Copper–salicylate gel for pain relief in osteoarthritis: a randomised controlled trial

Nicholas A Shackel, Richard O Day, Bruce Kellett and Peter M Brooks

Chelated copper and salicylate in an ethanol gel is a topical preparation commonly recommended by the manufacturers for temporary pain relief in a range of musculoskeletal conditions, including osteoarthritis. Copper and salicylate have anti-inflammatory actions both individually and as a complex.[1] In gel formulation, they are absorbed percutaneously[2] and have been shown to suppress inflammation in rats.[3] Therefore, copper–salicylate gel may have local and systemic anti-inflammatory action and a resultant analgesic effect in humans. Controlled clinical trials are needed to investigate this. The possibility that the gel also has a significant analgesic effect independent of its anti-inflammatory action has been suggested, but remains uncertain.

Although the copper–salicylate gel has the potential to cause local and systemic adverse reactions, most commonly skin hypersensitivity,[4] it has not been associated with the serious systemic adverse effects seen with non-steroidal anti-inflammatory drugs (NSAIDs).[5,6] Therefore, the copper–salicylate gel, if effective, would be preferable to NSAIDs as therapy for mild inflammatory joint disease.

Osteoarthritis is the most common form of musculoskeletal disease and causes significant joint pain, especially on movement. Inflammation may contribute to this pain.[7] As copper–salicylate gel is widely used in osteoarthritis, we undertook a randomised, double-blind, placebo-controlled, parallel study to investigate its safety and efficacy in patients with pain associated with osteoarthritis of the knee and/or hip.

Abstract

Objective: To assess the efficacy and safety of a copper–salicylate gel in osteoarthritis of the hip and knee.

Design: Randomised, double-blind, placebo-controlled study.

Setting: Rheumatology Clinic of St Vincent's Hospital, Sydney, New South Wales (a tertiary referral hospital), June 1993 to October 1994.

Patients: 116 patients with pain associated with osteoarthritis of the hip and/or knee (diagnosed by criteria of the European League against Rheumatism), drawn from patients attending the Clinic or self-referred after newspaper advertisements.

Intervention: Copper–salicylate or placebo gel (1.5 g) applied twice daily to the forearm for four weeks.

Outcome measures: Self-assessment of pain before the trial and after two and four weeks of treatment; patient and investigator assessments of efficacy; additional analgesia required; adverse reactions; and withdrawal rates.

Results: Pain scores at rest and on movement decreased in both the copper–salicylate and placebo groups by 13%–20%. There was no significant difference between the two groups for decrease in pain score, patient and investigator efficacy ratings, number of patients requiring paracetamol for extra analgesia (active, 77%; placebo, 71%) and average dose of paracetamol (active, 555 mg/day; placebo, 600 mg/day). Significantly more patients in the copper–salicylate group reported adverse reactions (83% versus 52% of the placebo group), most commonly skin reactions, and withdrew from the trial because of these reactions (17% versus 1.7% of the placebo group).

Conclusion: Copper–salicylate gel applied to the forearm was no better than placebo gel as pain relief for patients with osteoarthritis of the hip or knee, but produced significantly more skin rashes.

Methods

Subjects and setting

The study was conducted at St Vincent's Hospital, Sydney, between June 1993 and October 1994. Subjects were outpatients referred to the rheumatology clinic or community patients self-referred after advertisements in the local paper. Patients were eligible for the study if they were aged 18 years or older, had pain associated with osteoarthritis of the knee and/or hip (diagnosed according to criteria of the European League against Rheumatism)[8] and were contactable by telephone for follow-up.

