Original article

Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study

M.A. Mibielli¹,a,b
¹Centro Universitário Serra dos Órgãos (UNIFESO)
²Sociedade Brasileira de Ortopedia e Traumatologia, Rio de Janeiro, Brazil

M. Geller¹,c
¹Centro Universitário Serra dos Órgãos (UNIFESO)
²Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

J.C. Cohen⁶
⁶Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

M.T. Cohen⁶,d,e
⁶Centro Ortopédico Traumatológico (COTRAUMA)
⁸Instituto Nacional de Traumatologia e Ortopedia (INTO) Rio de Janeiro, Brazil

C.P. Nunes⁶,f
⁶Centro Universitário Serra dos Órgãos (UNIFESO)
⁸Instituto de Pós-Graduação Médica Carlos Chagas (ICC), Rio de Janeiro, Brazil

L.B. Oliveira⁸
⁸Instituto de Pós-Graduação Médica Carlos Chagas (ICC), Rio de Janeiro, Brazil

A.S. da Fonseca⁸,a,f
⁸Centro Universitário Serra dos Órgãos (UNIFESO)
³Universidade Estadual do Rio de Janeiro (UERJ), Rio de Janeiro, Brazil

Address for correspondence:
Prof. Dr Mauro Geller, Av. Ataulfo de Paiva, 135 sl. 1103–1104, Rio de Janeiro – RJ – Brazil 22440-030, Tel.: (55-21) 3875-6660; Fac.: (55-21) 2259-3395; mgeller@infollnk.com.br

Key words:
Cyanocobalamin – Diclofenac – Low back pain – Lumbago – Pyridoxine hydrochloride – Thiamine mononitrate

Abstract

Objectives:
To assess the influence of vitamins B1, B6 and B12 on the analgesia success achieved by diclofenac in subjects with acute lumbago.

Research design and methods:
A randomised, double blind controlled clinical study in parallel groups, in which subjects received twice-daily oral administration of either the combination therapy, Group DB (50 mg diclofenac plus 50 mg thiamine, 50 mg pyridoxine and 1 mg cyanocobalamin) or diclofenac monotherapy, Group D (50 mg diclofenac). The study period lasted a maximum of 7 days. If sufficient pain reduction was achieved (defined as Visual Analogue Scale <20 mm and patient’s satisfaction), subjects could withdraw from the treatment after 3 or 5 days. All subjects gave written informed consent to participate in the study.

Main outcome measures:
The primary confirmatory study objective was to determine the number of patients with sufficient pain reduction after 3 days of treatment.

Results:
Three hundred and seventy-two subjects were allocated at random to either treatment group: Group DB – 187 subjects and Group D – 185 subjects. After 3 days of treatment, a statistically significant higher proportion of subjects in Group DB (n = 87; 46.5%) than in Group D (n = 55; 29%) terminated the study due to treatment success (£2: 12.06; p = 0.0006). Furthermore, the combination therapy yielded superior results in pain reduction, improvement of mobility and functionality. Drug safety monitoring profile throughout the trial was within the expected safety profile of diclofenac.

Conclusions:
The combination of diclofenac with B vitamins was superior to diclofenac monotherapy in lumbago relief after 3 days of treatment. As a study drawback, daily VAS measurements were only recorded until subject withdrawal from treatment, whether after 3, 5, or 7 days. There were no differences in safety profile between the two study groups.

Introduction

Low back pain (LBP) or lumbago consists of pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without leg pain. It may be acute and become chronic if persisting for 12 weeks or more³. LBP is the fifth most common reason for all physician visits. The lifetime prevalence of LBP in Europe is 60–80%; the prevalence of serious cases is about 14%,²,³. Approximately 25% of adults do suffer from this disorder and about one
third of these patients report substantial limitation in their activity including inability to work due to persistent or recurring episodes of LBP.

In only a small number of cases LBP is caused by a specific disorder such as cancer, spinal infection, fracture, spinal stenosis, or symptomatic disc herniation. In contrast, in more than 85% of patients LBP cannot be attributed to a specific disease or spinal abnormality and is therefore classified as non-specific LBP. LBP presents as a complex, multifaceted musculoskeletal pain syndrome.

Current guidelines for the management of LBP recommend the use of a simple analgesic (e.g. paracetamol) or a non-steroidal anti-inflammatory drug (NSAID) as first-line or second-line oral treatment.

