Rheumatology 2000;39:714–719

A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee

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Abstract

Objective. To evaluate the efficacy and safety of a homeopathic gel *vs* an NSAID (piroxicam) gel in the treatment of osteoarthritis of the knee.

Method. One hundred and eighty-four out-patients with radiographically confirmed symptomatic osteoarthritis of the knee were entered into a pragmatic, randomized, double-blind controlled trial and treated with 1 g of gel three times daily for 4 weeks. Main outcome measures were pain on walking as a Visual Analogue Score (VAS) and a single-joint Ritchie index.

Results. One hundred and seventy-two of the 184 enrolled patients had endpoints for the main outcome parameters. The pain reduction was 16.5 mm VAS in the homeopathy group ($n = 86$) and 8.1 mm in the piroxicam group ($n = 86$); the difference between treatment groups was 8.4 mm (95% confidence interval 0.8–15.9), and after adjustment for pain at baseline it was 6.8 mm (95% confidence interval –0.3 to 13.8). There was no significant difference between treatment groups in the single-joint Ritchie index ($P = 0.78$). Adverse events occurred in 28 patients (12 homeopathy group, 5 withdrawn; 16 piroxicam group, 9 withdrawn); 18 of the events involved a local reaction (7 homeopathy group, 2 withdrawn; 11 piroxicam group, 5 withdrawn).

Conclusion. The homeopathic gel was at least as effective and as well tolerated as the NSAID gel. The presence of a clinically relevant difference between treatment groups cannot be excluded. The homeopathic gel supplemented by simple analgesics if required may provide a useful treatment option for patients with osteoarthritis.

KEY WORDS: Homeopathy, Topical NSAIDs, SRL® gel, piroxicam gel, Randomized controlled trial.

Mild to moderate osteoarthritis is often treated with non-steroidal anti-inflammatory drugs (NSAIDs). However, treatment with oral NSAIDs is not always effective and may have significant side-effects [1–3]. As a safe alternative to oral NSAIDs, a number of topical NSAIDs are now available in many countries and their use is increasing: in the UK alone, £33 million (approximately US$50 million) was spent on prescribed topical NSAIDs in 1997 (Prescription Pricing Authority data). Apart from this, the over-the-counter market for topical NSAIDs is growing rapidly. Between June 1996 and June 1997 more than 15 million tubes were sold in the UK alone, a growth of 43% over the previous year (Institute for Medical Statistics, UK). For a long time, evidence of the efficacy of topical NSAIDs was inconclusive [4–6]. Recently, a quantitative systematic review of topical NSAIDs [7] concluded that these products are effective in relieving pain.

Hahnemann, the founder of homeopathy, first suggested the possibility of administering homeopathic medicines via the skin [8]. Recently, the topical administration of homeopathic medicines has rapidly gained in popularity. In The Netherlands, SRL® (current trade name Spiroflor SRL®; the trade name is used because SRL® gel does not have a chemical name or an international non-proprietary name), a gel containing three homeopathic ingredients, is one of the topical antirheumatic preparations most frequently prescribed by Dutch general practitioners [9, 10]. Very similar products are on the market in several European countries and in the USA (e.g. Triflora® gel). However, evidence of efficacy from rigorous, controlled trials is lacking. We conducted a pragmatic, randomized, double-blind controlled trial comparing SRL® gel with piroxicam gel in osteoarthritis of the knee. The main hypothesis under investigation was that SRL® gel is as effective as piroxicam gel. We therefore aimed to

Submitted 16 November 1999; revised version accepted 10 January 2000.

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compare the efficacy and safety of SRL® and piroxicam gel and to establish the clinical relevance of the observed effects. Analysis was according to the latest principles laid down for equivalence trials [11]. This analytical approach was adopted after the trial was completed but prior to commencement of the analyses. A 'per protocol' compliers-only analysis was specified *a priori*. No specific covariate analyses were defined *a priori*.

