over 50% in the knee and about 20% in the hip in women aged 80 years and older. In elderly men the prevalence of OA of the knee is about 25%, and the hip is affected in more than 10%. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for OA. Available evidence from three randomised trials on the relative effectiveness of NSAIDs compared with paracetamol (acetaminophen) for OA of the hip or knee shows consistent, yet modest, differences in their effect on pain in favour of NSAIDs. However, it is generally known that NSAIDs are associated with gastrointestinal complications, whereas paracetamol is associated with very few side effects. Therefore, the national practice guidelines for OA management, issued by the Dutch College of General Practitioners, recommend paracetamol as initial treatment in the treatment of pain and disability related to OA of the knee. Similar recommendations are made in the EULAR guidelines and the British, Canadian, and American guidelines.

The EULAR guideline explicitly emphasises the need to tailor treatment to the individual patient. Indeed, for OA there may be reasonable doubt whether the results of large randomised controlled trials (RCTs) can be generalised to individual patients in general practice. For instance, a patient who consults a general practitioner for chronic knee pain and stiffness may not meet all the selection criteria of the RCTs, reported outcome measures may not be relevant for this specific patient, or the type or dosage of drugs studied in the RCTs may not be similar to the drugs the patient is using. Normally, when a doctor has any doubts about the applicability of treatment recommendations to a specific patient, the trial and error method is used. This means that a particular drug will be prescribed, continued if considered effective, or changed if considered not beneficial. However, the fact that both patient and doctor are aware of the change in treatment can influence the evaluation of its effectiveness. Individual preferences and expectations of both doctor and patient can play an important part in the assessment. If the doctor or the patient doubts the effectiveness of a treatment with a drug, and prefers an objective evaluation, the n of 1 trial is a useful tool.

n of 1 trials are carried out with one patient. The patient is his or her own control and receives several periods of both the intervention treatment and the control treatment. The sequence of treatments is randomised. Because n of 1 trials are meant to evaluate the effects of treatments for each individual patient (and not to estimate the average effect for a larger population), the size of a series of n of 1 trials is of minor importance. Nevertheless, a series of n of 1 trials will be able to demonstrate the potential variation in outcome across patients.

Knowing that patients with OA may continue to use analgesics for a prolonged period of time, it is worthwhile reconsidering drug treatment. This study aimed at investigating for individual patients who have been using NSAIDs regularly, whether paracetamol is as effective as NSAIDs in the treatment of pain and disability related to OA of the hip or knee.

METHODS
Patient selection
Twenty five general practitioners in Amsterdam and the surrounding area were asked to select patients from their medical records. Selection criteria were OA of the hip or knee (as diagnosed by the general practitioner); regular use of

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomised controlled trial
diclofenac, ibuprofen, or naproxen (at least for a period of one month, five days a week); no contraindications for NSAIDs; no contraindications for paracetamol; no corticosteroid injections in the three months preceding the study; no (planned) arthroplasty; and no concomitant physiotherapeutic treatment. Additionally, the patients had to be able to fill in a questionnaire in Dutch. If more than one hip or knee was affected by OA the patient was asked to indicate the joint that caused the most severe complaints.

**Design**

The study comprised a series of n of 1 trials. Each patient received five pairs of treatments starting between November 1998 made 2000. Each pair consisted of a two-week period of NSAID treatment and a two-week period of paracetamol treatment. For each pair of treatments the order of NSAIDs and paracetamol was randomised. The random sequence was prepared in advance by the hospital pharmacist for each patient separately. The patient, the general practitioner and the investigator were unaware of the sequence of treatment. Identical capsules with similar colour, smell, and taste were used to ensure blinding. If necessary, placebos were given, so that the patients received the same number of capsules in all treatment periods. For example, if 1000 mg paracetamol three times daily was compared with 50 mg diclofenac twice daily, the patient received additional placebos once daily in each diclofenac period. The study was approved by the ethics review board of the VU University Medical Centre, and all participating patients gave written informed consent at the start of the study.

