A randomised clinical trial comparing the analgesic and anxiolytic efficacy and tolerability of Stilpane® and Tramacet® after third molar extraction

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Background: Successful treatment of moderate to severe acute pain often necessitates several analgesics that target different sites of the nociceptive pathway. Fixed-dose combination analgesics facilitate a reduction in dose of individual components, increased compliance and strong-opioid sparing. The aim of this study was to compare the analgesic and anxiolytic efficacy and tolerability of two widely prescribed combination analgesics, Stilpane® (paracetamol/codeine/meprobamate) and Tramacet® (paracetamol/tramadol).

Methods: A prospective randomised parallel group phase IV clinical trial was conducted in 100 patients experiencing moderate to severe pain after third molar extraction at the Oral and Dental Hospital, University of Pretoria. Pain intensity and pain relief were assessed using Likert and visual analogue scales. Medication efficacy, time to perceptible pain relief and meaningful pain relief were also assessed. Primary variables included the Pain Intensity Difference (PID) between baseline and scheduled visits, and hourly pain relief (PAR). The Summed Pain Intensity Difference (SPID), Sum of hourly PAR, hourly PIDs from baseline (SPRID) and Total Pain Relief (TOTPAR) were calculated according to standard methods. Beck Anxiety Questionnaire assessed anxiety. Tolerability was assessed chiefly by the reporting of adverse events.

Results: Stilpane® and Tramacet® were equally effective at relieving moderate to severe acute pain. No differences in anxiolytic efficacy were found between the two treatment arms and differences in tolerability failed to reach statistical significance.

Conclusions: Despite their distinctive compositions and mechanisms of action, Stilpane® and Tramacet® are equally effective and well-tolerated combination analgesics in patients experiencing moderate to severe acute pain.

Keywords: acute pain, anxiolytic, codeine, combination analgesics, meprobamate, paracetamol, Stilpane®, Tramacet®, tramadol

Introduction

Acute pain is disabling and common, and while it may be inevitable, treatment with effective analgesics may alleviate the suffering.[1] Aggressive control of acute pain may also reduce the risk of developing chronic or even lifelong pain.[2] Successful treatment of moderate to severe acute pain often necessitates several analgesics that target different sites of the nociceptive pathway. Subject to the cause of the pain as well as other patient and external factors, a traditional stepwise approach includes commencing treatment with paracetamol, adding a non-steroidal anti-inflammatory drug (NSAID) and thereafter, co-prescribing a weak opioid such as codeine or tramadol.[3] This rational practice facilitates additive or even synergistic efficacy and furthermore results in a reduction of the use of the more potent opioids.[4,5] The strong opioid-sparing effects of these compounds may lead to reduced nausea, vomiting, constipation, urinary retention, respiratory depression and sedation, which are important factors particularly when considering pain associated with ambulatory surgery and the increasing need to facilitate an earlier hospital discharge.[5]

Carefully designed oral fixed-dose combination analgesics have potential advantages over monotherapy which include a reduction in dose of each of the components, theoretically resulting in improved tolerability and safety. The simplified oral regimens of combination analgesics may also be invaluable in promoting compliance.[6] For instance, Stilpane®, a combination analgesic widely prescribed in South Africa contains relatively small doses of 320 mg paracetamol and 8 mg codeine, which are usually prescribed individually in increments of 500 mg and 30 mg respectively in acute pain management.[7,8] Low-dose meprobamate

(150 mg) is also included in this preparation.[9] Pain is often accompanied by anxiety, and in the past it was therefore considered beneficial to add this sedative to analgesic regimens specifically for its anxiolytic properties.[9] Yet it appears that meprobamate also possesses intrinsic analgesic properties, which may further complement the overall analgesic efficacy of Stilpane®.[10] Another popular South African combination analgesic, Tramacet®, comprises paracetamol (325 mg) and the weak opioid tramadol (37.5 mg), illustrating again that synergistic pharmacodynamic interaction allows for a substantial reduction in the usual individual dose.[11] Analgesic superiority has been demonstrated for this combination compared to its individual components.[11] Of note is that neither of these fixed dose preparations contains NSAIDs, which are associated with gastric ulceration and haemorrhage, and possibly a delay in post-surgical bone healing.[12] Opioids are preferred to NSAIDs in this context as well as in patients with renal impairment, bleeding disorders, on anticoagulant therapy or who have other contraindications including pregnancy and allergies.