Methods

Protocol

Patients were recruited and treated at the out-patients rheumatology clinic of St Bartholomew's Hospital and also recruited from St Leonard's and Homerton Hospitals, London. Eligibility criteria are listed in Table 1. Previous use of SRL® gel was not an exclusion criterion because it was not available on the UK market. The radiographic confirmation of the diagnosis was based on a report by an independent radiologist of an X-ray of the knees within the previous 6 months. The radiological criteria for diagnosis of osteoarthritis were narrowing of the joint space and/or the presence of osteophytes or tibial spiking, with or without effusion.

Demographic and baseline data collected were age, sex, weight, pain in the knee on movement (moderate/severe), information regarding other illnesses, and use of other drugs for osteoarthritis and other conditions. Patients were seen twice for the purpose of this trial: at recruitment/baseline and after 4 weeks of treatment. There were no prospectively defined stopping rules.

SRL® gel contains the homeopathic ingredients *Symphytum officinale* (comfrey), *Rhus toxicodendron* (poison ivy) and *Ledum palustre* (marsh-tea). It was manufactured by VSM Geneesmiddelen (The Netherlands) in accordance with the official German Homeopathic Pharmacopoeia [12]. Piroxicam gel (Feldene®) contains 0.5% piroxicam and was manufactured by Pfizer Ltd UK.

Patients were instructed to apply approximately 1 g of gel three times daily. For application, a spatula with a sticker indicating the length of approximately 1 g of gel was supplied. If both knees were affected, only the knee with the most clinically evident osteoarthritis was treated and evaluated. Treatment compliance was estimated by weighing returned tubes of study medication. Paracetamol up to 3 g per day was allowed as a rescue analgesic. Oral NSAIDs and any other medication were continued during the trial. Patients were not given specific additional instructions with regard to exercise, restriction of activities, etc.

Table 1. Criteria for eligibility

Inclusion criteria
Radiographically confirmed osteoarthritis of the knee
At least moderate pain on movement in the affected knee
Age between 18 and 86 years
If oral NSAIDs and/or analgesics were taken, stable treatment during the previous month
Exclusion criteria
Oral piroxicam 7 days prior to or at any time during the trial
Previous use of piroxicam gel
Additional joint disease other than osteoarthritis
Skin affections on the treated knee
Known hypersensitivity to NSAIDs or to *Rhus toxicodendron*
Severe osteoarthritis requiring surgical intervention
Non-ambulant patients (Steinbrocker functional class 4)

Primary outcome measures were pain on walking during the previous 24 h, recorded on a 100 mm Visual Analogue Scale (VAS) [13], and pain on palpation of the affected knee, scored according to Ritchie *et al.* [14] (0 = no pain, 1 = pain without wincing, 2 = pain with wincing, 3 = pain leading to withdrawal). Secondary outcome measures were the number of paracetamol tablets (rescue analgesic) used and an overall assessment by the investigator and the patient on a six-point scale ('worse than useless', 'useless', 'poor', 'fair', 'good', 'excellent'). Patients also completed a weekly score on a 100 mm VAS indicating relief obtained during the preceding week.

Based on the literature available on piroxicam gel at the time of protocol development, the recruitment target was set at 225 patients in order to obtain about 200 patients with outcome data (similar to n in the largest piroxicam gel trial). A formal power calculation was not conducted because of the complete absence of data on the effect of treatment on VAS when the study was designed.

Because the use of a single-joint Ritchie score for osteoarthritis is uncommon, it was not possible to define a minimum clinically important difference. Based on the literature [15] and consensus in the Department of Rheumatology at St Bartholomew's Hospital, 5 mm on a VAS for pain on walking was defined as a minimum clinically important difference (equivalence range: -5 mm to $+5$ mm) prior to the initiation of the analyses. Analysis of the VAS data was based on the latest available guidelines for the analysis of equivalence trials [11], which involves the use of 95% confidence intervals in relation to the equivalence range. To enable the use of confidence intervals, the population with a follow-up measurement (endpoint) was used. All other main analyses of outcome were based on the intention-to-treat population (all patients randomized), using the convention that missing values assume the worst possible outcome.