**Drug treatment**

During the NSAID treatment periods each patient received the same type of NSAID and, if possible, in the same dosage, as before the start of the study. The dosage of paracetamol was adjusted to the dosage of the NSAID. For example, if a patient took 400 mg ibuprofen three times daily, 1000 mg paracetamol was prescribed three times daily. Maximum dosages were 3000 mg paracetamol divided into three or four doses a day, 400 mg ibuprofen four times daily, 50 mg diclofenac twice daily or 25 mg diclofenac three times daily, and 750 mg naproxen divided into two doses a day. Pill counts were taken to measure compliance.

**Outcome assessment**

Outcomes were assessed by daily diaries and during home visits made by the investigator every two weeks at the end of each treatment period. Because of the possibility of carry-over effects in the first week of each treatment period, only data for the second week of each treatment period were taken into account in the analysis. We considered a washout period of one week sufficient, given the short half life of the NSAIDs for each specific patient. Subsequently, the patients scored their OA.

**Breaking the randomisation code**

Before analysis of the data the randomisation code was partially broken. This means that the type of treatment was indicated as either A or B, without the investigator (AW) knowing whether A or B represented treatment with an NSAID or treatment with paracetamol. Subsequently, recommendations were formulated for further treatment. After analysing and formulating the recommendations, the supervisor (DW) decoded the randomisation completely and conferred with the general practitioner about the results of the trial. Finally, the recommendation was discussed with the patient.

**Analysis**

Because the single case design was used, all outcome measures were analysed for each patient separately. For the second week of each treatment period, median scores were calculated for the total diary score and the individual main complaint. Differences in scores between the NSAID and paracetamol were calculated for each outcome measure. Finally, the proportion of pairs of treatment periods for which treatment A was better than treatment B, and vice versa, was calculated for the primary outcome measures.

**Decisions for future treatment (recommendations)**

The following rules were used to decide on treatment recommendations: firstly, the median difference between treatments for the total diary score had to be at least one point in favour of the NSAID to recommend NSAID treatment, otherwise paracetamol was recommended; secondly, the results for at least 75% of the treatment pairs had to be in favour of the NSAID for at least one of the primary outcome measures (for example, 4/5 pairs) to recommend NSAID treatment, otherwise paracetamol was recommended; and finally, improvements in severe complaints were considered to be more important than improvements in only mild or moderate complaints. Three months after completion of the n of 1 trials, the patients were contacted by telephone and asked to indicate which drugs they were currently using for their OA.
RESULTS

Subjects
A search in the medical records identified 22 patients who were eligible for participation according to their general practitioners. Nine patients were excluded for the following reasons: (a) no actual use of diclofenac, ibuprofen, or naproxen (three patients used paracetamol and one patient piroxicam); (b) no frequent use of NSAIDs (one patient); (c) contraindications for NSAIDs (three patients); and (d) no informed consent (one patient used suppositories and refused oral drugs). Thirteen patients were selected for participation: 11 women and two men (table 1). Their ages ranged between 50 and 91 years (median 77 years). In 12 patients the main problems concerned the knee, and in one the hip. Before the start of the study nine patients were taking diclofenac, ibuprofen, and one naproxen.

Six patients did not complete the study: four because of perceived lack of efficacy, one because of perceived side effects, and one because of concomitant disease and loss of motivation (table 1). After withdrawal, these patients continued to use NSAIDs. Seven patients did complete their 20 week trial period. All seven patients who completed the study took more than 94% of their trial capsules. From the third week, patient No 7 was prescribed additional paracetamol by the general practitioner for concomitant disease. As a consequence, for this patient the first two weeks could not be compared with the other 18 weeks, and only four pairs of treatments could be analysed.

Effectiveness of paracetamol compared with NSAID
In five patients who completed the study there was little or no difference in outcome between NSAIDs and paracetamol, and paracetamol was recommended (patients Nos 1, 3, 4, 5, 9). In two patients (patients Nos 6 and 7) the median difference between treatments for the total diary score was one point in favour of NSAIDs (table 2). The percentage of pairs in which NSAIDs were favoured above paracetamol was >75% for at least one of the primary outcome measures in both these patients. However, the improvements in complaints for patient No 7 mainly concerned changes from mild to very mild, whereas in patient No 6 improvements in complaints in favour of the NSAID were from severe to moderate. For these reasons, only patient No 6 was recommended to continue with NSAID treatment. For the other patients who completed the study (including patient No 7) paracetamol treatment was recommended.