Diclofenac shows experimentally and clinically proven anti-inflammatory and analgesic efficacy. Diclofenac is the most frequently used NSAID worldwide, mainly used to symptomatically relieve nociceptive pain at a daily dosage ranging between 75 mg and 150 mg. The major analgesic mechanism involved is the suppression of prostaglandin synthesis by inhibition of cyclooxygenases (COX). There is some evidence that diclofenac inhibits the lipoxygenase pathways as well, thus reducing inflammation involving leukotrienes and phospholipase A2. Potassium ion channels may also be involved in the antinociceptive action of diclofenac.

Some studies have compared various NSAIDs including diclofenac with placebo in the treatment of acute LBP and reported global improvement of pain under the active therapy.

Experimental investigations related to the fixed dose combination used in this clinical trial have shown a synergistic action of the vitamins B1, B6 and B12 with diclofenac. In rat models of inflammation and pain, diclofenac-induced analgesia was potentiated by simultaneous administration of the B-vitamin combination.

Earlier double-blind, randomised clinical studies compared the analgesic efficacy of diclofenac monotherapy with a fixed combination therapy of diclofenac and B vitamins in patients with LBP or vertebral column diseases with painful degenerative changes. These studies showed better analgesic results with the fixed-dose combination therapy. A statistically significant larger number of patients in the group treated with diclofenac and B vitamins showed an earlier onset of pain relief as compared to the group treated with diclofenac alone.

Diclofenac is classified as one of the well-tolerated NSAIDs. However, as with any NSAID, diclofenac involves the risk of gastrointestinal side effects by damaging the gastric mucosa due to inhibition of the COX 1 enzyme. In addition, cardiovascular risks are present as well, such as cardiac or brain ischaemia or infarction. To lower the risk of such adverse events, the duration of diclofenac treatment should be limited. As such, increased efficacy of the diclofenac B vitamin combination treatment could result in shortening the therapy time and to potentially reduce side-effects.

In order to confirm and expand on the current data available, the present prospective randomised study was performed, comparing the efficacy of diclofenac (50 mg) plus vitamins B1 (50 mg), B6 (50 mg) and B12 (1 mg) versus diclofenac tablets (50 mg) given two times daily in patients with an acute episode of LBP.

The primary study objective was to investigate whether a higher percentage of subjects treated with the fixed dose combination of diclofenac and vitamins B1, B6 and B12 (Group DB) compared to diclofenac monotherapy, experienced an earlier onset of pain reduction, enabling them to terminate the study after 3 days. Pain reduction was measured and defined by a visual analogue pain scale (VAS) <20 mm and subjects' satisfaction with pain reduction.

Secondary study endpoints included pain reduction after 5 or 7 days of treatment, allowing subjects to stop the study medication. Severity of pain and Finger-to-Floor Distance (FFD) as a parameter of mobility, and signs of functionality before treatment and at subsequent visits were also included.

Patients and methods

The study was conducted in accordance with the declaration of Helsinki as well as the Note for Guidance on Good Clinical Practice (ICH Topic E6 1995) and the Brazilian regulatory requirements (Resolução 196/96 do Conselho Nacional de Saúde). The study was approved by the local ethical committee (UNIFESO) under the number 003/2004 and carried out in compliance with the study protocol at Hospital Universitário Constantino Oraviano – a UNIFESO university hospital in Rio de Janeiro, Brazil. Patients were also referred from additional centres in Rio de Janeiro: Centro Ortopédico Traumatológico, Universidade Federal, Santa Casa de Misericórdia and Hospital Souza Aguiar.

Study population

Following approval of the protocol by the local ethical committee, 372 subjects were randomised to treatment on an ambulatory basis. As defined by the study eligibility criteria, subjects were between 18 and 65 years of age, with a clinical presentation of acute, non-traumatic lumbago lasting no longer than 3 days, and with a VAS (0–100 mm) between 20 mm and 80 mm. Pre-menopausal female subjects were required to submit a urine pregnancy test and maintain adequate birth control for the duration
Study procedures

Subjects were randomised in order of arrival at the study centre, and received a three-digit sequential patient number that was used as the randomisation code. The study statistician used Random Allocation Software (Version 1.0.0) to generate the randomisation codes, in equal size blocks of 20. Only the statistician was aware of the randomisation sequence. All other study assessors and personnel were blinded to the randomisation sequence until the final patient had completed treatment.