Adjustment for covariates with pain reduction (mm VAS) as a dependent variable was achieved by analysis of covariance after the validity of the model had been verified (i.e. parallel regression slopes). The contingency tables of the change in Ritchie score and the investigators' and patients' overall assessment were analysed using the Exact Mann–Whitney U-test.

The study was conducted along the lines of the guidelines for Good Clinical Practice: ethical approval was obtained, patients gave written informed consent, monitoring during the trial included source document verification, and data management involved double data entry and logical checks. Statistical analyses were

conducted using SPSS for Windows version 7.0 (SPSS Inc., USA). Statistical testing was two-tailed.

Assignment

The unit of randomization was individual patients entered. Treatment allocation was based on randomization in blocks of four using randomization software (RCODE version 3.4, Schwabe, Germany) at the Research Department of VSM Geneesmiddelen. A special randomization list was printed to allow the treatment code to be broken for individual patients in exceptional circumstances. Treatment assignment was done at inclusion by the clinical metrologist, and was based on the lowest unused randomization number.

Masking

Both products are carbomer-based gels of similar consistency, but they differ in appearance and smell: SRL® gel is brownish in colour (due to the tinctures for external use) and has a characteristic odour (due to the addition of pine oil). Because it was intrinsically impossible to make both treatments identical, or to use the double-dummy technique, the original SRL® (80 g) and piroxicam (60 g) tubes were used. Masking was achieved by sealing the tubes in a double layer of opaque blue plastic. The standard blue ribbed caps of piroxicam gel tubes were replaced by white caps of a different shape and size. The patient received a sealed, numbered box containing the study medication and rescue analgesics and was instructed to open it only on returning home, making sure the clinical metrologist did not see its contents. Treatment masking was broken for each patient, after all other measurements had taken place, when the clinical metrologist checked whether the study drugs and all strips of used and unused rescue analgesics were returned. There were no differences in expected drug (side) effects which could have affected masking. Discussion between subjects was unlikely: patients did not know which other patients had been included in the study and were given separate (only one) follow-up appointments. A sealed full randomization list and the special list enabling individual code-breaks was available at St Bartholomew's Hospital.

The treatment codes were not broken for any patient. In one patient unintentional damage to the plastic masking of the tube was reported. Four patients (two SRL, two piroxicam) deliberately opened the covering.

Results

Participant flow and follow-up

In total, nine patients (six SRL®, three piroxicam) discontinued the trial (Fig. 1). In three patients on piroxicam who completed the trial, not all outcome measures were obtained for the following reasons: case report form mislaid; no baseline assessments due to misunderstanding; patient didn't understand the VAS concept.

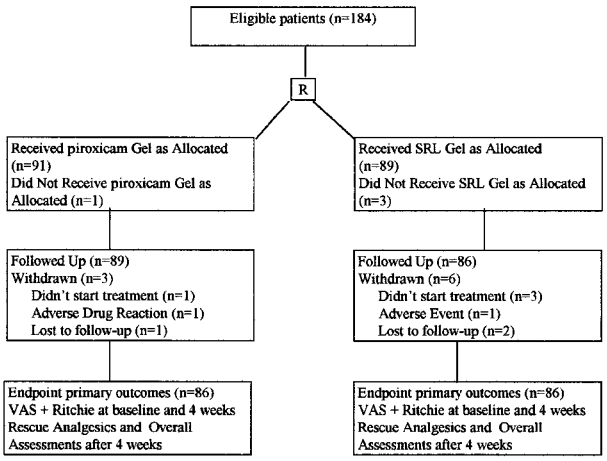


FIG. 1. Trial profile.

Analysis

Due to local administrative problems, recruitment suffered such delays that it was decided to stop the trial after184 patients had enrolled. One hundred and seventy-two patients had endpoints for the main outcome parameters. Three patients had violations of the eligibility criteria: one was 87 years old, in one there was no radiographic confirmation of osteoarthritis, and one was not stable on oral NSAIDs.

