Original Research Article

A Novel Paracetamol 1,000 mg Sustained Release Formulation vs Conventional Paracetamol 500 mg Formulation in Patients with Fever and Pain: A Randomized Noninferiority Trial

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Abstract

Objective. To compare the efficacy and safety of newly developed paracetamol 1,000 mg sustained release (SR) tablets (test product) with conventional paracetamol 500 mg tablets (reference product) in patients with fever and pain.

Design. An open label, multicentric, comparative, randomized, noninferiority trial.

Methodology. Eligible patient, as per predefined inclusion and exclusion criteria, were randomized to receive either one tablet of test product twice daily or one tablet of reference product four times a day for 3 consecutive days. Primary efficacy parameter (an antipyretic activity) was measured through recording changes in body temperature while secondary efficacy parameter (an analgesic activity) was measured by recording changes in visual analog scale (VAS) from the baseline. Safety assessment was done by recording adverse drug reactions occurred during treatment period. Analysis of variance was used for the statistical evaluation of data.

Results. Of 500 randomized patients, 249 were received paracetamol 1,000 mg SR tablets (Group-I), and 247 were received conventional paracetamol 500 mg tablets (Group-II). Group-I reported temperature reduction from 101.35°F to 98.80°F, while temperature reduction in Group-II was from 101.42°F to 98.9°F. Group-I reported reduction in mean VAS was from 6.16 to 1.44 in comparison to Group-II from 5.97 to 1.38. No significant adverse reactions were observed in either group.
Conclusion. Both the formulations of paracetamol were clinically and statically equivalent. Paracetamol 1,000 mg SR formulation is noninferior to conventional paracetamol 500 mg tablets.

Key Words. Paracetamol; Pain; Fever

Introduction

Pain and fever are the most common and early symptoms of many diseases which make us aware about the presence of the disease and its cause. Most of the time, pain and fever go together. Unbearable pain and high-grade fever oblige proper medical care and attention for the well-being of the patient [1].

Paracetamol (also known as acetaminophen) is one of the most widely prescribing analgesics and antipyretics [2] which exhibit its actions through inhibition of prostaglandin synthesis in the central nervous system via inhibition of cyclooxygenase-3 pathway [3]. Due to better tolerability and minimum chances of serious side effects, paracetamol is often drug of choice for pain and fever management in a variety of patients such as pregnant women, pediatrics, and geriatrics [4]. Moreover, it is also beneficial for patients in whom use of nonsteroidal anti-inflammatory drugs (NSAIDs) are restricted such as patient with risk of gastrointestinal complications and aspirin-sensitive asthmatic patients [4,5].

As per the UK recommendation, 500–1,000 mg paracetamol maximum up to 4 gm daily is needed for the pain and fever reduction. Even though wide applicability of paracetamol in the treatment of pain and fever, its short half-life (around 2–3 hours) create problem [6]. Frequent dosing of paracetamol (i.e., four times in a day) is required to maintain steady state plasma level [6]. To overcome this limitation of paracetamol dosing, sustained release (SR) formulation may be of great significance [7].

A novel SR formulation of paracetamol has been developed which contains 1,000 mg paracetamol in bilayer tablet form (paracetamol 1,000 mg SR tablet). It delivers 300 mg paracetamol as immediate release (IR) (30%) layer and 700 mg paracetamol as SR (70%) layer. Paracetamol 1,000 mg SR formulation has been designed to be taken every 12 hourly (twice in a day) to deliver 2,000 mg paracetamol per day without compromising its analgesic and antipyretic effect.

The present study was planned with the objective to evaluate the noninferiority of paracetamol 1,000 mg SR tablets (test product) in comparison to conventional paracetamol 500 mg tablets (reference product) in terms of efficacy and safety in patients with fever and pain.

Methods

Study Conduct and Approval

This was an open label, multicentric, comparative, randomized, noninferiority trial conducted at five different sites in India. This study’s sites were Sanjeevan Hospital, New Delhi (C01); Osmania General Hospital, Hyderabad (C02); Beg Hospital and Family Maternity Centre, Bareilly (C03); Chhatrapati Shahuji Maharaj Medical University, Lucknow (C04), and Dr. Satyarnarayan Gupta Smarak Hospital and Maternity Home, Etawah (C05). Study centers C02 and C04 obtained study protocol approval from their Institutional Ethics Committees, “Institutional Ethics Committee,” Osmania Medical College, Hyderabad and “Local Ethics Committee,” Lucknow Medical College, Lucknow, respectively. Because study centers C01, C03, and C05 did not have their own Institutional Ethics Comitees, the study protocol for these centers were approved by Independent Ethics Committee “Ethimax Ethics Committee.”