Side effects and co-interventions
There were no differences in the occurrence of side effects between the NSAID and the paracetamol treatment periods. The patient who did not complete the study because of perceived side effects reported increasing stomach complaints during treatment with both diclofenac and paracetamol (patient No 11). There were no differences in co-interventions between the NSAID and the paracetamol treatment periods. Patient No 10 had back pain and used more additional paracetamol as the study progressed. She finally withdrew from the study after eight weeks.

Treatment policy
Table 2 presents the treatment which the general practitioners thought to be best for each patient before the start and at the end of the study for the seven patients who completed the study. In general, after completion of the n of 1 trials, the general practitioners were at least as certain about their treatment preferences as before the n of 1 trials.

Table 1 Patient characteristics and reasons for withdrawal of 13 participants with OA of the hip or knee in a series of n of 1 trials

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex (M/F), age, joint</th>
<th>Drug treatment before the start of the trial</th>
<th>Trial drug</th>
<th>Number of weeks completed, reasons for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 71, hip</td>
<td>3×day 400 mg ibuprofen</td>
<td>3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>M, 82, knee</td>
<td>3×day 50 mg diclofenac</td>
<td>2×day 50 mg diclofenac v 3×day 1000 mg paracetamol</td>
<td>0 (only 3 days): Perceived lack of efficacy (stiffness)</td>
</tr>
<tr>
<td>3</td>
<td>F, 80, knee</td>
<td>(sometimes 4) ×day 400 mg ibuprofen</td>
<td>3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>F, 91, knee</td>
<td>Mostly 1×day 50 mg diclofenac (sometimes more)</td>
<td>1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>M, 50, knee</td>
<td>1×day 50 mg diclofenac</td>
<td>1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>F, 54, knee</td>
<td>or 2×day 500 mg naproxen</td>
<td>1×day 250 mg naproxen and 1×day 500 mg naproxen v 3×day 1000 mg paracetamol</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>F, 73, knee</td>
<td>1×day 50 mg diclofenac</td>
<td>1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol. After 2 weeks she was prescribed 1000 mg additional paracetamol because of concomitant disease (gout)</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>F, 62, knee</td>
<td>or 2×day 100 mg diclofenac</td>
<td>2×day 50 mg diclofenac v 2×day 1000 mg paracetamol*</td>
<td>4: Perceived lack of efficacy (pain)</td>
</tr>
<tr>
<td>9</td>
<td>F, 82, knee</td>
<td>1×day 75 mg diclofenac and 500 mg paracetamol</td>
<td>1×day 25 mg diclofenac and 1×day 50 mg diclofenac v 3×day 1000 mg paracetamol (after 4 weeks 2×day 1000 mg paracetamol)</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>F, 72, knee</td>
<td>1×day 50 mg diclofenac, sometimes 2×day 50 mg diclofenac</td>
<td>1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 1000 mg paracetamol</td>
<td>8: Concomitant disease (back pain) and loss of motivation</td>
</tr>
<tr>
<td>11</td>
<td>F, 77, knee</td>
<td>3×day 50 mg diclofenac</td>
<td>2×day 50 mg diclofenac v 3×day 1000 mg paracetamol</td>
<td>4: Perceived side effects (stomach complaints and nausea)</td>
</tr>
<tr>
<td>12</td>
<td>F, 79, knee</td>
<td>3×day 50 mg diclofenac</td>
<td>2×day 50 mg diclofenac v 3×day 1000 mg paracetamol</td>
<td>2: Perceived lack of efficacy (pain)</td>
</tr>
<tr>
<td>13</td>
<td>F, 90, knee</td>
<td>3×day 400 mg ibuprofen (and almost every day 500 mg paracetamol/codeine, sometimes also 1×day 500 g paracetamol)</td>
<td>3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol</td>
<td>4: Perceived lack of efficacy (pain)</td>
</tr>
</tbody>
</table>

*The patient received 2000 mg instead of 3000 mg paracetamol daily because of alcohol use (about six units a day).
### Table 2  Results of the seven patients who completed the n of 1 trials: outcome measures, recommendations, drugs after three months, and confidence