Baseline characteristics were similar in the two treatment groups (Table 2). 180 patients returned the tubes with study medication. Daily gel use was 3.3 g in the SRL® group and 2.7 g in the piroxicam group, an average treatment compliance of 110% (95% confidence interval 99–121) in the SRL® group and 90% (95% confidence interval 83–97) in the piroxicam group. Fifty-seven patients (64%; 26% <80% compliance + 38% >120% compliance) in the SRL® group and 51 (56%; 40% <80% compliance + 16% >120% compliance) in the piroxicam group were outside the prespecified compliance range of 80–120%. This indicates that SRL® patients tended to be overcompliant and piroxicam patients undercompliant.

TABLE 2. Characteristics of patients in the treatment groups. Figures are mean (SD) unless stated otherwise

Characteristic	SRL®	Piroxicam
No. of patients	92	92
Age (years)	65.3 (8.8)	63.1 (9.5)
Sex (male:female)	21:71	27:65
Weight (kg)	80.7 (16.2)	79.9 (16.2)
Other illness (no. of patients)	61	53
Median duration of other illness (25–75 percentiles)	5.0 (1.9–12.5)	6.7 (3.1–11.5)
Other drugs for osteoarthritis (no. of patients)	62	57
Extent of pain on movement (moderate, severe)	46, 46	50, 42
Pain on walking (mm VAS)	59.8 (21.8)	56.4 (20.7)
Single-joint Ritchie index (0:1:2:3)	16:23:34:19	24:21:38:8

Pain reduction and adverse events

Mean pain reduction was 16.5 mm (S.D. 24.6) VAS in the SRL® group and 8.1 mm (S.D. 25.7) in the piroxicam group, an 8.4 mm (95% confidence interval 0.8–15.9) difference between treatment groups (Fig. 2). A full factorial analysis of covariance took place, including the potential confounders 'tablets rescue analgesics taken' ($F = 0.18$; $P = 0.67$) and 'pain at baseline' ($F = 26.6$; $P = 0.00$) after model validity had been confirmed. In a stepwise procedure 'tablets rescue analgesics taken' was removed. The difference between treatment groups adjusted for pain at baseline was 6.8 mm (95% confidence interval −0.3 to 13.8). This confidence interval did not lie entirely inside the equivalence range (− 5 to +5), which means that the presence of a clinically relevant difference between the two treatments (i.e. superiority of SRL® gel) cannot be excluded. Additionally, the VAS reduction in the intention-to-treat population was analysed assuming the worst observed outcome (− 68 mm) for missing data. This meant that the distribution of the VAS outcome data was non-normal. Therefore the non-parametric Mann–Whitney *U*-test was used (mean rank, SRL® group 100.7; mean rank, piroxicam group 84.3, $P = 0.036$).

Changes in the single-joint Ritchie index ranged from −2 to +2. Results for the SRL® group were as follows: −2 ($n = 10$), −1 ($n = 8$), 0 ($n = 45$), +1 ($n = 23$), +2 ($n = 6$), including six missing values recoded to −2, the worst possible outcome. Results for the piroxicam group were as follows: −2 ($n = 5$), −1 ($n = 15$), 0 ($n = 46$), +1 ($n = 19$), +2 ($n = 7$), including five missing values recoded to −2. There was no difference in the Ritchie index between treatment groups in the intention-to-treat population (χ^2 test, $P = 0.37$) and in the subset with an endpoint (χ^2 test, $P = 0.159$).

Fifty-six patients (61%) in the SRL® group (including six recoded missing values) used paracetamol as a rescue analgesic *vs* 58 (63%) in the piroxicam group (including four recoded missing values) (χ^2 test, $P = 0.76$). The number of tablets used in this subpopulation ($n = 114$) was slightly less in the SRL® group (mean rank 52.8) than in the piroxicam group (mean rank 62.0), assuming the worst observed outcome (80 tablets) in patients with missing data (Mann–Whitney *U*-test, $P = 0.138$).