The study protocol outlined four visits to the study centre: Visit 1, pre-treatment visit which included screening, randomisation and baseline evaluations; Visit 2 following 3 days of treatment; Visit 3 following 5 days of treatment; and Visit 4 after 7 days of treatment.

If the subject experienced significant pain reduction (VAS < 20 mm and subject satisfaction with pain reduction) at Visit 2 or Visit 3, the subject could terminate the study after completing final evaluations. Any subject presenting an adverse event at the final study visit was asked to return to the study centre after a maximum of 10 days for a follow-up evaluation. If resolution of the adverse event had not been reached after 10 days, the subject was asked to return again within 10-day intervals until resolution of the adverse event.

At Visit 1, consenting subjects were screened by the study medical staff, with a complete physical examination and laboratory evaluations. The investigating physician assigned a three-digit study number to subjects who fulfilled the inclusion criteria based on order of arrival to the study centre. Subjects received the study drug in a vial containing identical tablets. Subjects were divided into two groups, Group DB and Group D. Group DB received tablets containing: 50 mg of diclofenac, 50 mg of thiamine mononitrate (B1), 50 mg of pyridoxine hydrochloride (B6), and 1 mg of cyanocobalamin (B12). Group D received tablets containing 50 mg of diclofenac. Both treatments were identical in size, shape, colour and packaging. Subjects received the study drug for the next 3 days of treatment, plus 1 day (as back up). Subjects were carefully instructed to swallow one tablet with breakfast and one tablet with dinner. After the first 3 days of treatment, the subjects returned to the study centre for follow-up evaluations (Visit 2) and, provided study treatment was to continue, were given study medication for the next 2 days of treatment, plus an extra day (as back up). This procedure was repeated at Visit 3. At each study visit, subjects were asked to return all study medication and packaging, and drug compliance was evaluated (defined as number of tablets taken divided by number of tablets to be taken, multiplied by 100).

Efficacy and tolerability evaluations

At pre-treatment, a medical history (including previous lumbago, spine accidents and surgeries) was taken and a complete physical evaluation was performed, as well as laboratory tests. The following information was collected from the subjects and registered in the CRF at pre-treatment: date of birth, gender, ethnicity, height, weight, waist circumference, BMI, vital signs (heart rate and blood pressure), general nutrition status, alcohol consumption, smoking, manual labour and sports activities. Pre-treatment laboratory evaluations included a complete blood count, partial thromboplastin time (PTT), international normalised ratio (INR), fasting blood sugar, glycosylated haemoglobin A (HbA1c), alanine aminotransferase (GOT), aspartate aminotransferase (GPT), gamma-glutamyl transferase (GGT) creatinine, creatinine kinase, uric acid, blood urea nitrogen, blood sedimentation rate (BSR), and urine pregnancy test for female subjects.

Efficacy evaluations included VAS, patient functionality questionnaire, and mobility evaluation (Fingerto-Floor Distance). For the VAS, the investigator asked the subject to place a vertical mark along a 100 mm line on the data collection form, from 0 mm (no pain) to 100 mm (most severe pain). The score was registered as the distance from the left side of the scale (0 mm) to the mark made by the subject.

For the Patient Functionality Questionnaire (PFQ, Figure 1), the subject answered either 'yes' or 'no' to 12 items. Due to my back pain:
1. I do not sleep well
2. I have to lie down more often
3. It is difficult for me to get up from my bed or a chair
4. I can stand only for a short while
5. I can walk up stairs only slowly
6. It is difficult for me to wash or dry off my whole body
7. It is difficult for me to put on my clothes
8. I can only walk short distances
9. I try to avoid picking things up from the floor
10. I have to change my posture more often
11. I cannot carry heavy things
12. I have to ask other people for assistance

Figure 1. Patient Functionality Questionnaire.
questions about management of daily needs. One point was given for each ‘yes’ answer. Scores were compared relative to treatment as well as total score and question specific score on every visit.

