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Comparison of the Efficacy and Tolerability of a Paracetamol/Codeine Fixed-dose Combination with Tramadol in Patients with Refractory Chronic Back Pain

Frank Otto Müller^a, Christoffel Lombard Odendaal^b, Frank Robert Müller^a,
Juliette Raubenheimer^c, Michelle Vivienne Middle^a, and Michael Kummer^d

South Africa Clinical Trials (Pty.) Ltd.^a, George, The Pain Control Centre,
University of the Orange Free State^b, Bloemfontein, Farmovs Research Centre for
Clinical Pharmacology and Drug Development^c, Bloemfontein (South Africa), and
Pharmaforschung Euro Consult GmbH^c, Garmisch-Partenkirchen (Germany)

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Summary

Fifty-five patients suffering from refractory chronic back pain took part in a double-blind, multiple-dose, randomised, cross-over study to compare the efficacy and tolerability of a fixed-dose capsule preparation containing 500 mg paracetamol (CAS 103-90-2) and 30 mg codeine phosphate 1/2 H₂O (CAS 41444-62-6) (talvosilen[®] forte, test preparation) with a reference capsule preparation containing 50 mg tramadol hydrochloride (CAS 22204-88-2), in a regimen of two capsules 8-hourly.

There were two treatment periods of up to 7 days each. Cross-over took place, without wash-out, at the end of 7 days, or sooner if patients were unable to tolerate the first treatment. The test preparation was at least as efficacious as the reference in the treatment of back pain (81 % of patients experienced good or satisfactory pain relief). 81 % of patients tolerated the test well compared to only 69 % receiving the reference, as per protocol analysis.

The results of this study suggest that the test product is at least as efficacious as tramadol in the treatment of patients with refractory chronic back pain, whilst being better tolerated.

Zusammenfassung

Vergleich der Wirksamkeit und Verträglichkeit einer fixen Paracetamol-Codein-Kombination mit Tramadol bei Patienten mit therapie-refraktären chronischen Rückenschmerzen

55 Patienten mit therapie-refraktären chronischen Rückenschmerzen nahmen an einer doppelblinden, randomisierten, Cross-over-Mehrfachdosierungs-Studie teil, um die Wirksamkeit und Verträglichkeit einer fixen Kombination von 500 mg Paracetamol (CAS 103-90-2) und 30 mg Codeinphosphat 1/2 H₂O (CAS 41444-62-6) in Kapselform (talvosilen[®] forte, Testpräparat) mit 50 mg Tramadol-hydrochlorid (CAS 22204-88-2), ebenfalls in Kapselform, als Referenz zu vergleichen. Die Prüfpräparate wurden in Dosierungen von zwei Kapseln alle 8 Stunden verabreicht. Es gab zwei Behandlungsperioden von jeweils bis zu 7 Tagen. Nach 7 Tagen – oder früher, wenn die erste Behandlungsphase nicht toleriert wurde – wurde ohne Auswaschphase im Cross-over auf die jeweils andere Medikation umgestellt. Das Testpräparat war bei der Behandlung refraktärer Rückenschmerzen mindestens gleich wirksam wie die Referenz (81 % der Patienten erfuhren eine gute oder befriedigende Schmerzerleichterung). 81 % der Patienten tolerierten die Behandlung mit dem Testpräparat gut, verglichen mit nur 69 % derjenigen die das Referenzpräparat erhielten.

Die Ergebnisse dieser Studie lassen den Schluß zu, daß bei chronischen refraktären Rückenschmerzen das Testpräparat in der Wirksamkeit dem Referenzpräparat ebenbürtig, diesem aber in der Akzeptanz durch die Patienten überlegen ist.

Key words Analgesics · Back pain · CAS 103-90-2 · CAS 22204-88-2 · CAS 41444-62-6 · Codeine · Paracetamol · talvosilen[®] forte, tolerability · Tramadol

1. Introduction

Despite major advances in pain control, the impact of pain on society is great. Normally, acute pain quickly subsides as healing processes decrease pain-producing stimuli. However, pain may sometimes persist for months to years, leading to a chronic pain state with features quite different from those of acute pain. Pain is always subjective and a complex concept. Proper patient care must include evaluation of pain management. This includes alleviation of pain symptoms, and an assessment of medication side effects, patient activity and quality of life.