Stilpane® and Tramacet® are effective analgesics for moderate to severe pain and are often used interchangeably in South Africa.[13–15] However, their mechanisms of action are somewhat different, and it is not known whether these preparations are equally effective. The aim of this study was therefore to compare the analgesic and the anxiolytic efficacy and tolerability of Stilpane® and Tramacet® in an acute pain model. Removal of wisdom teeth (the four third molars) is usually accompanied by moderate to severe pain arising from significant tissue injury.[16] Understandably the procedure may also cause considerable distress to the patient and precipitate acute anxiety, particularly

prior to surgery.[17] It is therefore a useful model for the clinical evaluation of both the analgesic and anxiolytic efficacy of medicines.

Methods
Study design
A prospective single-blind randomised parallel group single centre phase IV clinical trial was conducted to compare the analgesic and anxiolytic efficacy and tolerability of Stilpane® and Tramacet® using a validated acute third molar extraction pain model.[18]

The study was approved by the University of Pretoria Research Ethics Committee (236/2112) and was registered with NHREC (DOH-27–0313-4234). The Medicines Control Council was also notified.

Patients were recruited from February 2013–November 2013.

Study population
One hundred eligible patients presenting to the Oral and Dental Hospital, University of Pretoria, generally in good health according to the American Society of Anaesthesiologists' Scale (Stage I or II), aged 18 years and above, of either sex, scheduled for elective outpatient extraction of three or four impacted molars, two of which were mandibular thus requiring bone removal, with an impaction score of ≥ 8, meeting the inclusion/exclusion criteria and having given written informed consent, were selected to participate in the study. Patients who were pregnant or lactating, illiterate or diagnosed with psychotic or bipolar disorders, those whose intake of alcohol exceeded 25 units a week, those with serious cardiovascular disease, brain injury or seizure disorders, and those on concurrent opioids, cocaine, stimulants, antidepressants, antipsychotics or anxiolytic medication, were excluded from the study.

Patients who scored 2 (moderate) or 3 (severe) on the 4-point Likert scale for pain intensity[19] and at least 50 mm on a 100 mm pain visual analogue scale,[20] within 2 h post-surgery, were randomised in block sizes of ten to one of the two treatment groups where they received either two Stilpane® capsules or two Tramacet® tablets six hourly. Patients were unaware of the treatment received and identical medication bottles were coded and packaged with study medication according to the randomisation sequence in order to maintain the blind. Rescue medication comprised paracetamol (500 mg), the ingredient common to both preparations, in order to limit the confounding potential of additional drug–drug interactions.

In accordance with the Declaration of Helsinki, the European Union Clinical Trials Directive, the Food and Drug Administration and other Good Clinical Practice regulations, patients had the right to withdraw from the study without prejudicing their subsequent medical care.

Analgesic efficacy
Patients reported pain intensity on the 4-point Likert Scale, where 0 represented no pain, 1: mild pain, 2: moderate pain and 3: severe pain, as soon as they were coherent post-surgery.[19] Patients also recorded their pain intensity on a visual analogue pain scale (VAS) where 0 mm signified no pain and 100 mm extreme pain, prior to receiving the first dose of study medication.[20]

Thereafter, pain intensity was assessed at 30 min, 1, 2, 3, 4, 5, 6, 48 h and 5 days after the first dose of study medication. Pain relief

(PAR) was also measured at these time points using the 5-point Likert Scale where 0 denoted none, 1: a little, 2: some, 3: a lot and 4: complete.[21]

Other analgesic efficacy variables included the self-reported 5-point Likert scale to assess medication efficacy (poor to excellent) at 6 and 48 h post first dose, and stopwatch-measured time to perceptible pain relief as well as meaningful pain relief after the administration of the initial dose of analgesic.

Anxiolytic efficacy
The Beck Anxiety Questionnaire which measures cognitive and somatic components of anxiety was used to assess patients' anxiety before and after surgery (prior to the first dose of study medication) and at 6 h, 48 h and 5 days after the first dose. Scores of 0–16 represented mild, 17–30: moderate, and 31 and above: severe anxiety.[22]

Tolerability and safety
Vital signs including blood pressure, body weight, height, respiration and heart rates were recorded before and immediately after surgery, then at 6 h, 48 h and 5 days after the first dose of analgesic.

Any adverse changes in a patient's medical condition was recorded as an adverse event. Patients received a diary card to record adverse events at home and the investigator categorised these by their relationship to study medication, intensity and seriousness. The outcome of the event was also recorded. Serious Adverse Events were reported to the University of Pretoria's Ethics Committee within 24 h of occurrence.