Schober’s and Straight-Leg Raise Tests were performed in order to compare subjects’ similarity in relation to the LBP clinical conditions between Groups DB and D. To perform the Schober’s Test, with the subject in upright position, the investigating physician placed a mark on the osseous protrusion of the fifth lumbar vertebra. A second mark was made 10 cm above the previous, on the medial line. The subject was asked to bend forward as far as possible, and the distance between the two marks was registered in centimetres. For the Straight-Leg Raise Test, with the subject lying supine on a flat surface, the investigator assisted the subject in raising one leg, maintaining the knee absolutely straight, until the point where the subject reported feeling pain in the thigh, buttocks and calf. The opposite leg remained straight on the flat surface. The investigating physician then recorded the angle (degrees) at which pain occurred. If Lasègue’s sign was present at Visit 1 (considered an indication of disc hernia), the subject was not randomised to treatment. During the Finger-to-Floor Distance Test, the subject was asked to plant his/her feet firmly on the floor and lean forward as far as possible with arms outstretched to the front. The distance between the subject’s middle finger and the floor was measured and recorded in centimetres.

At the following study visits (Visit 2, after 3 days of treatment, Visit 3, after 5 days of treatment, and Visit 4, after 7 days of treatment), subjects underwent a comprehensive physical evaluation including vital signs and mobility evaluations, VAS and PFQ evaluations, and laboratory tests (haemoglobin, hematocrit, red blood cell count [RBC], white blood cell count [WBC], PTT, INR, fasting blood sugar, GOT, GPT, creatinine and BSR). At each study visit, adverse event monitoring and concomitant medication evaluations were performed, as was a drug compliance assessment. At Visits 2, 3 and 4, the subject was asked if, in his/her opinion, the pain reduction already experienced was satisfying. If the subject answered ‘yes’ and VAS score was below 20 mm, the subject was considered a treatment success and was removed from the trial. Similarly, if the subject’s condition had clinically worsened in relation to pre-treatment, the principal investigator could decide to remove the subject from the trial due to treatment failure.

When terminating the trial, the following evaluations were carried out: general efficacy and tolerability of the treatment (estimated by the investigating physician) and general compliance (defined as the number of tablets taken divided by the number of tablets to be taken multiplied by 100), and final subject status was recorded.

Statistical analysis

Sample size estimation was based on a group delta of 12.5% (alpha: 0.05, beta: 0.20) for the number of patients being able to stop treatment after 3 days, leading to the requirement for a total of 360 subjects.

Statistical analysis followed a pre-established data analysis plan laid out in the study protocol for the intent-to-treat population, including all subjects randomised to treatment who had received at least one dose of the study medication.

Data analysis was performed by employing BIAS software. Statistical significance was defined with a two-tailed p-value of less than 0.05. Estimated confidence intervals were cited as p = 0.95 (i.e. CI of 95%).

Confirmatory statistical testing of the primary target variable was performed by the Wilcoxon–Whitney U-Test for non-parametric samples.

Descriptive secondary endpoint analysis was carried out using one-sample t-Test for parametric values within one group, Wilcoxon Test for non-parametric values within one group, Welch-Test for comparing parametric samples having possibly unequal variances within one group, Mantel–Haenszel (chi-square test to compare categorical data), and Spearman’s Rank Correlation Test as part of the BIAS software.

Results

Demographic data and pre-treatment evaluations at Visit 1

Figure 2 shows the flow of subjects through the study. A total of 610 subjects were screened from September–December 2007, and 372 of them were randomly allocated to either treatment:

- Group DB (diclofenac plus B vitamins); n = 187 subjects
- Group D (diclofenac); n = 185 subjects

Two hundred and thirty-eight subjects were excluded, as either they did not meet the eligibility criteria for participation in this trial (n = 224) or refused to participate (n = 14).

The subjects’ demographic data are summarised in Table 1. Regarding the age of the participants, there was a statistically significant difference between the two groups of 2.05 years (p = 0.03; P: 0.95 = 0.2–3.9); overall median age was 37 years in both groups. Subjects’ clinical conditions of LBP may be considered as similar when comparing Schober’s and Straight-Leg Raise Test ratings between groups.

The calculated mean value of the VAS scores in Group DB sums to 48.0 ± 12 mm and in Group D to 52.6 ± 12 mm (Δ: mean 3.7 mm). There was also a small difference.
Figure 2. Subject treatment scheme and outcome through the study.

regarding the Finger-to-Floor Distance between the two study groups before treatment was started, Group DB: 19.6±6 cm, Group D: 21.2±6 cm (Δ: mean = 1.6 cm). The sum of PFQ scores in Group DB (mean 9; 4–12) did correspond to the sum of PFQ scores in Group D (mean 9; 5–12). The intensity of pain (VAS mm) did correlate with the Finger-to-Floor Distance (cm) at Visit 1 (Spearman’s correlation coefficient Group DB $\rho = 0.34$, $P: 0.95: 0.256-0.52$, Group D $\rho = 0.41$, $P: 0.95: 0.27-0.48$).

