The usage and efficacy of a combination analgesic preparation

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Summary
Combination analgesics are frequently prescribed for the treatment of a multitude of conditions. Many of these preparations contain agents with no proven analgesic efficacy. We examined 3059 patients using a new combination agent containing only paracetamol, codeine, and ibuprofen. It appears that despite a wide variation in the administration of the tablet that good pain relief was obtained by the patients. Patient compliance and tolerance of the tablet was good. A small number of adverse events was noted and these were mostly related to the non-steroidal anti-inflammatory component of the tablet. None of the adverse events were considered serious. The tablet was prescribed for a wide range of conditions, most of which involved pain of an inflammatory nature. Most patients indicated that they would use this preparation again if needed.

Keywords:
Analgesics, paracetamol, codeine phosphate, ibuprofen, non-steroidal anti inflammatory agents (NSAID), pain.

Introduction
South African doctors have the largest choice of combination analgesic preparations available for prescription. These preparations contain various combinations of the analgesics paracetamol, codeine, propoxyphene, and meprobamate. These may be supplemented with non-steroidal anti-inflammatory agents (NSAID's), and many other additives including caffeine, antihistamines, pemoline, amino acids, and vitamins.

The World Health Organisation (WHO) recommends that analgesia be administered according to a three rung "Pain Ladder". This entails starting analgesic therapy with paracetamol. Should this prove ineffective then a NSAID should be added together with the paracetamol. Should this also prove inadequate then an opioid should be added to the paracetamol/NSAID regime. Each of these substances acts on different receptors so it follows that their actions would be synergistic. It would thus make pharmacological sense for a combination agent to contain the three substances recommended by the WHO. The exact role, if any, of any other additives is open to debate and is beyond the scope of this paper.

The next contentious issue is exactly how much of each agent should be administered to be effective as an analgesic for mild to moderate pain. The dose of paracetamol should not exceed 6 grams per day, the recommended dose of codeine is 10 – 60 mg per day, while that of the NSAID would differ according to the NSAID administered. This is the case when these agents are given as individual preparations. It must be remembered that the drug combination would lessen the dose of each component required for efficacy because of their synergism.

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Objectives of the study
The primary objective of the study was to assess patient satisfaction and tolerance of the combination agent as prescribed in everyday practice for pain relief.

The secondary objective was to correlate efficacy of the treatment with the demographic characteristics of the patients and the diagnosis of the condition for which the preparation was prescribed.

Method
The study is an open, uncontrolled, multicentre study. No placebo control was used, as it would be unethical to withhold analgesia from the patients experiencing pain. Specialists and General Practitioners were selected from 296 centers in South Africa. Each doctor would recruit 10 patients experiencing pain and prescribe the study drug at his or her discretion.

We examined the different combination analgesics. After excluding any combination containing any other substances other than those recommended by the WHO we randomly chose one tablet to study. The components of this tablet approximate the dosages required to deliver effective analgesia for mild to moderate pain. Each tablet contains paracetamol (350 mg), ibuprofen (200 mg), and codeine phosphate (10 mg). It was decided that the most recently released product (MYBULEN™) would be studied as this could help minimize patient recognition of this tablet as well as any previous exposure and re-

sponse to the product.

At visit one the patient would be examined, a diagnosis made, and treatment with the agent would be commenced. The dosing schedule would be MYBULEN™ 1-2 tablets every six hours in accordance with the package insert. The study would record gender, age, clinical diagnosis, and dose regimen of MYBULEN™.

The second visit was to occur within 5-10 days. At this visit the adverse events, patient satisfaction, and patient compliance were recorded.

Statistical analysis

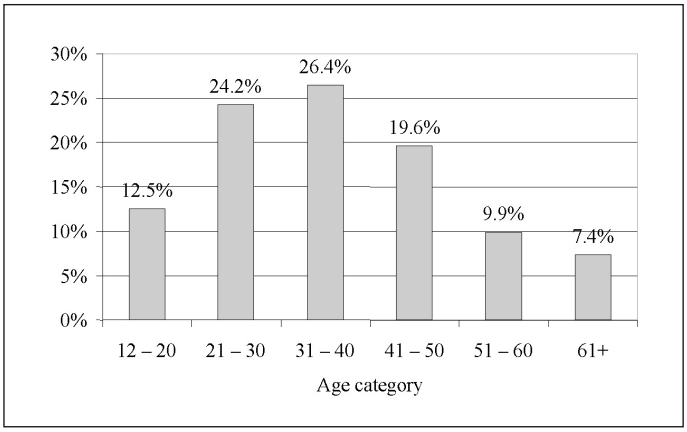
For the purpose of analysis all the data was combined and treated as one dataset. The analysis of the data was strictly objective and in accordance with ethical statistical practice. Specific interest was shown to patient compliance, patient satisfaction, and adverse events.