Statistical analyses
A sample size of at least 26 patients per group was required for a power of 0.80 to detect large, and 64 to detect medium differences at a level of significance of 0.05. Thus a sample size of 50 was chosen. Efficacy analyses were performed on the intent to treat (ITT) and per-protocol (PP) populations, while safety analyses included randomised patients who took at least one dose of study treatment. Continuous data was summarised using descriptive statistics such as number of observations (*n*), mean, standard deviation (SD), median, minimum (min) and maximum(max). Categorical data was presented as absolute numbers (*n*) and percentage (%).

Study primary variables included the Pain Intensity Difference (PID) between baseline and scheduled visits, and hourly pain relief (PAR) at each time point. The Summed Pain Intensity Difference (SPID), Sum of hourly PAR, hourly PIDs from baseline (SPRID) and Total Pain Relief (TOTPAR) were calculated according to standard methods. Analysis of covariance (ANCOVA) was used to analyse SPID and SPRID, the VAS and the Beck Anxiety Scores. Analysis of variance (ANOVA) was used to analyse TOTPAR and included treatment arms as factors. Shapiro–Wilk test was used for normality checks. Least mean square difference was reported with corresponding *p*-values, and 95% confidence intervals. Comparisons were performed at a 5% level of significance.

Results
Demographic and other baseline characteristics
A total of one hundred 18–40 year old patients (52 in the Stilpane®, and 48 in the Tramacet® group) enrolled in and completed the study. All were included in the safety and ITT populations (Figure 1). The study population comprised more women than men and the mean age (22 years) of the patients in the two groups was similar (Table 1).
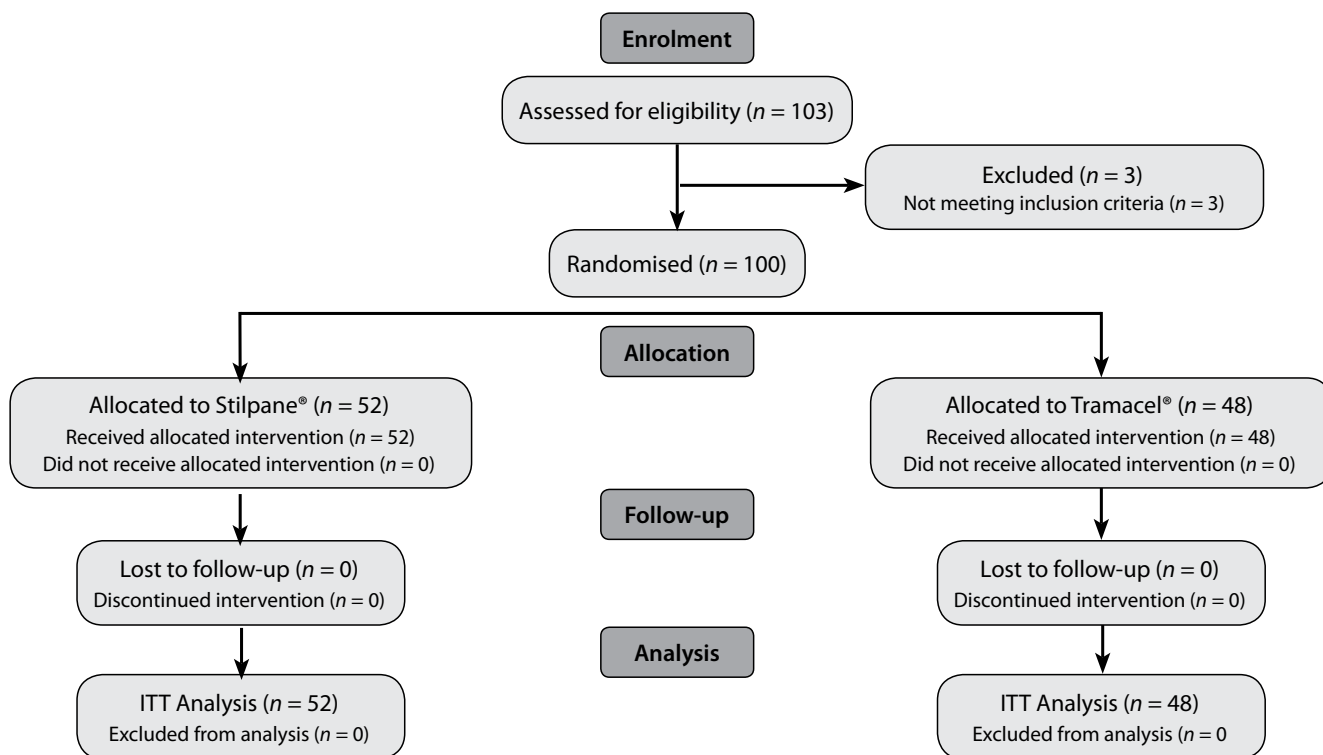
Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Table 1: Demographic characteristics (gender and race)