Study was conducted in accordance with Declaration of Helsinki, Indian guidelines for Good Clinical Practice and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research. Patients were informed about the study both verbally and in writing and written informed consent was obtained from the patients or their legal representatives prior to participation into the study.

Patient Recruitment

Study enrolled hospitalized patients with 18–65 years of age, willing to give informed consent, and suffering from fever (defined as body temperature greater or equal to 98.6°F) and/or any kind of mild to moderate pain justifying paracetamol treatment for a minimum duration of 24 hours. Considering the wide applicability of paracetamol as an antipyretics and analgesics, in the discretion of investigator, patient with any kind of mild to moderate pain and/or fever which justify the treatment with paracetamol were included in to the study. In contrast to this, patient receiving concomitant analgesic (NSAIDs) or any steroids, history of hypersensitivity with paracetamol, suffered from concomitant illness (such as digestive disorders, hepatic disorders, cancer, acquired immune deficiency syndrome, or cardiovascular diseases) which increases the risk of adverse drug reactions were excluded from the study.

Patient Assessment and Treatment Allocation

Screening of hospitalized patients were done by taking demographics details, medical history, clinical examinations, and laboratory examinations (only if the fever of unknown origin). On the day of screening itself, eligible patients were equally randomized into two treatment groups using computer-generated randomization sheet. Patients randomized into Group-I received test product (a novel paracetamol 1,000 mg SR tablet) at every 12 hours.
interval while patients in Group-II received reference product (conventional paracetamol 500 mg tablet) at every 6-hours interval. The entire randomized patients in both the groups cumulatively received 2,000 mg paracetamol at the end of each day along with their regular treatment for current medical illness excluding analgesic and antipyretic.

Outcome Measures

Primary efficacy parameter (i.e., antipyretic activity) and secondary efficacy parameter (i.e., analgesic activity) were measured by recording changes noted in body temperature, and pain score respectively across each group was from baseline to day 1 to day 3’s mean.

Antipyretic activity of all the patients were recorded by measuring body temperature using the validated “Omron®” brand of digital thermometer (Omeron Healthcare India Pvt. Ltd., Gurgaon, Haryana, India). Research nurse measured the body temperature by placing digital thermometer into the mouth below the tongue for 10 seconds at 0th and every 1st, 4th, 5th, 6th, 8th, 10th, 12th, 13th, 16th, 17th, and 24th hour for 3 consecutive days. Analgesic activity was measured using visual analog scale (VAS). Patients were asked to define their feeling of pain using VAS marked “0–10” (where 0 indicates no pain and 10 indicates severe pain). Pain score was taken by research nurse at 0th and every 6th, 12th, and 24th hour for 3 consecutive days. Mean reduction in body temperature as well as pain score were calculated by averaging 3 days’ mean daily reduction results of temperature and pain score.

Incidences of any adverse drug reactions were monitored throughout the course of treatment for safety assessment. All the safety and efficacy parameters were recorded in respective patient’s case report form for the final assessment.

Statistical Analysis

Data from all the centers were pooled for “per-protocol” analysis. The change from the baseline in body temperature and pain score was assessed statistically using analysis of variance. Measured data were expressed as mean and standard deviation, whereas categorical data were expressed as percentages. Subsequent to the treatment, changes in temperature and pain score value from the baseline were compared using "t"-test at significant level (α) \( P < 0.05 \).

Results

Disposition of Patients

In the present study, a total of 500 patients were enrolled from which 249 were received paracetamol 1,000 mg SR tablets twice daily, and 247 were received conventional paracetamol 500 mg tablets four times daily for 3 consecutive days. One patient was considered lost to follow up as after day 1 as he left away the trial site, and three patients withdrew their consent before treatment allocation as they did not want to continue with their willingness about study participation. By taking this into consideration, data of 496 patients were included in the statistical analysis.

Efficacy Assessment

Primary Efficacy Parameter: Antipyretic Activity

The statistical analysis of primary efficacy parameter was the mean changes in antipyretic activity of both the formulations of paracetamol from the baseline to day 1 to day 3’s mean. Reduction in body temperature of Group-I patients was from 101.35°F ± 1.23°F to 98.80°F ± 0.72°F while in Group-II patients was from 101.42°F ± 1.33°F to 98.91°F ± 0.85°F, respectively, was from baseline to day 1 to day 3’s mean (see Table 1). The overall mean reduction in body temperature from the baseline to end of day 3 treatment was 2.50% in Group-I patients while 2.48% in Group-II patients. Daily mean body temperature did not differ significantly between the test product and reference product (Day 0—\( P = 0.1662 \), Day 1—\( P = 0.1346 \), Day 2—\( P = 0.0548 \) (see Table 2).