Results

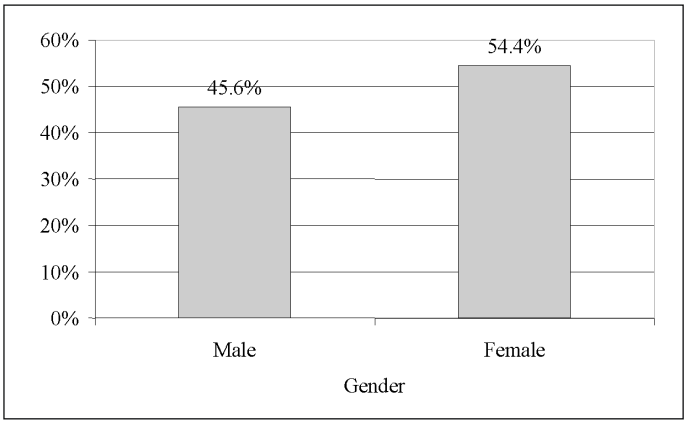
A total of 3059 patients were included from 296 sites. (56 Specialists, 240 General Practitioners).

1. Demographic data

Analysis of the data revealed the following details.



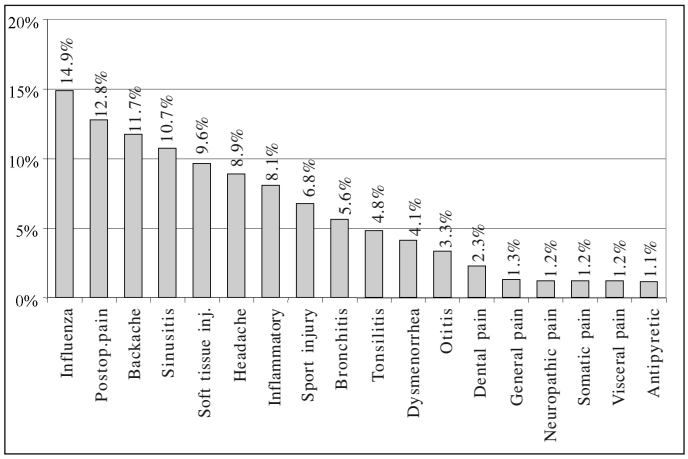
Patient age distribution



Gender ratio

2. Clinical diagnoses

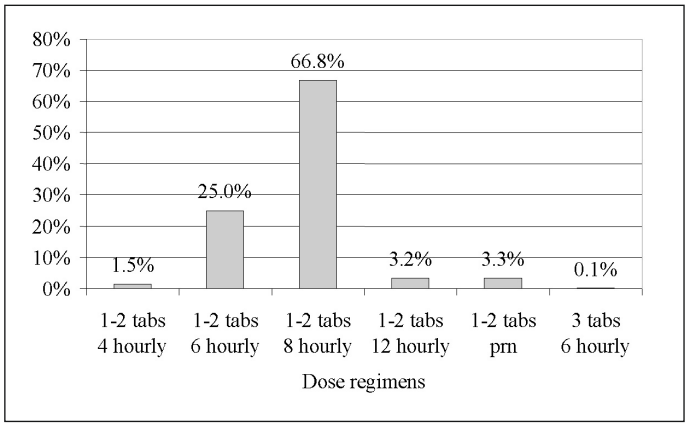
The total exceeds 3059 as patients may have had more than one assigned diagnosis. The percentages were calculated out of 3059.



3. Dose regimens

Regimen	Number (%) of patients	Duration of treatment, days: Minimum/maximum
1-2 Tablets 4 hourly	46 (1,5)	1/20
1-2 Tablets 6 hourly	763 (25,0)	2/30
1-2 Tablets 8 hourly	2037 (66,8)	1/42
1-2 Tablets 12 hourly	99 (3,2)	2/42
1-2 Tablets prn	102 (3,4)	1/30
3 Tablets 6 hourly	2 (0,1)	4/4
Total	3049* (100)	1/42

* Dose regimen not reported for 10 patients

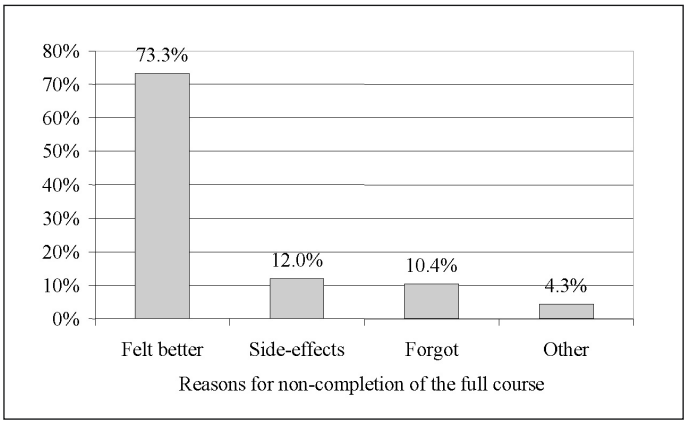


4. Patient compliance

3045 responses were received at the follow-up visit. 2553 (83.8%) of the patients had completed the full course of therapy while 492 patients had not. 490 patients gave reasons for non-compliance. These reasons are summarized below:

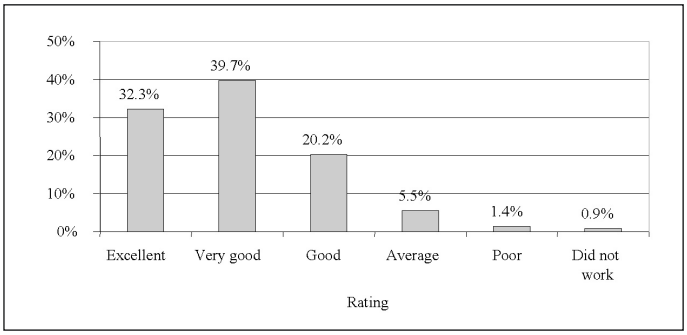
Reason		Number (%) of patients
Felt better		359 (73,3)
Side-effects		59 (12,1)
Forgot		51 (10,4)
Other: Did not work	8 (1,6)	
Other illness/other drug/hospitalization	7 (1,4)	
Can't swallow tablets	2 (0,4)	
Too expensive	2 (0,4)	
Never started	1 (0,2)	
Language problem	1 (0,2)	
		21 (4,3)
	Total	490 (100)

Non-compliance factors



5. Patient satisfaction

Patients were asked to rate the medication. 3012 responses were obtained. The ratings are summarized in the table below.



155 patients indicated that they would not use MYBULEN™ again. 142 patients documented their reasons for this decision.

Reason	Number (%) of patients
Did not work/not effective/no relief/pain persisted	73 (51,4)
Side effects	56 (39,4)
Preferred other medication	13 (9,2)
Total	142 (100)

6. Adverse events

A total of 368 patients indicated that they had experienced adverse events. Some patients experienced more than one adverse event. None of these events were reported as being serious. Some patients reported on the duration of the adverse events and the treatment administered to counteract these events.

Adverse event	Number (%) of patients
Gastric discomfort	152 (39,4)
Sedation	86 (22,3)
Constipation	66 (17,1)
Nausea	55 (14,2)
Allergic reaction	7 (1,8)
Dried up/dry mouth/dry throat	5 (1,3)
Cardiovascular discomfort	4 (1,0)
Shaky/shivers	3 (0,8)
Felt funny/weak/sweaty	2 (0,5)
Headache	2 (0,5)
Ill tempered/aggressive	2 (0,5)
Sleeplessness	1 (0,3)
Light rectal bleed	1 (0,3)
Total	386 (100)

Discussion

It is evident that the combination preparations are prescribed for a very wide range of clinical conditions. Most of the diagnoses involved mild to moderate pain and the majority included pain with an inflammatory component. The agents were also used for managing some of the symptoms of infective processes such as pyrexia. The effects of this drug combination on neuropathic pain are questionable but there is evidence that some neuropathic pains do respond to opioids albeit a small percentage.

A wide variation in dosing was noted. This can partially be explained by a variation in patient weight but this was not recorded for the study population. The dose as recommended on the package insert was clearly not adhered to but despite this it was shown that the majority of the patients obtained satisfactory pain relief. The synergistic effects of the three components of the preparation may account for the good analgesia experienced by the majority of the subjects despite the variation in drug dose.

Closer examination of the data from the 490 patients who did not complete the full coarse of therapy reveals some interesting points. Patients who forgot to take the medication or never started the medication make up 10.4% of this group. It must be asked if this group ever had any pain, as the usual response of someone in pain is to seek pain relief. To simply forget or not take medication would imply other reasons for the primary consultation rather than pain. The vast majority of this defaulting group (73.3%) of patients only stopped taking the medication, as they were relieved of their pain. Only 7.8% of the patient cohort rated the treatment as average, poor, or did not work.

The incidence of adverse effects was very low. Only 368 patients reported that they experienced adverse events. These episodes were mostly related to the known side effects of the individual components of the preparation. The ibuprofen caused the gastric symptoms via cyclooxygenase-1 inhibition while the codeine was responsible for the constipation via its action on gut opioid receptors. Treatment of the events was purely symptomatic and easily remedied. The prescribing physician would obviously not prescribe the combination agent in patients with known sensitivity to any of the component drugs or patients with a previous history of adverse reactions to any of the drug components.

Conclusion

The use of a combination pharmaceutical preparation containing the three agents paracetamol, ibuprofen, and codeine makes good pharmacological sense when treating mild to moderate pain. The synergistic effect of the components means that less of each agent needs to be used to get good pain relief. The fact that less of each agent is used would imply that the incidence of adverse events experienced by patients would be lessened and this fact was borne out by the study. Patients experienced good pain relief from the preparation and the combination was well tolerated by the patient cohort. The fact that the majority of subjects expressed that they would use this combination agent when it was required further demonstrates good acceptance. It would appear that patient compliance is enhanced by their satisfaction with the pain relief obtained from a combination preparation such as "MYBULEN™". It is questionable whether the extra addition of the myriad of substances found in some multi-agent pharmaceutical preparations would enhance their analgesic properties to any significant degree. There is no question that these additives would certainly increase the advent of adverse events resulting from use of these preparations. Pharmacological preparations should target specific receptors to enhance their actions and it is here that the "KISS" principle should apply…..Keep It Simple Stupid!

Acknowledgements

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