Title of Study: A Randomized, Placebo-Controlled Trial in Indonesia of the Analgesic Effect of Nimesulide After Extraction of an Impacted Wisdom Tooth

Studied Period: 01 April 2001 to 30 June 2003	**Clinical Phase:** IV

Objective:

This study was aimed to test whether nimesulide is an effective alternative to diclofenac in the treatment of pain in subjects undergoing extraction of a lower impacted wisdom tooth.

Methodology:

A mono-center, randomized, placebo-controlled, parallel-group design was chosen and conducted in conformance with Good Clinical Practice. The placebo-controlled, comparative design is recommended as the best design, presenting the strongest evidence in efficacy trials. Although the dental impaction model is considered to be the most sensitive pain model in discriminating between study drug and standard treatment, the proper choice of the methods of pain assessment and the definition of endpoints may have a substantial impact on the result. This study was designed by incorporating visual analog scale (VAS) measurements for pain intensity and pain relief as supportive data with the objective to augment the sensitivity of the dental impaction model.

The dental Impaction model allows only for a parallel-group design, since pain intensity subsides within a short period of time, thus, not allowing for crossover.

Number of Subjects:

Two hundred and twenty five (225) patients were screened. Thirteen (13) patients (5.8 % out of total screening) were excluded. Of the 212 patients, 8 patients discontinued due to different reasons. In Nimesulide group there were 2 patients (2.7 %) withdraw from the study due to lost to follow up, from Diclofenac and Placebo groups there were 3 patients each, 2 patients were withdrawn from the study incompliance, and 1 patient was lost to follow up resulting in 204 patients who completed the study (65 patients in Nimesulide group, 71 patients in Diclofenac group and 68 patients in placebo group). There was no statistically significant difference between the three study groups in terms of baseline demographic characteristics (p-value was higher than 0.05).

Diagnosis and Criteria for Inclusion:

Men and women aged 18 years or older undergoing as outpatients an extraction of a lower impacted wisdom tooth. If the subject needed more than one tooth extraction, he or she was included in the trial if one of the teeth extracted was a lower impacted wisdom tooth. The other inclusion criteria were that the end of surgery should not be later than 12:00 PM, and subjects must have at least "moderate" pain (score = 2 or more) at baseline on the five-point pain intensity scale.

Test Product, Dose, Mode of Administration: NIMED (nimesulide) oral 100-mg tablet; one or two tablets taken as necessary. Drug was dispensed in aluminum foil packages.

Reference Therapy, Dose, Mode of Administration:

VOLTAREN (diclofenac) oral 50-mg tablet; one or two tablets taken as necessary.

Placebo oral tablet; one or two tablets taken as necessary.

Drug was dispensed in aluminum foil packages identical to those of test product.

Duration of Treatment:

Each patient received either one tablet of 100 mg nimesulide, 50 mg diclofenac, or placebo at the end of surgery and only after the pain assessment at baseline showed at least moderate pain. A second tablet of the study medication was then dispensed to the subjects in each treatment group. The subjects were allowed to take the second tablet not earlier than 3 hours after the first administration of the study drug if no adequate reduction of pain has been achieved during this time, ie, if the score was still 2 ("moderate") or more on the five-point pain intensity scale.

The subjects were then additionally supplied with a "rescue" analgesic in case of lack of efficacy. Paracetamol tablets (Panadol[®]) were used as a "rescue" analgesic. Each subject was given 4 tablets of 500 mg Panadol[®]. If after the second administration of the study drug, the subject still needed a further analgesic treatment (score >2 on the five-point pain intensity scale) he/she was allowed to take one or more tablets of Panadol[®]. However, he/she was instructed to strictly observe a period of at least 1 hour after each drug intake. The maximum total dose of paracetamol was not to exceed 2 grams. The pain assessments, times of administration, and number of paracetamol tablets taken were documented by the subject in the subject's booklet.

Prior to surgery, subject eligibility was checked and the subject was fully informed on all aspects of the study performance. The extraction of the lower impacted wisdom tooth was performed in the morning and the surgical procedure was completed no later than 12:00 PM. The observation period was 8 hours after the first administration of the study drug. Safety laboratory tests for control were done within 2 days after the end of the observation period.