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Joint</th>
<th>Most important complaint</th>
<th>Function test</th>
<th>Total diary score</th>
<th>Individual main complaint</th>
<th>Pain</th>
<th>Satisfaction</th>
<th>Function test (seconds)</th>
<th>Total diary score</th>
<th>Individual main complaint</th>
<th>Pain</th>
<th>Recommend</th>
<th>Drug treatment after 3 months</th>
<th>Proportion of pairs N−P for the primary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Pain during standing up</td>
<td>W</td>
<td>0 (3, 3)</td>
<td>0 (3, 3)</td>
<td>−1</td>
<td>6, 7</td>
<td>0 (2, 2)</td>
<td>0.5 (10.5, 10.4)</td>
<td>1/5</td>
<td>1/5</td>
<td>3/5</td>
<td>P N</td>
<td>0 (N, P)</td>
</tr>
<tr>
<td>3</td>
<td>K</td>
<td>Pain walking</td>
<td>W</td>
<td>−0.5 (3, 3.5)</td>
<td>0 (4, 4)</td>
<td>0</td>
<td>6, 6</td>
<td>0 (3, 3)</td>
<td>0 (2, 2)</td>
<td>0 (2.1)</td>
<td>2/5</td>
<td>1/5</td>
<td>P N</td>
<td>1 (N, P)</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>Pain during walking</td>
<td>W</td>
<td>0 (2.5, 2.5)</td>
<td>0 (3, 3)</td>
<td>0.7</td>
<td>7, 7</td>
<td>0 (2, 2)</td>
<td>0.7 (16.0, 16.9)</td>
<td>0/5</td>
<td>0/5</td>
<td>3/5</td>
<td>P N</td>
<td>0 (N, N)</td>
</tr>
<tr>
<td>5</td>
<td>K</td>
<td>Pain during sleeping</td>
<td>W</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0</td>
<td>0, 0</td>
<td>0 (0, 0)</td>
<td>0.2 (68.6, 6.6)</td>
<td>0/5</td>
<td>0/5</td>
<td>3/5</td>
<td>P N</td>
<td>1 (N, N)</td>
</tr>
<tr>
<td>6</td>
<td>K</td>
<td>Pain during sleeping</td>
<td>ST</td>
<td>−1 (3.4)</td>
<td>−1 (3.4)</td>
<td>0</td>
<td>7, 8</td>
<td>0 (3, 5)</td>
<td>−0.8 (20.8, 16.9)</td>
<td>4/5</td>
<td>4/5</td>
<td>2/5</td>
<td>N N</td>
<td>1 (N, N)</td>
</tr>
<tr>
<td>7</td>
<td>K</td>
<td>Pain during standing up</td>
<td>S</td>
<td>−1 (1.2)</td>
<td>−0.5 (1.2)</td>
<td>−3</td>
<td>3, 5.5</td>
<td>0.5 (1.5, 1)</td>
<td>0.8 (18.6, 18.9)</td>
<td>3/4</td>
<td>2/4</td>
<td>3/4</td>
<td>P N</td>
<td>1 (P, P)</td>
</tr>
<tr>
<td>9</td>
<td>K</td>
<td>Pain during standing up</td>
<td>W</td>
<td>0 (3, 3)</td>
<td>0 (3, 3)</td>
<td>−1</td>
<td>6, 7</td>
<td>0 (2, 2)</td>
<td>−3.6 (20.2, 22.7)</td>
<td>1/5</td>
<td>1/5</td>
<td>3/5</td>
<td>P N</td>
<td>0 (P, P)</td>
</tr>
</tbody>
</table>

H, hip; K, knee; W, walking; ST, walking stairs; S, sitting and standing up; N, NSAID; P, paracetamol.

*Negative scores favour NSAIDs; †scores range between 0 = no complaints and 6 = unbearable complaints for the total diary score and the individual main complaint, between 0 = no pain and 10 = very severe pain for the intensity of pain, and between 0 = very satisfied and 6 = very dissatisfied for the satisfaction with drugs; ‡confidence of general practitioner in the preferred drug at the start of the study minus at the end of the study. Positive scores indicate that the general practitioner is more certain after the study; ‡walking upstairs; ‡walking downstairs; ‡data of only four pairs could be compared.