In the developed world, low back pain is considered to be the most common reason for patients to consult their doctors [1]. The modern-day management of refractory (stubborn) chronic back pain experienced by patients who have had unsuccessful back surgery requires a multi-disciplinary approach, also involving the use of analgesics. This may include paracetamol, codeine and tramadol, and non steroidal anti-inflammatory drugs (NSAIDs). The latter are often contra-indicated due to side effects resulting from non-selective cyclo-oxygenase inhibition. Paracetamol is well tolerated and available without prescription. The analgesic effect of paracetamol is thought to be mediated peripherally [2, 3] and centrally [4, 5]. Codeine and tramadol act at several sites within the central nervous system [6]. When pain relief is insufficient with paracetamol alone, codeine may be added in combination. The rationale for combining two analgesics with presumably different mechanisms of action is the enhancement of efficacy, limiting the dose of each active drug and thus reducing the expected incidence of side effects [2, 7].

The aim of this study was to compare the efficacy and tolerability of a fixed dose paracetamol/codeine combination product with tramadol hydrochloride in patients suffering from refractory chronic back pain.

2. Methods

2.1. Study population

Fifty-five (55) Caucasian male ($n = 29$) and female ($n = 26$) patients suffering from refractory chronic back pain for at least 3 months who satisfied the inclusion criteria were admitted to the study (Table 1). Severity of back pain associated with active movement had to be ≥ 35 mm on a 10 cm VAS (visual analogue scale), as assessed by the patient upon screening.

Patients selected for the study gave written informed consent. They received detailed instructions about the study performance and restrictions and were informed about possible adverse events that might be elicited by the study drugs. They had to be willing to discontinue existing analgesic and/or NSAID treatment, and female patients had to be either sterilised, post-menopausal, sexually inactive or otherwise practising reliable forms of contraception. The following exclusion criteria applied: known or suspected hypersensitivity to the study drugs, any treatment with glucocorticosteroids within two months before entering the study, treatment of back pain by means of local anaesthetic infiltrations during the 30 days preceding the study, surgical interventions to the

Table 1: Summary of demographic data ($n = 55$).

	Age (years)	Body mass (kg)	Height (cm)	VAS ^{a)} (mm)
Mean	52	86	173	70
Range	20–73	58–141	152–191	37–92

a) Visual analogue scale, severity of back pain associated with active movement.

back ≤ 3 months before the study, confinement to bed rest, analgesic abuse, participation in another clinical study involving an investigational agent/procedure within one month of the study, pregnancy (Human Fertilix Duo urine slide test), lactation, impaired renal function (serum urea $> 125\%$ and serum creatinine $> 150\%$ of upper limit of normal range), impaired liver function (alanine aminotransferase and aspartate aminotransferase $> 100\%$ of upper limit of normal range), use of NSAIDs with prolonged elimination half-lives (e.g. naproxen, piroxicam and meloxicam) within 7 days of the study or manipulation under general anaesthesia within 10 days of the study. Treatment with monoamine-oxidase inhibitors and drugs with a known potential to depress the central nervous system, excluding polycyclic antidepressants and nocturnal hypnotics, was also an exclusion criterion.

The study was approved by the ethics committee of the University of the Orange Free State (Bloemfontein, South Africa) and performed in accordance with Good Clinical Practice guidelines [8].

2.2. Study design

This was a double-blind, multiple-dose, randomised, cross-over study. Assuming that the true proportion (P_r) of patients for whom the test treatment would be rated at least as effective as the reference treatment is 90%, a sample size of 54 would yield a power of 83% to reveal that the test treatment is at least as effective as the reference treatment (lower bound of the one-sided 95% confidence interval for $P_r > 75\%$).

Patients randomly received one of the following treatments. The capsules were identical in appearance. Trial supplies were obtained from the respective manufacturers.

1. Test: 2 capsules containing 500 mg paracetamol (CAS 103-90-2) and 30 mg codeine phosphate $\frac{1}{2}$ H₂O (CAS 41444-62-6) (talvosilen[®] forte capsules, batch no. 678 055; manufacturer: bene Arzneimittel GmbH, Munich, Germany) 8-hourly for 7 days.
2. Reference: 2 capsules containing 50 mg tramadol hydrochloride (CAS 22204-88-2) (batch no. 290 596) 8-hourly for days; capsules were prepared using intact 1×50 mg tramadol hydrochloride tablets.