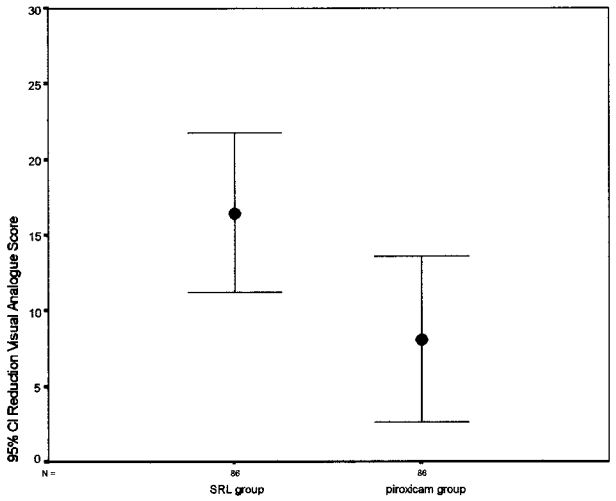


FIG. 2. Mean pain reduction (mm VAS) according to treatment group, with 95% confidence intervals.

The overall assessments of the usefulness of the study gel by the investigator and patient are given in Table 3. The χ^2 test for the investigator assessment yielded $P = 0.19$. The χ^2 test for the patient assessment yielded $P = 0.06$. The subset with an endpoint yielded similar results: $P = 0.27$ for the investigator and $P = 0.05$ for the patients. In the investigator endpoint table, four cells (33.3%) have an expected count of < 5, which means that the corresponding *P*-value may not be completely valid. These results indicate a trend in favour of SRL® gel.

Adverse events are summarized in Table 4. Local reactions to SRL® gel were generally mild, ranging from transient itchiness around the site of application to transient burning sensations and redness. Local reactions to piroxicam were similar to those to SRL® gel but additionally three patients developed an itchy dermatitis in the area of application. One patient in the piroxicam group developed a generalized itchy dermatitis. In these four patients the relationship between the adverse event and the study drug was rated as 'definite' by the rheumatologist.

Unexpectedly, a significant interaction was found between the use of pain medication (oral NSAIDs and/or analgesics) and treatment. Between-treatment differences (adjusted for the VAS at baseline) were 0.3 mm (in favour of SRL®) in the pain medication users ($n = 106$; 55 SRL®, 51 piroxicam; 95% confidence interval −8.5 to 9.1) and 17.2 mm (in favour of SRL®) in the non-users of pain medication ($n = 66$; 31 SRL®,

TABLE 3. Investigators' and patients' overall assessment of the usefulness of the treatment

	Worse than useless[a]	Useless	Poor	Fair	Good	Excellent	Total
Investigator							
SRL®	8 (6)	16	13	23	27	5	92
piroxicam	4 (3)	24	16	29	15	4	92
Patient							
SRL®	7 (6)	19	9	19	30	8	92
piroxicam	6 (4)	22	10	34	14	6	92

[a]The number of patients with missing data recoded to 'worse than useless' is given in parentheses.

TABLE 4. Summary adverse event-related analyses (number of patients)

	SRL®	piroxicam
Occurrence of adverse events	12	16
Withdrawn due to adverse event (yes, no)	5, 7	9, 7
Local reactions	7	11
Withdrawn due to local reaction (yes, no)	2, 5	5, 6
Definite relationship with study drug	0	4
Maximum severity (mild, moderate, severe)	7, 3, 2	7, 4, 5

35 piroxicam; 95% confidence interval 5.9–28.4). Further analysis of the 170 patients for whom the exact nature of the pain medication could be established revealed that this difference was largely due to piroxicam gel being effective mainly in patients taking oral NSAIDs ($n = 33$; 16.0 mm VAS reduction) and relatively ineffective in patients receiving simple analgesics or no pain medication ($n = 51$; 1.4 mm VAS reduction).

Discussion

The significantly higher average daily amount of gel used in the SRL® group may in part be explained by the difference in tube aperture, but it can also be argued that more gel is likely to be used if it appears effective. The latter assumption was supported by an exploratory analysis in the SRL® group, which showed that patients with a greater use of gel tended to have greater pain reduction (data not shown).