The following patients were excluded:
- Women who were pregnant, lactating or of child-bearing age and not using medically accepted birth control;
- Patients with known hypersensitivity to copper preparations or with Wilson's disease;
- Patients taking anticoagulants (other than low dose aspirin) or who had taken non-steroidal anti-inflamma-

Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW.
Nicholas A Shackel, MB BS, Registrar;
Richard O Day, MD, FRACP, Professor of Clinical Pharmacology.
B & N Kellett Statistical Consultants, Melbourne, VIC.
Bruce Kellett, PhD, Director.
Medical Professorial Unit, St Vincent's Hospital, Sydney, NSW.
Peter M Brooks, MD, FRACP, Professor of Medicine.
Reprints will not be available from the author. Correspondence: Professor P M Brooks, Medical Professorial Unit, St Vincent's Hospital, Darlinghurst, NSW 2011.
E-mail: P.Brooks@unsw.edu.au

tory drugs in the previous seven days or corticosteroids (oral or parenteral) in the previous 28 days; and
- Patients who had altered their arthritis treatment in the 28 days before the first scheduled application of the study medication.

All subjects gave written informed consent. The protocol was approved by the Research Ethics Committee at St Vincent's Hospital, Sydney.

Interventions and assessments

Patients were randomised according to a random number table to receive either copper–salicylate or placebo gel, applied to the inner aspect of the forearm twice daily for four weeks. This application site was chosen as the skin is relatively thin, allowing rapid absorption of the gel, and as we wished to assess the systemic effect of the gel on distant joints.

The gels consisted of methanol (20 mg/g), camphor (10 mg/g), and eucalyptus oil (10 mg) in an ethanolic base and were equivalent in texture. The copper–salicylate gel contained copper (4.3 mg/g) and salicylate (43.8 mg/g), in the form of methyl salicylate (120 mg/g) and salicylic acid (20.9 mg/g). Both gels were supplied by F. H. Faulding & Co. Pty Limited.

Patients were instructed to apply 1.5 g of gel every 12 hours, massaging it firmly and rapidly into the skin until it disappeared completely. Patients were also provided with rescue medication (500 mg paracetamol tablets) to use for poorly controlled pain.

At the start of the study, patients underwent a comprehensive physical examination, and a medical and medication history was taken. Patients also assessed the intensity of their pain at rest and on movement of the affected joint on a visual analogue scale (a 100 mm line, with 0 = no pain and 100 = "your pain could not be worse"). When more than one joint was affected assessment was for all joints combined. Patients were then assessed after two and four weeks of the trial. During week four, each patient kept a daily record of pain over the preceding 24 hours.

The main measure of treatment efficacy was the difference between baseline pain score and mean pain score over

1: Comparison of treatment and placebo groups in a trial of copper–salicylate gel in osteoarthritis

	Copper–salicylate gel (n=58)	Placebo (n=58)
Sex		
Male	27	25
Female	31	33
Age		
Mean (SD)	62.4 (11.5)	59.0 (12.9)
Range	32–86	19–85
Using low dose aspirin	5 (9%)	3 (5%)
Time on study		
Mean (SD)	26.2 (6.6)	27.0 (5.8)
Range	6–31	3–31
Median	28	28
Withdrew before treatment	0	2*
Withdrew during trial	14 (24%)	7 (12%)
Adverse reactions	10 (17%)	1 (1.7%)
Treatment lacked efficacy	3 (5.2%)	2 (3.4%)
Disease deteriorated	0	2 (3.4%)
Concomitant illness	1 (1.7%)	0
Non-compliance	0	2 (3.4%)
Lost to follow-up	1 (1.7%)	1 (1.7%)

SD = standard deviation.
* One was withdrawn because of failure to comply with the protocol, the other because of unstable blood pressure.

week four. Secondary measures were patient and investigator global assessments of efficacy at the end of the study, on a four-point Likert scale, and times and doses of rescue medication taken. Tablets of rescue medication were counted for each patient at the beginning and end of the study. Adverse events were also monitored throughout the study.

Statistical analyses

Data for the copper–salicylate and placebo arms were compared with χ^2 tests and paired t tests, supplemented by analysis of covariance and bootstrap analysis of log-transformed data. Analysis was based on intention to treat.[9]

The required sample size was determined a priori by assuming a power of 0.8 for a two-tailed t test with $\alpha = 0.05$. Defining γ, population "effect" size, as 0.5 standard deviations, then 62 patients were required in each arm of the study.[10] With a sample size of 58, the effect size was 0.52 standard deviations.