Variable	Categories	Stilpane® Capsules N = 52	Tramacet® Tablet N = 48	Overall N = 100
			n (%)	
Gender	Male	17 (32.7)	20 (41.7)	37 (37.0)
	Female	35 (67.3)	28 (58.3)	63 (63.0)
Race	Caucasian	30 (57.7)	22 (45.8)	52 (52.0)
	Black	19 (36.5)	24 (50.0)	43 (43.0)
	Asian	0	1 (2.1)	1 (1.0)
	Other	3 (5.8)	1 (2.1)	4 (4.0)

Analgesic efficacy

Stilpane® and Tramacet® were equally effective at relieving the moderate to severe acute pain associated with third molar extraction. The difference from baseline in pain intensity for the two treatment groups (Summed Pain Intensity Difference) was not statistically significant at any of the various time points assessed. (Table 2) This was corroborated by the results of the pain intensity assessment by VAS (Table 3) as well as total pain relief (TOTPAR) (Table 4), sum of hourly pain relief and hourly pain intensity difference (SPRID) (Table 5) where no differences from baseline were statistically significant between the Stilpane® and Tramacet® groups. Furthermore, analyses of secondary variables including hourly pain intensity difference (PID), hourly visual analogue pain scale (VAS), hourly pain relief, medication efficacy, time taken for perceptible pain relief and time taken for meaningful pain relief were comparable between the two groups (data not shown).

At 6 h post first dose, most of the patients (Stilpane®: 40%; Tramacet®: 38%) rated the efficacy of their analgesics as very good. At this time, 2% in both groups thought it was poor, 4% in

Table 2: Summed pain intensity difference at different time points (ITT population)

Visit	Stilpane® capsules N = 52 Mean (SD)	Tramacet® tablet N = 48 Mean (SD)	Adjusted[a] difference from tramacet®(95% CI)	*p*-value
Visit 2 (3 hours post first dose)	−3.46 (1.64)	−3.05 (2.12)	−0.13 (−0.76, 0.51)	0.6878
Visit 2 (6 hours post first dose)	−6.58 (14.10)	−3.51 (20.05)	−3.04 (−9.97, 3.90)	0.3873
Visit 3 (48 ± 24 h)	−86.54 (36.36)	−90.14 (39.65)	7.45 (−6.74, 21.65)	0.3001
Visit 4 (5 ± 2 days)	−252.69 (86.99)	−250.14 (91.57)	9.56 (−21.58, 40.70)	0.5436

[a]Difference in the adjusted mean between the two groups.
Analysis of covariance was used to estimate treatment difference, including treatment arms as factor and the baseline pain intensity score as covariate.

Table 3: Visual analogue pain scale (ITT population)

Visit	Stilpane® capsules N=52 Mean (SD)	Tramacet® tablet N=48 Mean (SD)	Adjusted[a] difference from Tramacet®(95% CI)	*p*-value
Visit 2 (3 h post first dose)	−55.32 (24.21)	−52.38 (23.28)	−0.57 (−8.92, 7.78)	0.8931
Visit 2 (6 h post first dose)	−61.25 (27.67)	−60.76 (23.05)	1.34 (−8.44, 11.12)	0.7862
Visit 3 (48 ± 24 h)	−68.02 (23.74)	−71.21 (15.95)	5.58 (−1.01, 12.16)	0.0960
Visit 4 (5 ± 2 days)	−73.50 (20.59)	−70.63 (20.84)	−0.63 (−7.58, 6.32)	0.8572

[a]Difference in the adjusted mean between the two groups.
Analysis of covariance was used to estimate treatment difference, including treatment arms as factor and the baseline pain intensity score as covariate.