Pain on palpation, scored as a single-joint Ritchie Index, was chosen in an attempt to obtain an independently assessed, objective outcome parameter. In retrospect, there is no clear justification for its use because this parameter is not validated for use in osteoarthritis. When this study was designed (1992) there was no international consensus on outcome measures for osteoarthritis. Even now, consensus is not complete. However, a consensus is emerging [16], and this study examined two of the three recommended outcome measures (pain and patient global assessment).

The concordance of the primary and secondary outcome measures adds further weight to the evidence for superior pain reduction in the SRL® group.

Although several precautions were taken, masking was inevitably imperfect in this trial. However, we felt that the imperfect masking was unlikely to be a major cause of bias because both the patient and the investigators were assuming that two active products were being compared with the aim of showing equivalence.

Although this is not formally recorded, very few eligible patients refused to enter the trial. The inclusion criteria were such that few patients who might otherwise have been treated with a topical gel were excluded. Similar results were obtained with SRL® gel in 95 patients with clinical manifestations of osteoarthritis in an open trial in general practice (24 mm VAS reduction after 4 weeks) [17].

Post hoc analysis was performed on the significant interaction between treatment and use of oral pain medication. The result suggested that, contrary to the results of an open study [18], topical piroxicam is effective only when used alongside oral NSAIDs. Although this analysis was mainly hypothesis-generating, we felt the size as well as the clinical importance of this finding justified reporting it. Since a systemic action of topical piroxicam is unlikely because of low absorption [19], a possible explanation is that topical application of piroxicam, when used with oral NSAIDs, boosts the local concentration of the drug. However, when used as a monotherapy, piroxicam gel appears to give subtherapeutic concentrations. If confirmed, this finding would remove one of the main rationales for the use of NSAID gels, which is to avoid the systemic side-effects of oral NSAIDs.

Although it might be claimed that SRL® gel is a herbal remedy because it contains tinctures of herbal ingredients, it is officially registered as a homeopathic medicine in The Netherlands. Its 'homeopathicity' is related to the nature rather than the dilution of its ingredients: its main ingredients are widely used in homeopathy for rheumatological conditions [20], and it is manufactured according to the German Homeopathic Pharmacopoeia.

We are aware of eight published controlled clinical trials of homeopathy for rheumatological conditions [21, 22], two of them in osteoarthritis, one positive [22] and one negative [23].

Some authors have expressed doubts about the appropriateness of the use of NSAIDs in osteoarthritis because of its minor inflammatory component [24]. It has not been established unequivocally that oral NSAIDs are more effective in controlling symptoms of osteoarthritis than simple analgesics [24, 25]. Empirical evidence suggests that many long-term NSAID users can be safely switched to simple analgesics without compromising their pain relief [26]. Strategies to take patients off oral NSAIDs are important because a reduction in mortality and morbidity from NSAID side-effects, as well as the use of cheaper drugs, could lead to substantial savings.

This study provides some evidence that the homeopathic gel used is more active than placebo. However, this cannot be proved from the study in its present design. For this, an additional placebo-controlled trial in patients with no use of oral NSAIDs (to be washed out if used) and limited use of paracetamol would be needed. A placebo-controlled, multicentre trial of this nature (involving 214 patients with symptomatic primary osteoarthritis of the knee) was recently conducted in The Netherlands and Belgium (in preparation). As mentioned above, an investigation of the role of the homeopathic gel in taking patients off oral NSAIDs is of particular clinical as well as economic relevance.

The meta-analysis by Moore *et al.* [7] has shown that topical NSAIDs are more efficacious than placebo. This has led to a shift of emphasis in the debate on the therapeutic role of topical NSAIDs. Topical NSAIDs should be compared with other (cheaper) topical products and treatment regimens [27] in order to find out whether prescribing them is appropriate. Our study contributes to this emerging research agenda. The homeopathic gel investigated here, with the addition of simple analgesics if required, may provide a useful treatment option for patients with osteoarthritis.

Acknowledgements

We thank T. Huskisson, J. Dacre and D. D'Cruz for being principal investigators, the clinical metrologists Penny Crofts and Rachel Bryans, Paul Duijzings for

monitoring the trial, Christine Stam for clinical data management and Janice Thomas for her role as advisory statistician. The study was supported by a research grant from the Medical Scientific Department of VSM Geneesmiddelen, The Netherlands.