Criteria for Evaluation:
Study variables

1. Primary parameters
   a. Sum of Pain Intensity Differences for the whole observation period of 8 hours as assessed by the subjects on the five-point category scale at hourly intervals.
   b. Total Pain Relief Score for the whole observation period of 8 hours as assessed by the subjects on the five-point category scale at hourly intervals.
2. Secondary parameters
   a. Sum of Pain Intensity Differences for the observation period of 8 hours as assessed by the subjects on VAS at hourly intervals.
   b. Total Pain Relief Score for the whole observation period of 8 hours as assessed by the subjects on a VAS at hourly intervals.
   c. Global efficacy as assessed by the subjects on a five-point category scale at the end of the observation period.
   d. The percentage of subjects needing a second tablet of the study medication.
   e. Time when a second tablet was requested.
   f. Withdrawal rates due to lack of efficacy or occurrence of adverse events (AEs).
   g. Incidence of AEs associated with the study medication.

In this study five-point category scales for pain intensity and pain relief were used. The category scale for pain intensity consists of five intensity descriptors:

    0 = no pain

    1 = mild pain (analgesic treatment is not indicated)

    2 = moderate pain (analgesic treatment is indicated)

    3 = severe pain (analgesic treatment is needed)

    4 = unbearable pain (analgesic treatment is urgently needed)

The category scale for pain relief consists of five descriptors:

    0 = no effect

    1 = little effect

    2 = moderate effect

    3 = good

    4 = excellent

The five point category scale for global efficacy assessment consists of 5 efficacy descriptors :

    0 = no help

    1 = fair

    2 = good

    3 = very good

    4 = excellent

The global assessment for efficacy was performed for the study medication only and for the whole observation period, including the possible use "rescue" medication.

In this study Visual Analogue Scales (VAS) for pain intensity and pain relief was used in addition to the five-point category scales. The VAS for pain intensity is a 100 mm horizontal line whose extreme limits are delineated by perpendicular lines. The left limit of the horizontal VAS was defined as "NO pain" and correspond to 0 mm. The

right limit of the VAS was defined as "WORST pain" and correspond to 100 mm. The subjects were instructed to mark his/ her actual pain intensity with a single vertical line on the VAS.

The VAS for pain relief is also a 100 mm horizontal line whose extreme limits are delineated by perpendicular lines. The right limit of the horizontal VAS was defined as "NO relief of pain" and correspond to 0 mm. The left limit of the VAS was defined as "TOTAL relief of pain" and correspond to 100 mm. The subjects were instructed to mark her/his actual pain relief since last evaluation with a single vertical line on the VAS.

Pain parameters were evaluated post surgery at baseline and, if the patient reports at least moderate pain on the five-point categorical scale, at hourly intervals for an evaluation period of 8 hours using visual analogue scales, and five-point category scales for pain intensity and pain relief. At the end of the 8-hours-evaluation period or at earlier withdrawal the global efficacy of the study medication was assessed by the patient on a category scale. Any adverse events occurring during the study, were thoroughly evaluated, as well as the number of patients prematurely withdrawn due to lack of efficacy or due to AEs.

Laboratory Evaluations

Samples of blood for the following evaluations were obtained from each patient at pre-study and at study completion.

1. Haematology, including haematocrit, haemoglobin, RBC, WBC, platelet count, neutrophil, eosinophil, basophil, monocytes, lymphocytes, and prothrombin time.

2. Blood chemistry, including glucose, urea, uric acid, creatinine, total bilirubin, total protein, alkaline phosphatase (AP), serum glutamic oxaloacetic transaminases (SGOT), serum glutamic pyruvic transaminases (SGPT), and potassium.

Statistical Methods:

The intention is to test for differences between the treatment groups regarding the average reduction of pain. The assumptions on which the sample size calculation is based are:

- Null hypothesis:	Means of average reduction of pain are the same in all three treatment-groups.
- Experiment-wise level of significance:	0.05
- Power (1-ß):	0.80
- Difference between treatments	20%
- Estimated drop-out rate	0.10

The resulting number of patients per treatment group is 68 without correcting for dropouts and 75 after correction. Therefore a random assignment of 225 patients to the three treatment groups on a 1:1:1 basis is recommended.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy:

Pain intensity difference (PID) is defined as the difference of pain intensity from baseline to any time point measurement. There was no statistically significant difference between the three groups at baseline in terms of pain intensity scale, but there were statistically significant differences at 1, 2, 3, and 4 hours after the drug administration. At hour 1 up to hour 3, there was a statistically significant difference between nimesulide and either diclofenac or placebo indicating greater pain relief with nimesulide. At hour 4, the nimesulide group was still showing statistically significant difference from the placebo group, but not statistically significant difference from the diclofenac group.