Table 4: Assessment of total pain relief (TOTPAR) (ITT population)

Visit	Stilpane® Capsules *N* = 52 Mean (SD)	Tramacet® Tablet *N* = 48 Mean (SD)	Adjusted[a] difference from Tramacet®(95% CI)	*p*-value
Visit 2 (3 h post first dose)	5.58 (1.58)	5.54 (1.93)	0.04 (−0.66, 0.73)	0.9204
Visit 2 (6 h post first dose)	15.52 (13.59)	17.88 (19.22)	−2.36 (−8.92, 4.21)	0.4782
Visit 3 (48 ± 24 h)	145.56 (44.06)	157.0 (30.83)	−11.44 (−26.65, 3.77)	0.1387
Visit 4 (5 ± 2 days)	413.25 (96.35)	430.33 (80.34)	−17.08 (−52.45, 18.28)	0.3401

[a]Difference in the adjusted mean between the two groups.
Analysis of covariance was used to estimate treatment difference, including treatment arms as factor and the baseline pain intensity score as covariate.

Table 5: Sum of hourly pain relief and hourly pain intensity difference (ITT population)

Visit	Stilpane® capsules *N* = 52 Mean (SD)	Tramacet® tablet *N* = 48 Mean (SD)	Adjusted[a] difference from Tramacet®(95% CI)	*p*-value
Visit 2 (3 h post first dose)	2.45 (1.72)	2.82 (2.06)	0.01 (−0.50, 0.52)	0.9656
Visit 2 (6 h post first dose)	9.28 (27.02)	14.70 (38.69)	−5.77 (−19.12, 7.57)	0.3925
Visit 3 (48 ± 24 h)	59.36 (43.10)	67.20 (43.83)	−2.70 (−18.46, 13.07)	0.7348
Visit 4 (5 ± 2 days)	160.89 (93.12)	180.53 (78.64)	−4.39 (−30.91, 22.13)	0.7432

[a]Difference in the adjusted mean between the two groups.
Analysis of covariance was used to estimate treatment difference, including treatment arms as factor and the baseline pain intensity score as covariate.

the Stilpane® group and 13% in the Tramacet® group fair, 33% in the Stilpane® group and 38% in the Tramacet® group good, and 22% in the Stilpane® group and 10% in the Tramacet® group excellent (data not shown). These differences failed to reach statistical significance.

In both treatment groups, approximately 70% of patients achieved perceptible pain relief and 35% of patients achieved meaningful pain relief after 60 min of starting their respective treatments (data not shown).

Anxiolytic efficacy
Anxiety was assessed prior to and post-surgery, and thereafter, at various time points after the first administration of either Stilpane® or Tramacet®. The shift in anxiety levels from baseline is outlined in Table 6. More than 90% of patients in both treatment arms experienced mild anxiety (Beck's score of 0–16) at 6 h post first dose which was largely sustained for the duration of the study period. At 48 h, however, two patients in the Tramacet® group developed moderate anxiety, one of whom returned to a state of mild anxiety by study day 5. One of the two patients in the Tramacet® group who initially experienced moderate anxiety, reported mild anxiety by 48 h. Three patients in the Stilpane® group experienced moderate anxiety throughout the study period. No significant differences were found between the two treatment arms.

Tolerability and safety
No significant safety concerns were revealed in the study. Vital signs and physical examinations were within normal ranges. The most common treatment emergent events were nausea (Stilpane® 9.6 %, Tramacet® 12.5%), vomiting (Stilpane® 5.8 %, Tramacet® 6.3%), somnolence (Stilpane® 15.4%, Tramacet 14.6%), dizziness (Stilpane® 1.9 %, Tramacet 6.3%), headache (Stilpane® 1.9 %, Tramacet® 2.1%), insomnia (Stilpane® 1.9%, Tramacet® 2.1%), pruritus (Stilpane® 5.8 %, Tramacet® 2.1%) and rash (Stilpane® 0 %, Tramacet® 4.2%). No patients discontinued treatment due to adverse effects and no serious adverse events were reported.

Discussion
Combination analgesics may offer effective relief of moderate to severe pain. This study compared the analgesic and anxiolytic effects of Stilpane® and Tramacet® in patients after third molar extraction, a procedure commonly associated with substantial pain and anxiety. An impaction grading score of ≥ 8 was required to ensure that patients underwent similar degrees of surgery. The maximum achievable score of 16 took cognisance of whether teeth were erupted and whether impaction involved soft tissue, partial bone, complete bone or unusual impaction such as horizontal/inverted or posterior/anterior.[18] All patients required bone removal for two mandibular impacted molars. Not surprisingly, all enrolled patients experienced moderate to severe post-operative pain and were therefore eligible for inclusion in the study.