### DISCUSSION

Follow up from the n of 1 trials was due to subtherapeutic dosages of drugs during the study. A series of n of 1 trials will be able to demonstrate the potential variation in outcome across the participants, but only if a large proportion of the participants complete their trial. However, drop out from an n of 1 trial is an important issue. The potential variation in outcome across the participants, but only if a large proportion of the participants complete their trial. However, drop out from an n of 1 trial is an important issue.

Three months after the end of the study, four of the six patients who had been recommended paracetamol treatment for OA on the basis of the n of 1 trials had taken NSAIDs, one because of a misunderstanding of the instructions, one because of lack of efficacy, and one because of a lack of drug compliance. The patients who had been recommended paracetamol treatment for OA on the basis of the n of 1 trials had taken NSAIDs, one because of a misunderstanding of the instructions, one because of lack of efficacy, and one because of a lack of drug compliance. The patients who had been recommended paracetamol treatment for OA on the basis of the n of 1 trials had taken NSAIDs, one because of a misunderstanding of the instructions, one because of lack of efficacy, and one because of a lack of drug compliance.
outcome itself. As stated above, four of the six patients who
did not complete their trial almost certainly withdrew
because of subtherapeutic dosages of drugs during the study.
Therefore, we suggest that future research should consider
comparing paracetamol with NSAIDs in the actual dosage
taken by the patient just before the start of the study. In this
way, we believe that drop out can be prevented in many cases.
March et al and Nikles et al conducted n of 1 trials in
patients with OA, using three pairs of treatment periods
consisting of paracetamol and diclofenac or paracetamol
and ibuprofen. The proportion of patients who did not
complete their trial in our series (46%) is comparable with
the results for these two other series (40% and 43%).

Although a direct comparison is difficult because of
differences in selection criteria, drugs, and outcome mea-
sures, all three studies show that for some patients
paracetamol is as effective as NSAIDs. However, there is a
large variation in outcome among individual patients. The
results of these three studies show that for some patients
paracetamol is as effective as NSAIDs, but that there is a
large variation in outcome among individual patients. The
series by March et al received some criticism of the statistical
analysis and the interpretation of the results. March et al
considered paracetamol as the preferred drug if diclofenac
was not significantly better than paracetamol. However, each
patient received only three pairs of treatments, which limited
the statistical power to detect treatment differences.

In our study each patient received five pairs of treatments.
In contrast with March et al, we used the individualised
questionnaire developed by Guyatt et al for n of 1 trials. This
questionnaire examines the severity of symptoms as identi-
fied by the individual patient and scored by the patient on
seven point ordinal scales. Our data were not suitable for quan-
titative analysis, partly owing to the non-normal distribution
of the data. More importantly, we did not investigate whether one
treatment was better than the other, but whether one treatment
was as effective as the other. In other words, the n of 1 trials
were equivalence trials, rather than superiority trials. This
implies that conventional significance testing could not be
used for analysis and for formulating recommendations. Therefore,
we applied decision rules, which were formulated in advance.
Although these rules can be considered to be
arbitrary, for five of the seven patients who completed the
study the differences between NSAIDs and paracetamol were
very small and the recommendations were straightforward
(table 2). In two patients (Nos 6 and 7) the decision rules
were very helpful in deciding on recommendations.

In conclusion, the results of the n of 1 trials varied across
patients (fig 1). These findings support the assumption that
the best treatment for OA differs in individual patients.
However, there is, as yet, insufficient evidence about which
factors predict which patient can or cannot successfully
switch from NSAIDs to paracetamol. Therefore, an n of 1 trial
can be used to investigate which treatment is best for any
specific individual patient. Practical reasons, such as the size
or the number of tablets that needs to be taken, may play an
important part in a patient’s decision to switch from NSAIDs
to paracetamol or not. Therefore, before the start of the n of 1
trial, patients should be well informed about the objectives
and consequences of the trial. When the results of the trial
become available patients should be well instructed to follow
the recommendations. In this way, unnecessary prolonged
treatment with NSAIDs may be avoided in patients with
complaints due to OA of the hip or knee.

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