2.3. Study performance

At visit 1 patients were screened for inclusion. Eligible patients were randomised on Day 1 (visit 2), and a global evaluation of efficacy was done on Day 8 (visit 3) and Day 15 (visit 4). Patients completed a diary every morning and evening between visits 2 and 4. As far as possible, visits took place between 7:00 and 9:00 and on the same day of the week for each patient. With few exceptions, the same investigator interviewed the same patients throughout the study.

Following visit 1, eligible patients using NSAIDs with prolonged half-lives were switched to 50 mg diclofenac sodium (CAS 15307-79-6) plus 200 μ g misoprostol (CAS 59122-46-2), one to three tablets daily, as needed. All

analgesic and anti-inflammatory therapy was discontinued 24 h before randomisation (Day 1). Concomitant therapies not listed as prohibited and that were continued in stable doses for at least 14 days before screening (visit 1) were allowed during the study, since each patient served as his/her own control.

Trial medication was self-administered between 6:00 and 8:00, 12:00 and 14:00 and 20:00 and 22:00 daily for 7 days. Cross-over to the alternative treatment took place on Day 8 after visit 3. Visit 3 could be scheduled sooner than after 7 days of treatment if the particular treatment was poorly tolerated or judged ineffective. This was followed immediately by the alternative treatment if the patient did not withdraw consent.

Patients would have been excluded from the study if capsule counts indicated non-compliance (< 90 % of trial medication taken). Dropouts for non-trial related reasons would have been replaced.

At visits 3 and 4 patient diaries were retrieved and concomitant medication and adverse events recorded. At visits 1 and 4 the pre- and post-study physical examinations, haematological and clinical chemistry evaluations were performed.

2.4. Criteria for evaluation

2.4.1. Efficacy and tolerability

Primary: Patients' assessment based on a three-point rating scale ("poor", "satisfactory", "good") and whether they would prefer to continue with the medication ("yes", "uncertain", "no").

Secondary: Information obtained from patient diaries: quality of sleep assessed every morning (10 cm VAS); degree of pain for each 12-h period preceding morning and evening assessments (10 cm VAS); treatment preference at the end of the study; number of withdrawals for treatment-related reasons.

2.4.2. Safety

This comprised the incidence and severity of adverse events and the results of special investigations.

Table 2: Summary of pre-study therapeutic interventions (n = 55).

Intervention	Yes	No
Spinal/disc/lumbar surgery	22 (40 %)	33 (60 %)
Local anaesthetic infiltration	11 (20 %)	44 (80 %)
Analgesics/NSAIDs ^{a)} at screening	45 (82 %)	10 (18 %)
Treatment with glucocorticosteroids	0 (0 %)	55 (100 %)

a) Non-steroidal anti-inflammatory drugs.

2.5. Statistical analysis

An intention-to-treat (ITT) as well as a per-protocol analysis (PPA) were performed. Patients who dropped out for non-study drug-related reasons before visit 3 were excluded from both analyses. ITT analysis was performed in respect of eligible patients who took at least one dose of study medication. Treatments were assessed as either "poor", "satisfactory" or "good". The ratings "satisfactory" and "good" were pooled and the test was compared to the reference as follows: a point estimate and one-sided 95 % confidence interval (CI) for the proportion of patients who rated the test at least as good as the reference was calculated. The test was considered at least as effective as the reference if the lower bound of the CI was ≥ 75 %. Treatment outcome was rated "poor" in the case of discontinuation due to lack of efficacy or intolerability.

The VAS data (end of each treatment period) were analysed by calculating a non-parametric point estimate and 90 % CI for the "test-reference" mean difference in VAS score. VAS data from patient diaries and withdrawals for study drug-related reasons were analysed descriptively.

Incidence, severity and causal relationship of adverse events were tabulated by body system organ class. Haematological and clinical chemistry results were summarised descriptively.

Table 3: Efficacy response rates (intention-to-treat analysis).