Results

One hundred and sixteen patients were enrolled in the trial (58 in each arm). Two patients were withdrawn before starting treatment, a further 21 chose to withdraw during the trial and two were lost to follow-up. Patient characteristics and reasons given for withdrawal are shown in Box 1. There were no significant differences between the copper–salicylate and placebo groups in sex distribution, age or time on the trial.

During the trial, eight patients continued to take low dose aspirin, to control platelet aggregation, and six took "prohibited" medications, such as ibuprofen, ketoprofen, naproxen, codeine and prednisolone. As these "prohibited" medications were not taken regularly or in significant amounts, these patients were included in the intention-to-treat analysis.

Changes in pain scores during the trial are shown in Box 2. For both the copper–salicylate and placebo groups, pain scores at rest and on movement decreased between entry and week four of the trial (by 13%–20%). However, these decreases were not significant, and did not differ significantly between the copper–salicylate and placebo groups when tested by t test. As pain scores varied widely, the groups were also compared by bootstrap analysis of log-transformed data,[9] which also failed to find a significant difference between the copper–salicylate and placebo groups.

Other outcome measures are also shown in Box 2. No significant differences were found between the copper–salicylate and placebo groups for patient and investigator assessments of gel efficacy or for patient use of rescue medication. However, the copper–salicylate group had significantly more adverse events, predominantly local skin reactions ($P = 0.002$), and a higher rate of discontinuing treatment because of these events (17% versus 1.7% of the placebo group) (see Box 1).

Discussion

We found no significant difference between a commonly used copper–salicylate gel and placebo in pain relief for patients with osteoarthritis. Self-assessed pain levels at rest and on movement of the affected joint decreased during the

2: Outcomes of therapy with copper–salicylate and placebo gels among patients with osteoarthritis

	Copper–salicylate gel	Placebo	P
Pain scores*	(n = 58)	(n = 56)	
At rest			
Start of trial (SD)	34.8 (29.3)	30.5 (29.7)	
Week four† (SD)	28.4 (25.4)	24.9 (25.8)	
Change	–4.58	–5.07	
P for change	0.4‡	0.2‡	0.94§
On movement			
Start of trial (SD)	45.5 (26.0)	46.8 (26.1)	
Week four† (SD)	36.1 (27.6)	39.8 (29.1)	
Change	–9.1	–6.9	
P for change	0.06‡	0.09‡	0.72§
Efficacy ratings	(n = 58)	(n = 56)	
Patient ratings			0.99¶
Very good	6 (10%)	6 (11%)	
Good	16 (28%)	15 (27%)	
Fair	10 (17%)	11 (20%)	
Poor	20 (35%)	21 (38%)	
Not rated	6 (10%)	3 (5%)	
Investigator ratings			0.71¶
Marked	7 (12%)	6 (11%)	
Moderate	20 (35%)	18 (32%)	
Minimal	10 (17%)	8 (14%)	
No efficacy	15 (26%)	21 (38%)	
Not rated	6 (10%)	3 (5%)	
Rescue medication (paracetamol 500 mg)	(n = 56)	(n = 55)	
Number of patients who took rescue medication	43 (77%)	39 (71%)	0.63¶
Days rescue medication taken	545	579	0.34¶
Proportion of days with rescue medication	37%	40%	0.64§
Average dose in mg/day (SD)	555 (790)	600 (855)	0.43§
Adverse events	(n = 58)	(n = 56)	
Number of patients reporting adverse events	48 (83%)	29 (52%)	
Number of adverse events			0.002¶
Skin	80	27	
Musculoskeletal	5	9	
Gastrointestinal	6	6	
Nervous system	2	9	
Respiratory	1	1	
Miscellaneous	6	6	
Serious adverse events††	1**	0	
Action taken (number of events)			
Treatment discontinued	27	7	
Treatment interrupted	3	4	
Dose adjusted	4	0	
Symptoms treated	4	11	