Table 6: Shift in anxiety level (ITT population)

| | Baseline | | | | | |
| | Stilpane® (*N* = 52) *n* (%) | | | Tramacet® (*N* = 48) *n* (%) | | |
	Mild	Moderate	Severe	Mild	Moderate	Severe
Visit 2 (6 Hours post first dose)						
Mild	49 (94.2)	3 (5.8)	0	46 (95.8)	2 (4.2)	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Visit 3 (48 ± 24 h)						
Mild	49 (94.2)	3 (5.8)	0	44 (91.7)	1 (2.1)	0
Moderate	0	0	0	2 (4.2)	1 (2.1)	0
Severe	0	0	0	0	0	0
Visit 4 (5 ± 2 days)						
Mild	49 (94.2)	3 (5.8)	0	45 (93.8)	1 (2.1)	0
Moderate	0	0	0	1 (2.1)	1 (2.1)	0
Severe	0	0	0	0	0	0

Stilpane® and Tramacet® contain similar doses of paracetamol, combined with different weak opioids. Codeine, which is present in Stilpane®, and tramadol present in Tramacet® are both pure agonists of pain-modulating μ opioid receptors.[23] Tramadol also increases synaptic serotonin and noradrenaline levels, thereby acting on an additional site along the nociceptive pathway. Nonetheless, per milligram, codeine and tramadol are considered to have similar opioid analgesic equivalence.[24] The analgesic potency of the 37.5 mg tramadol in Tramacet® is thus conceivably four to five fold greater than the 8 mg codeine in Stilpane®. Despite this obvious discrepancy, Stilpane® was as effective as Tramacet® in alleviating the moderate to severe acute pain associated with dental surgery. Notably, at 6 h post first dose, 22% of patients graded the efficacy of Stilpane® as excellent which contrasted with 10% of patients in the Tramacet® group.

Stilpane®'s analgesic prowess may be attributed to its final component, meprobamate. Although it harbours analgesic properties, it is unlikely that low dose meprobamate possesses an intrinsic analgesic activity sufficient to account for codeine's dosage (ca. 30 mg) shortfall. Rather, this sedative may potentiate codeine's analgesic effects via a different and unknown synergistic mechanism. This notion is supported by acute[25] and chronic[8] pain studies that have demonstrated comparable efficacy for tramadol 37.5 mg/paracetamol 325 mg and a much higher dose of codeine 30 mg/paracetamol 300 mg than the one used here. Taken together, it appears that meprobamate is a crucial component of the ultra-low dose codeine combination analgesic.

Meprobamate's mechanism of anxiolytic action is related to its barbiturate-like modulatory effects on $GABA_A$ receptors.[9,10] Therefore it was anticipated that Stilpane® would achieve a far greater anxiolytic effect than Tramacet®. However, the fixed-drug combinations displayed comparable anxiolytic effects. On further reflection, this was not surprising given that compared to preoperative anxiety, postoperative anxiety was reduced significantly in both groups prior to their receiving either Stilpane® or Tramacet®, ostensibly because the anticipatory fear related to surgery had been diffused by completion of the intervention. The severity of anxiety experienced by most patients in each treatment group prior to the administration of the combination analgesics was mild, which made assessing any subtle changes and interpretation of the data difficult. Of note is that a Beck's anxiety score of 0–16 is interpreted as mild anxiety. It is thus conceivable that these patients experienced no anxiety at all. Furthermore, it is likely that whatever procedure-related anxiety was present, continued to diminish due to adequate analgesia as well as to the healing passage of time. Studies assessing the preoperative anxiolytic effects of these preparations may prove more informative.

Although there appeared to be a greater trend for pruritus in Stilpane® treated patients and dizziness and rash in patients who received Tramacet®, adverse effects were similar and mild in both treatment groups. It should be noted that nausea and vomiting may add to the subjective experience of pain, and that these adverse events were reported in approximately 5–10% of patients in both groups. Cessation of treatment due to side effects was not required, underscoring the advantage of reducing the dose of individual components in combination analgesics.

Assessing physical dependence and/or addiction potential of low dose, short term use of tramadol, codeine or meprobamate was beyond the scope of this study.

Conclusion

This study demonstrated that despite their distinctive compositions and mechanisms of action, Stilpane® and Tramacet® are equally effective and well-tolerated combination analgesics in eligible patients experiencing moderate to severe acute pain. Potential clinically relevant differences in their anxiolytic and side effect profiles may ultimately dictate their preferential use in patients with coexisting high levels of acute anxiety or co-morbid medical conditions. Meanwhile, the interchangeable use of Stilpane® and Tramacet® specifically for acute pain control appears justified.

Conflict of interest – I declare that I have no financial or personal relationship which may have inappropriately influenced me in writing this paper.

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