Question	Paracetamol/codeine (test product) (n = 54)	Tramadol (reference) (n = 52)	Difference in response rates (test minus reference) (%)	95 % CI for difference (%)
Response: good or satisfactory	43 (80 %)	42 (81 %)	-1	-16 to 14
Tolerated treatment well or satisfactorily	43 (80 %)	36 (69 %)	10	-6 to 27
Choice to continue with medication				
Yes	27 (50 %)	21 (40 %)	10	-9 to 29
Uncertain	6 (11 %)	6 (12 %)	0	-13 to 12
No	21 (31 %)	25 (48 %)	-10	-28 to 10

Table 4: Efficacy response rates (per-protocol analysis).

Question	Paracetamol/codeine (test product) (n = 54)	Tramadol (reference) (n = 52)	Difference in response rates (test minus reference) (%)	95 % CI for difference (%)
Response: good or satisfactory	43 (81 %)	42 (81 %)	0	-15 to 15
Tolerated treatment well or satisfactorily	43 (81 %)	36 (69 %)	12	-4 to 28
Choice to continue with medication				
Yes	27 (51 %)	21 (40 %)	11	-8 to 30
Uncertain	6 (11 %)	6 (12 %)	0	-12 to 12
No	20 (38 %)	25 (48 %)	-10	-29 to 9

Table 5: Most common adverse events at least possibly related to the study medication (number of patients out of 55 affected).

Paracetamol/codeine		Tramadol	
Dizziness	17 (31 %)	Dizziness	18 (33 %)
Nausea	16 (29 %)	Nausea	16 (29 %)
Constipation	15 (27 %)	Somnolence	15 (27 %)
Somnolence	12 (22 %)	Pruritis	15 (27 %)
Pruritis	9 (16 %)	Vomiting	11 (20 %)
Dry mouth	9 (16 %)	Dry mouth	9 (16 %)

3. Results

3.1. Pre-study therapeutic intervention

A summary of pre-study therapeutic interventions is provided in Table 2.

3.2. Primary efficacy/tolerability variables

Two patients were excluded from the per-protocol analysis (PPA) for the test and 3 from the reference because of failure to return (i.e. no data for the second phase of treatment). Intention-to-treat (ITT) analysis was performed on 54 patients receiving the test and 52 receiving the reference (Tables 3 and 4).

ITT analysis: 80 % of patients found the test preparation to be effective, compared with 81 % who found the reference to be effective in relieving their back pain. 80 % of patients tolerated treatment with the test well, compared to only 69 % who tolerated the reference well.

PPA produced essentially similar data.

More patients preferred treatment with the test product (Tables 3 and 4).

3.3. Secondary efficacy variables

The daily visual analogue scale (VAS) scores for quality of sleep and pain relief were similar for the two treatments. Withdrawals for treatment-related reasons: 10/55 (18 %) patients receiving the reference and 9/55 (16 %) receiving the test product (failed to complete the respective 7-day treatment phases because of unacceptable adverse events).

3.4. Safety

The same number of patients reported adverse events whilst receiving either treatment (69 %). The most commonly reported adverse event for both treatments was dizziness. Table 5 provides a listing of the most commonly encountered events possibly related to study medication. Haematology and clinical chemistry variables remained unchanged.

4. Discussion

Chronic pain presents an entirely different clinical picture than acute pain. It persists beyond the normal expected healing time, may not be associated with a specific injury, and by definition is refractory to traditional analgesic therapy. Although these patients are frequently treated with numerous drugs including antidepressants, treatment goes

beyond traditional pharmacotherapy to include whatever means will enable the patient to resume a normal lifestyle [9].

Paracetamol is an antipyretic and mild analgesic with little, if any, anti-inflammatory properties and no anti-platelet action. It has no irritant effect on the gastric mucosa. The usual adult analgesic dose by mouth is 1000 mg every 4 to 6 h up to a maximum of 4 g daily. Adverse reactions include rashes and blood dyscrasias, both of which are rare. There is no convincing evidence that paracetamol causes chronic liver disease or analgesic nephropathy when used regularly in therapeutic doses [10]. Codeine is the methyl ether of morphine but has only about 10 % of its analgesic potency. Although codeine is converted to morphine, it produces little euphoria and is of low addiction potential. As a result it has been used for many years as an oral analgesic for moderate pain at doses ranging from 15 to 60 mg every 4 h. Constipation and nausea are the most commonly encountered problems [10]. A variety of paracetamol/codeine fixed dose combinations are available, e.g., the test product, which contains 500 mg paracetamol and 30 mg codeine phosphate $\frac{1}{2}$ H₂O, recommended for moderate to severe pain at doses of 1 to 2 capsules up to three times daily. A recent review underscored the value of codeine added to paracetamol in the relief of pain with regard to both efficacy and safety [11].