* Self-assessed by patient on a visual analogue scale (100 mm line), where 0 = no pain and 100 = "your pain could not be worse". † Mean of daily scores for week four of treatment. ‡ Tested by paired t test. § Tested by two-sample t test. ¶ Tested by χ² test. ** Chest pain. †† Some patients had more than one event.

four-week trial in both the copper–salicylate and placebo groups by 13%–20%. For pain at rest, the decrease was smaller in the copper–salicylate group than in the placebo group. For pain on movement, the decrease was greater in the copper–salicylate group than in the placebo group, but the difference (2.2 units of a 100-unit scale) was too small to be significant with the sample size used. As this difference corresponds to an effect size of 0.07 standard deviations, more than 2000 patients in each arm would have been required to show it as significant (assuming a power of 0.8 and a significance level of 0.05).[8] In addition, large amounts of rescue analgesia (paracetamol) were used by both groups. Therefore, even if a beneficial effect of the gel was present, it is unlikely to be of clinical relevance to patients with osteoarthritis.

There was a significantly higher incidence of skin reactions and treatment discontinuations in the copper–salicylate group. This was as expected because of the known local hypersensitivity reactions produced by the copper–salicylate gel,[2] attributable to both the copper[1] and salicylate[11] components. Importantly, there was no evidence of systemic side effects in either the copper–salicylate or placebo groups.

A criticism of the study design may be that the gel was applied over the forearm rather than, as recommended by the manufacturer, over the painful joint. We chose this site of application as osteoarthritis often affects multiple joints and we wished to assess the systemic effect of the gel on distant joints. Although we cannot therefore rule out an effect on a nearby joint, we believe this would have only limited clinical use in osteoarthritis as multiple joints are usually affected.

In conclusion, the lack of efficacy of the copper–salicylate gel and the relatively high incidence of local (skin) reactions suggest that it is not of major benefit in the management of osteoarthritis.

Disclaimer of conflict of interest

References

1. Berthon G. Is copper pro- or anti-inflammatory? A reconciling view and a novel approach for the use of copper in the control of inflammation. *Agents Actions* 1993; 39: 210-217.
2. Walker WR, Beveridge SJ, Whitehouse MW. Dermal copper drugs: the copper bracelet and Cu(II) salicylate complexes. *Agents Actions* 1981; 1 Suppl: S359-S367.
3. Walker WR, Beveridge SJ, Whitehouse MW. Anti-inflammatory activity of a dermally applied copper salicylate preparation (Alcusal). *Agents Actions* 1980; 10 (1 Pt 2): 38-47.
4. Adverse drug reactions database. Canberra: Therapeutic Goods Administration, Department of Health and Family Sevices, 1997.
5. Henry D, Lim L-Y, Garcia-Rodriguez A, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta analysis. *BMJ* 1996; 312: 1563-1566.
6. Lehmann T, Day RO, Brooks PM. Toxicity of antirheumatic drugs. *Med J Aust* 1997; 166: 378-383.
7. Howell DS. Etiopathogenesis of osteoarthritis. In: McCarthy DJ, editor. Arthritis: and allied conditions. 11th ed. Philadelphia: Lea and Febiger, 1989: 1595-1604.
8. Modern trends in osteoarthritis research. Proceedings of a satellite symposium to the Vth EULAR Symposium. *Scand J Rheumatol Suppl* 1990; 81: S1-S31.
9. Walsh JF, Rezinkiff M. Bootstrapping: a tool for clinical research. *J Clin Psychol* 1990; 46: 928-930.
10. Welkowitz J, Ewen RB, Cohen J. Introduction to power analysis. In: Introductory statistics for the behavioural sciences. 1st ed. Florida: Harcourt Brace Jovanovich, 215-234.
11. Salzer EI, Wilson JWA. Allergic contact dermatitis due to copper. *Arch Dermatol* 1968; 98: 375-376.