Efficacy evaluations

Primary objective – termination of treatment at Visit 2
The evaluation of the results after 3 days of treatment (Visit 2) is shown in Table 2.

The data demonstrates that 46.5% of the subjects in Group DB could withdraw from the treatment after
3 days of therapy, whereas in Group D only 29.7% of the subjects could terminate, which results in a statistically significant difference of 16.8% ($\chi^2$: 12.32; $p = 0.0005$).

Secondary study endpoints – termination of treatment at Visit 3 and Visit 4
At Visit 3 (after 5 days of treatment), 123 out of the remaining 207 subjects were able to finish the study due to treatment success.

Similar to Visit 2, at Visit 3 a higher number of subjects in Group DB (71/87; 82%) could terminate the study due to treatment success. At Visit 3 (after 20 days of therapy) 59 subjects remaining in the trial, 35 subjects (86.76%) in Group D concluded the study with treatment success and 9 subjects (23.23%) concluded with treatment failure. The proportion of subjects finally concluding Visit 4 with treatment success or failure did not differ between treatment groups.

VAV scores – Visit 2
The mean values of VAS scores at Visit 2 in Group DB sums to: 24.5 ± 20 mm and in Group D: 31.9 ± 20 mm ($p = 0.0003$, $\Delta$: -7.5; $P$: 0.95: -11.5 to -3.4).

Subjects who continued in the study also showed a distinct difference in VAS values in favour of Group DB: (Group DB: 33.6 ± 10 mm, Group D 38.3 ± 9 mm; $p = 0.001$; $P$: 0.95: -7.4 to -2.1).

The intensity of pain was alleviated in both study groups after 3 days of treatment.

The mean reduction in VAS scores at Visit 2 in Group DB sums to: 24.5 ± 18 mm ($p = 0.04$; $P$: 0.95: 21.9–27.0) and in Group D: 20.7 ± 18 mm ($p = 0.06$; $P$: 0.95: 18.1–23.4); which shows a statistical difference between the two groups ($p = 0.044$; $P$: 0.95: 0.08–7.4).

Treatment with the fixed combination of diclofenac and B vitamins (Group DB) resulted in a higher number of subjects (63.1%) with improvement of VAS scores than treatment with diclofenac alone (Group D; 43.8%).

Categorising changes of the VAS scores from Visit 1 to Visit 2 into 3 main categories of responses (see horizontal axis in Figure 3 for all responses recorded), an improvement was seen in Group DB (Figure 3).
VAS scores – Visit 3
At Visit 3 the mean VAS scores for the remaining 207 subjects were further reduced. 72 subjects (82.8%) of Group DB scored less than 20 mm. In Group D, 53 subjects out of 120 (44.1%) had VAS scores below 20 mm. The difference between groups in numbers of subjects with a marked pain relief is significant (p<0.0001). The mean of VAS score in Group DB amounted to 12.9±10 mm, and in Group D to 20.1±12 mm.

Finger-to-Floor Distance (FFD)
After the first 3 days of treatment, the FFD declined within Group DB by 5.6±6 cm (p<0.005; P: 0.95; 5.1–6.6) and in Group D by 4.6±6 cm (p<0.001; P: 3.7–5.4) respectively, resulting in a mean group difference of 2.9 cm (Group DB: 13.7±7 cm, Group D: 16.6±7 cm; p = 0.0001; P: 4.4–1.5). A distinctly higher proportion of subjects in Group DB achieved a better result ($\chi^2$: 3.86; p < 0.05) compared to Group D (Figure 4). This improvement of mobility correlates directly with the decline in pain intensity (VAS). An average difference of 3 cm was calculated between the two treatment groups regarding FFD at Visit 3 (p<0.001; P: 0.95; -4.4 – -1.5).

Patient functionality questionnaire (PFQ)
The median sum of the questions answered with ‘Yes’ was equivalent in both groups before the study (Visit 1: median = 9). At Visit 2, this score was reduced to a median of 4 (0–12) in Group DB and to 6 (0–12) in Group D, indicating a trend towards a superiority of Group DB.