Sum of pain intensity difference (SPID) is defined as the average reduction of pain intensity, calculated as the sum of eight individual pain intensity difference (hour 1 up to hour 8), divided by eight. To compare the difference of average pain reduction between treatment group, two-way ANOVA analysis was performed with treatment group as a fixed factor and baseline pain intensity category as a nuisance factor. There was a statistically significant difference of SPID between groups, either scaled by VAS ($p < 0.001$), or in category measurement ($p < 0.001$).

In this study we can see that there were statistically significant differences between group regarding pain at 1, 2, 3 and 4 hours after administration of the first tablet of study drug. The result showed also that the nimesulide group showed pain relief greater than either the diclofenac or the placebo group. To explore the difference between groups, Dunnet post-hoc test was performed, and the result showed at 1, 2 and 3 hour after surgery (it

means that patients were exposed to first tablet of study drug only), nimesulide showed statistically significant pain relief compared with either diclofenac or placebo. At fourth hour after surgery (it means that subjects were, perhaps, exposed to a second tablet of study drug), nimesulide was not statistically significantly different from diclofenac, but still statistically significantly different from placebo.

Total pain relief (TOTPAR) is defined as the average increase of pain relief, calculated as the sum of eight individual pain relief (hour 1 up to hour 8), divided by eight. To compare the difference of average pain reduction between treatment groups, two-way ANOVA analysis was performed with treatment group as a fixed factor and baseline pain intensity category as a nuisance factor. The results showed there was a statistically significant difference in TOTPAR between groups, either scaled by VAS ($p < 0.001$), or in category measurement ($p < 0.001$).

The majority of subjects (36 out of 65, or 55.4 %) in the nimesulide group declared their feeling that the effect of medication was very good or excellent, as compared with the diclofenac group (18 subjects, or 25.3 %) or placebo group (16 subjects, 23.6 %). To explore further the efficacy effect of treatment on the three groups, Kruskall-Wallis test was performed, and the result showed there was statistically significant global efficacy difference between the three groups ($p < 0.001$).

Safety:

There were 34 of 204 patients (16.7 %) experiencing an adverse event, distributed among the three groups: nimesulide group, 10 subjects (15.4 %); diclofenec group, 10 subjects (14.1 %); and placebo group, 14 subjects (20.6 %).

There are three kind of adverse events happened in nimesulid group, i.e. Oedem (12.3 %), bleeding (1.5 %) and trismus (1.5 %). Meanwhile the occurrence of Oedem was 11.3 %, dizzy and trismus was happened in diclofenac group 1.4 % respectively. In placebo group there were 8 kind of adverse events i.e. Oedem in 5 cases (7.4 %), throat pain for swallowing in 2 cases (2.9 %), febris in 2 cases (2.9 %) and heart beats rapidly, bleeding, chest pain, breathe difficulty and trismus are happened in 1 case or 1.5 % each.

Based on laboratory value assessment, most post surgery parameters were not statistically significantly different from baseline with regard to changes relative to the laboratory test reference limits.

In the nimesulide group there was only statistically significant change of value of uric acid (p-value=0.015) compared to placebo. In diclofenac group there is no statistically significant change of laboratory value assessment compared to placebo.

CONCLUSIONS:

Based on the evaluation on efficacy and safety parameters described above, it can be summarized that:

1. Nimesulide showed a statistically significantly greater pain relief as indicated by the Sum of Pain Intensity Difference (SPID) score compared with diclofenac and placebo.

2. Nimesulide showed statistically significantly greater Total Pain Relief (TOTPAR) as compared with diclofenac and placebo.

3. Nimesulide showed statistically significantly better global efficacy compared with diclofenac and placebo.

4. The incidence of adverse events in the nimesulide group was not different from those in the diclofenec and placebo groups.

Therefore, it is concluded that nimesulide showed a better efficacy in the relief of acute pain after the surgical extraction of wisdom teeth than did diclofenac and placebo, without additional risk.

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