Tramadol is an opioid analgesic which appears to have a low addiction potential [12–14]. It may be given as the hydrochloride salt by mouth at doses of 50 to 100 mg up to 6-hourly for moderate to severe pain. The total daily dose per mouth should not exceed 400 mg [15].

This double-blind, randomised, cross-over study emphasised the pain-relieving potential of both the paracetamol/codeine combination (test) and tramadol (reference) in patients with refractory chronic back pain. The test product was at least as effective as the reference. The side effects recorded were typical of the two products. However, the test preparation was better tolerated and rated preferable to the reference. Patient compliance could be a major advantage of a fixed-dose paracetamol/codeine combination over administering each of the active ingredients separately.

A comparative in vitro dissolution test [16] of tramadol tablets and encapsulated tramadol tablets, as used in this study, revealed comparable pharmaceutical availability at 15 min, i.e., 97 % (SD 3,6 %) and 94,4 % (SD 0,7 %) dissolved, respectively, confirming the legitimacy of the double-blind technique.

5. Conclusion

The test product is at least as safe and efficacious as the reference product in the treatment of patients suffering refractory chronic back pain, with the test out-scoring the reference in respect of tolerability and patients preference.

6. References

- [1] Glynn, C., Continuing Medical Education (Medical Association of South Africa) **14**, 311 (1996)
- [2] Beaver, W. T., Am. J. Med. **9**, 38 (1984)
- [3] Jackson, C. H., MacDonald, N. C., Cornett, J. W. D., Can. Med. Assoc. J. **131**, 25 (1984)
- [4] Björkman, R., Hallman, K. M., Hedner, J. et al., Pain **57**, 259 (1994)
- [5] Piletta, P., Porchet, H. C., Dayer, P., Clin. Pharmacol. Ther. **49**, 350 (1991)
- [6] Reisine, T., Pasternak, G., Opioid analgesics and antagonists, Goodman and Gilman's: The Pharmacological Basis of Therapeutics, G. Hardman, L. E. Limbird (eds.), 9th ed., p 521–555, Mc Graw-Hill Health Professions Division, New York (1995)
- [7] Meadows, B. J., Curr. Ther. Res. Clin. Exp. **35**, 501 (1984)
- [8] CPMP Working Party on Efficacy of Medicinal Products, Pharmacol. Toxicol. **67**, 361 (1990)
- [9] Martin, B., Opioid and nonopioid analgesics, Modern Pharmacology, C. R. Craig, R. E. Stitzel (eds.), 4th ed., p 431–450, Little, Brown and Company, Boston (1994)
- [10] Ritter, J. M., Lewis, L. D., Mant, T. G. K. (eds.), A Textbook of Clinical Pharmacology, 3rd. ed., p. 227–243, Arnold, London (1995)
- [11] De Craen, A. J. M., DiGiulio, G., Lampe-Schoenmaeckers, A. J. E. M. et al., Br. Med. J. **313**, 321 (1996)
- [12] Flöhe, L. von, Arend, I., Cogal, A. et al., Arzneim.-Forsch./Drug Res. **28 (I)**, 213 (1978)
- [13] Richter, W., Barth, H., Flöhe, L. von, Giertz, H., Arzneim.-Forsch./Drug Res. **35 (II)**, 1742 (1985)
- [14] Osipova, N. A., Novikov, G. A., Beresnev, V. A. et al., Curr. Ther. Res. **50**, 812 (1991)
- [15] Reynolds, J. E. F. (ed.), Martindale, The Extra Pharmacopoeia, 31st ed., p. 102, Royal Pharmaceutical Society, London (1996)
- [16] DAB (Deutsches Arzneibuch) 1996, V.5.4: Monographie "Wirkstofffreisetzung aus festen oralen Arzneiformen" (1996)

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Correspondence: Prof. Frank Otto Müller, South Africa Clinical Trials (Pty.) Ltd., P.O. Box 4716, George East, 6539 (South Africa)

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