At Visit 3, a further reduction of about 50% was registered in both groups. The number of subjects with distinct changes in the sum of PFQ scores after 3 days of treatment is shown in Table 3.

It may be concluded that at Visit 2 the functionality of the subjects in Group DB shows greater improvement compared to Group D.

Figure 5 shows the percentage of patients with improvement at Visit 2 assessed for each of the questions individually. The improvement of the functionality did correlate with the reduction of the VAS score in both groups. Specific items related to mobility were in favour of Group DB (p < 0.05).

Table 3. Number and percentage of patients’ response to the PFQ between Visit 1 and Visit 2 with functionality scores classified in five categories.

<table>
<thead>
<tr>
<th>PFQ scores classified in 5 categories</th>
<th>Group DB (n = 187)</th>
<th>Group D (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>&gt;0–3</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>&gt;3–6</td>
<td>23</td>
<td>12.3</td>
</tr>
<tr>
<td>&gt;6–9</td>
<td>89</td>
<td>47.6</td>
</tr>
<tr>
<td>&gt;9–12</td>
<td>75</td>
<td>40.1</td>
</tr>
</tbody>
</table>

p value of Visit 1 vs. Visit 2

Group DB versus Group D: p = 0.00087

© 2009 Informa UK Ltd www.cmrojournal.com

Diclofenac plus B vitamins in low-back pain Mibelli et al. 2595
Table 4. Frequency of adverse events (AEs) during treatment phase.

<table>
<thead>
<tr>
<th>Treatment Groups Total No. of Pts with AEs AEs (n)</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DB</td>
<td>D</td>
<td>DB</td>
</tr>
<tr>
<td>Gl symptoms</td>
<td>19</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>7</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Glossitis</td>
<td>8</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>GOT/GPT elevation</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Glucose elevation</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Decreased PPT</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Palate alteration</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria, skin eruption</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased BSR</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of AEs</td>
<td>26</td>
<td>25</td>
<td>17</td>
</tr>
</tbody>
</table>

Gl symptoms: dyspepsia, flatulence, pyrosis nocturna, diarrhoea, constipation; CNS symptoms: nausea, vertigo, headache.

Safety – adverse events

Adverse events (AEs) were recorded at each visit during the treatment period. The distribution of AEs throughout the study is summarised in Table 4. Some patients experienced multiple AEs.

Out of Group DB, three subjects were withdrawn from the study at Visit 2 due to transient elevation of transaminases (n = 2) and dyspepsia (n = 1).

AEs registered during the treatment period may be considered as typical for NSAID treatment.

There were no clinically significant differences between the groups in vital signs throughout the study. In both groups, mean laboratory values remained within reference range at each study visit. There were no statistical differences between the groups at each visit in relation to pretreatment values.

Discussion

Statements and clinical findings

We report here on the enhanced analgesic effect of diclofenac, when combined with a compound of vitamins B1, B6 and B12. To test this hypothesis we conducted a randomised, controlled clinical trial comparing two groups of patients with acute episodes of low back pain (LBP). Patients were treated daily with either diclofenac alone (Group D) or diclofenac in combination with vitamins B1, B6 and B12 (Group DB). Drugs were given orally twice per day in a double blind study design.

LBP relief was assessed by three methods: (1) the subjective pain intensity measured by the patient with a Visual Analogue Scale (VAS), (2) the functional impairment in daily life as scored by the Patient Function Questionnaire (PFQ), a checklist with 12 items of daily activity where the patient could choose from according to his or her perceived impairments, and (3) the Finger-to-Floor Distance (FFD) of the forward bending patient, a test of impaired mobility of the lumbar spine due to the pain. The outcome of the trial shows consistent results in all three measures. Results from this study confirm and expand on previous study outcomes17–21, revealing a potentiation of diclofenac analgesia by supplementation of the B vitamins and, additionally, a concomitantly improved motor function. Thus, the present and historical data provide several justifications on the contribution of the B vitamin compound to analgesia in acute LBP.

Are these improvements clinically relevant?

As shown in Table 2, the number of subjects successfully terminating the treatment phase at Visit 2 (after 3 days of treatment) were 87 in Group DB (diclofenac + B vitamins) versus 55 in Group D (diclofenac monotherapy). The criterion for these changes was a decrease of the VAS pain intensity to a score of <20 mm during the 3 days of initial treatment. Thus, it can be concluded that after 3 days 32 more patients in Group DB in comparison to Group D could terminate treatment.