References

1. Henry D, Lim LLY. Garcia Rodriquez LA, Perez Gutthann SP, Carson JL, Griffin M *et al*. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J 1996;312:1563–6.
2. Palmer BF, Henrich WL. Systemic complications of non-steroidal anti-inflammatory drug use. Adv Intern Med 1996;41:605–39.
3. Simon LS. Actions and toxicity of nonsteroidal anti-inflammatory drugs. Curr Opin Rheumatol 1995;7:159–66.
4. Doogan DP. Topical non-steroidal anti-inflammatory drugs. Lancet 1989;2:1270–1.
5. Anonymous. Topical NSAIDs: a gimmick or a godsend? Lancet 1989;2:779–80.
6. Anonymous. More topical NSAIDs: worth the rub? Drugs Ther Bull 1990;28:27–8.
7. Moore RA, Tramèr MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. Br Med J 1998; 316:333–8.
8. Hahnemann S. Organon of medicine (translated by Kunzli J, Naude A, Pendleton P). Blaine, WA: Cooper Publishing Company, 1982.
9. Hameleers C. Homeopathie en huisarts; een onderzoek naar de prescriptie van homeopathische middelen door huisartsen in Nederland [thesis]. Rijksuniversiteit Limburg, Maastricht, 1991.
10. Medische Index Nederland. Den Haag: Instituut Medische Statistiek Nederland, juli-sept 1994.
11. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. Br Med J 1996;313:36–9.
12. Homöopathisches Arzneibuch. Stuttgart: Deutscher Apotheker Verlag, 1978–1985.
13. Huskisson EC. Measurement of pain. Lancet 1972;2: 1127–31.
14. Ritchie DM, Boyle JA, McInnes JM *et al*. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393–406.
15. Tugwell P, Boers M, Baker P, Wells G, Snider S. Endpoints in rheumatoid arthritis. J Rheumatol 1994(Suppl 42);21: 2–8.
16. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P *et al*. Recommendations for a core set of outcome measures for future Phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799–802.
17. Haselen van RA, Bol AWJM, Wijnsma R. Mogelijkheden en beperkingen van verschillende vormen van klinisch onderzoek. Een illustratie vanuit het perspectief van effectiviteitsonderzoek in de homeopathie. Tijdschr Integr Geneeskd 1996;12:7–12.
18. Browning RC, Johson K. Reducing the dose of oral NSAIDs by use of Feldene gel: An open study in elderly patients with osteoarthritis. Adv Ther 1994;11:198–207.
19. Marks R, Dykes P. Plasma and cutaneous drug levels after topical application of piroxicam gel: a study in healthy volunteers. Skin Pharmacol 1994;7:340–4.
20. Hershoff A. Homeopathy for musculoskeletal healing. Berkely, CA: North Atlantic Books, 1996.
21. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV *et al*. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet 1997;350:834–43.
22. Nahler G, Metelmann H, Sperber H. Treating osteoarthritis of the knee with a homeopathic preparation. Biomed Ther 1998;16:186–91.
23. Shipley M, Berry H, Broster G, Jenkins M, Clover A, Williams I. Controlled trial of homoeopathic treatment of osteoarthritis. Lancet 1983;1:97–8.
24. Dieppe PA, Frankel SJ, Toth B. Is research into the treatment of osteoarthritis with non-steroidal anti-inflammatory drugs misdirected? Lancet 1993;341:353–4.
25. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. Br Med J 1998;317:526–30.
26. Swift GL, Rhodes J. Are non-steroidal anti-inflammatory drugs always necessary? A general practice survey. Br J Clin Pract 1992;46:92–4.
27. Duerden M, Barton S, Johnstone E, MacLean K, Underhill J, Walley T. Topical NSAIDs are better than placebo: Safety, efficacy and therapeutic role of NSAIDs must be clarified. Br Med J 1998;317:280–1.