Similar improvement can be seen in the data obtained from the patients' functional impairment as scored by the Patient Functionality Questionnaire (PFQ). Referencing Table 3, at Visit 1, 164 patients (Group DB) and 159 patients (Group D) had an impairment score of >6 items
out of 12. At Visit 2 (3 days after the start of the study) 55 patients (Group DB) versus 81 patients (Group D) still presented an impairment score of >6 items out of 12. Therefore, 26 patients in Group DB show a lower impairment in comparison to Group D.

Evidently, the improvement attained from the PFQ score is less than that observed on the VAS measurement (see above). We could rationalise that the VAS is a rating of the actual and immediate pain intensity, whilst the impairment scored by the PFQ represents a more integrated rating, measuring historical experiences or situations over the course of several days.

The second mobility test, the Finger-to-Floor Distance (FFD), also demonstrated a significant patients' improvement between Visits 1 and 2 (Figure 4). The summed group differences of patients showing improvements (>5 cm) represents an increase of 31%. However, the result in this instance is imprecise as a small basal difference was found in FFD between Groups DB and D at Visit 1.

Accordingly, with the calculated improvements in favour of the DB Group we find a consistent covariation of the VAS, PFQ and FFD assessments, respectively. The scale of improvement in the DB versus D Groups at Visit 2 supports the claim that the treatment with diclofenac plus the B vitamin compound is clinically meaningful.

The initial assessment of the subjects at Visit 1 reveal a characteristic pattern of LBP, with correlations between pain intensity, restricted mobility, and diminished functionality. The small differences (VAS 3.7 mm; FFD 1.6 cm) between the two treatment groups (DB versus D) prior to the intervention can be disregarded, as they did not essentially affect the final outcome in each group.

Clearly, the primary benefit for the patients is the shorter duration and lower level of pain in the DB versus D Groups, where there is reduction of the overall suffering as well as improvement of the specific aspects of functionality, which greatly impact the capacity to carry out normal activities of daily life. Although not specifically addressed in this trial, previous epidemiological studies in LBP have highlighted the significance of the ability to go to work; pain reduction along with improvement of the PFQ as seen in this study would undoubtedly contribute to the subject's capacity to work and carry out other routine activities.

A further benefit of adding B vitamins is seen in the potential reduction of NSAID consumption. There is ample evidence of two types of relevant adverse events (AEs) of NSAID treatment, i.e. gastrointestinal and cardiovascular risks. Both AEs increase with the dose and duration of the drug intake. Therefore, any measure which could result in the reduction of the dose and duration of NSAID intake may contribute to the lowering of such risks.

Thus, adding B vitamins may help to reduce the risks of these potentially severe side effects associated with diclofenac. Furthermore, the addition of B vitamins to diclofenac did not increase the incidence of AEs (Table 4). However, the search for a statistically significant difference in AE incidence would require a larger study population.

Not only is the outcome of this large study (372 patients) aligned with the results of earlier investigations but additionally it expands on previous data by investigating patients' functionality scores, which is important for patients' daily lives.

Furthermore, all study parameters/tests which defined treatment success have been performed at one university centre excluding multicentre variation, which adds to the strength of this study.

The study limitation is in the design, as it did not include daily recordings of VAS scores to yield continuous time courses of pain intensity ratings right to the end of the treatment.

Mechanisms of low back pain

Low back pain (LBP) is a common complaint in primary care settings, while the aetiology and pathological mechanisms are still widely unknown. Over the past years our understanding of the variety of nociceptive, inflammatory, neuropathic and traumatic/mechanical stimuli that may contribute to the pathophysiology of LBP has developed greatly. For example, lumbar pain may include a mechanical aetiology within the musculoskeletal system causing nociceptive pain, but at the same time an irritation or lesion to the nervous system may contribute as well, causing neuropathic pain. Involvement of several components is rather common in LBP, and thus the concept and term of a 'mixed pain' aetiology was recently put forward. Mixed neuropathic and nociceptive pathophysiology may benefit from a therapeutic rationale, accounting for the different mechanisms involved. It is plausible that combining diclofenac and B vitamins would support this objective.

It is well known that nociceptive and inflammatory pain responds to diclofenac, both in animal models and patients. While B vitamins reveal antinociceptive effects on nociceptive/inflammatory pain either when used alone or on combination with diclofenac, they also inhibit allodynic behaviour in rats following a spinal nerve ligation. Allodynia is an expression of neuropathic pain of the hypersensitivty type in animals and humans. In rat models with nerve liggations or transections, allodynia is strongly suppressed by Vitamins B1 and B12, and to a lesser extent by vitamin B6.

Hence, vitamins B1 and B12 are potent inhibitors of allodynia in rat models of neuropathic pain. Several pharmacological mechanisms not related to the nutritional requirements of the B vitamins, were proposed to
contribute to the anti-allodynic/analgesic effects of B vitamins. These include the activation of guanylyl cyclase pathways or the restitution of Na⁺ currents in small dorsal root ganglion (DRG) neurons damaged by a compression lesion. However, diclofenac given to alldynic rats neither potentiates the anti-allodynic effects of B vitamins nor induces anti-allodynia when given alone, a finding corroborating the ineffectiveness of diclofenac in human neuropathic pain.

Therefore, diclofenac shows a preferential analgesic effect on nociceptive/inflammatory pain, while B vitamins tend to inhibit some of the processes involved in neuropathic pain. Taking into consideration these different mechanisms, we propose that the potentiation in analgesia of the diclofenac/vitamin B combination seen in our study may suggest that most, if not all, of our LBP patients are cases of mixed pain. Consequently, the diclofenac and the B vitamins may act in synergy in the treatment of low back pain. Future experimental and clinical work should aim to expand on these findings.

It might also be valuable to investigate these benefits in patients with a chronic course of LBP, providing insight into neuropathic pain involvement.

Conclusion

In the 372 patients evaluated, the combination of diclofenac with vitamins B1, B6 and B12 was superior in analgesia to a diclofenac monotherapy, in terms of the time of onset for pain relief and patient’s satisfaction after 3 and 5 days of treatment.

Since LBP is a multifaceted syndrome, treatment with a single drug such as diclofenac may not yield sufficient analgesia or may require a longer treatment time to achieve the desired results. In contrast, the combination of diclofenac with vitamins of the B group suggests an improved efficacy, shortening the treatment period and thus potentially lowering the risk for AEs.

Transparency

Declaration of funding

This study was funded by a research grant from Centro Universitário Serra dos Órgãos – UNIFESO. Merck SA, Brazil (an affiliate of Merck KGaA) donated the drugs for this study. Aside from donation of the medications used in the clinical trial, there was no funding or any other form of financial contribution and/or support from Merck. The authors did not receive honoraria for performing the study or preparing the manuscript.

Declaration of financial/other interests

All the authors have disclosed that they have no relevant financial relationships.

Some peer reviewers receive honoraria for their review work in CMRO. Peer Reviewer 1 has disclosed that he/she is a scientific consultant on clinical trials to Jamieson Laboratories Inc. Peer Reviewer 2 has no relevant financial relationships.

Acknowledgements

The authors acknowledge the commitment and collaboration of the following individuals: Renato Kaufman, MD (Hospital de Cardiologia de Laranjeiras) for patient referral and physical examination; Prof. Oscar Roberto Osuimaraes (Centro Universitário Serra dos Órgãos – UNIFESO) for laboratory exam collection and analysis. Prof. Rafael Varella (Centro Universitário Serra dos Órgãos – UNIFESO; Universidade Federal do Rio de Janeiro - UFRJ) for data collection. Ernst M.W. Koch, PhD (Schmerzentrum Frankfurt, Alsbach) for data revision and help with statistical analysis. Dieter Bonke, PhD (Merck KGaA) and Prof. Manfred Zimmermann (Neuroscience and Pain Research Institute, Heidelberg) for comments on the draft manuscript. Joko Gabriel Daher (Centro Universitário Serra dos Órgãos – UNIFESO), Mariana Thome (Centro Universitário Serra dos Órgãos – UNIFESO), Marcelo Paula Coutinho MD (Universidade Federal do Rio de Janeiro - UFRJ) for study monitoring.

References


32. Song XS, Huang ZJ, Song XJ. Thiamine suppresses thermal hyperalgesia, inhibits hyperexcitability, and lessens alterations of sodium currents in injured, dorsal root ganglion neurons in rats. Anesthesiology 2009;110:387-400