Secondary Efficacy Assessment: Pain Relief

Results showed that from the baseline to end of day 3, mean VAS score of Group-I patients was reduced from 6.16 ± 2.37 to 1.44 ± 1.70 while in Group-II patients, it was reduced from 5.97 ± 2.45 to 1.38 ± 1.78. The percentage reduction of VAS score is comparable for Group-I (76.82%) with Group-II (76.95%) (see Table 3). No major

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group-I (Paracetamol 1,000 mg SR Tablet)</th>
<th>Group-II (Conventional Paracetamol 500 mg Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp. (°F)</td>
<td>101.35 ± 1.23 98.80 ± 0.72 2.50</td>
<td>101.42 ± 1.33 98.91 ± 0.85 2.48</td>
</tr>
</tbody>
</table>

All values indicate mean ± SD.
SR = sustained release.
difference was observed in daily mean pain score of patients in both the groups (Day 0—$P = 0.8969$, Day 1—$P = 0.4279$, Day 2—$P = 0.7515$) (see Table 4).

Safety Assessment

Safety evaluations had been performed by incidence of adverse events and clinical examinations. A total of 23 adverse events (13 in Group-I and 10 in Group-II) such as headache, diarrhea, itching on legs, chest pain, and backache were reported. All of the reported adverse events were considered clinically nonsignificant as they were disease specific.

Discussion

Similar to many other analgesics, paracetamol has short elimination half-life of about 2–3 hours which obliges the frequent drug administration to maintain therapeutic plasma level, and hence, paracetamol SR formulation would be the desirable alternative [6]. Fewer daily dosage of SR paracetamol would become efficient in maintaining the therapeutic plasma level of paracetamol for longer period of time, and thereby, it may improve patient compliance and are of benefit to the patient at nighttime [8].

One noticeable difference was observed in the rate of achievement of therapeutic plasma concentration between the IR and SR formulation of paracetamol. IR formulation achieves therapeutic plasma concentration more rapidly than SR formulation and thereby provides faster pain relief. In contrast to this, therapeutic effect of SR formulation persists for longer period of time compared with IR formulation, and thereby, it may provide pain relief for longer duration of time. For this reason, the

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Table 2  Daily mean body temperature

<table>
<thead>
<tr>
<th>Course of Treatment</th>
<th>Group-I (Paracetamol 1,000 mg SR Tablet)</th>
<th>Group-II (Conventional Paracetamol 500 mg Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Body Temperature</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>Day 0</td>
<td>100.07</td>
<td>99.942</td>
</tr>
<tr>
<td>Day 2</td>
<td>98.868</td>
<td>98.787</td>
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Table 3  Overall mean reductions in pain score

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group-I (Paracetamol 1,000 mg SR Tablet)</th>
<th>Group-II (Conventional Paracetamol 500 mg Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 1 to Day 3’s Mean</td>
</tr>
<tr>
<td>VAS Score</td>
<td>6.16 ± 2.37</td>
<td>1.44 ± 1.72</td>
</tr>
</tbody>
</table>

All values indicate mean ± SD.

SR = sustained release; VAS = visual analog scale.

Table 4  Daily mean pain score

<table>
<thead>
<tr>
<th>Course of Treatment</th>
<th>Group-I (Paracetamol 1,000 mg SR Tablet)</th>
<th>Group-II (Conventional Paracetamol 500 mg Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Pain Score</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>Day 0</td>
<td>5.1136</td>
<td>4.8176</td>
</tr>
<tr>
<td>Day 1</td>
<td>3.444</td>
<td>3.2256</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.8805</td>
<td>1.6707</td>
</tr>
</tbody>
</table>

SR = sustained release.
A novel paracetamol 1,000 mg SR tablet has been developed for twice-daily administration which incorporated a total of 1,000 mg paracetamol in IR and SR layers. Present study results showed that paracetamol 1,000 mg SR tablet was therapeutically and statistically noninferior to conventional paracetamol 500 mg tablet for the treatment of mild to moderate pain and fever. This study finding matches with the study conclusion of two published study which evaluated the noninferiority of paracetamol SR formulation (Panadol Extend; GlaxoSmithKline Australia Pty Ltd., Emington, NSW) to paracetamol IR formulation after third molar surgery and in patients with knee pain secondary to osteoarthritis [7,9]. However, no published study available until date that evaluated the efficacy and safety of paracetamol SR formulation as an antipyretic. This is the first study which evaluated the noninferiority of paracetamol 1,000 mg SR tablet as an antipyretic in comparison to conventional paracetamol 500 mg tablet. Open-label study design was selected for the present study because in order to maintain the study blinding, eligible patients were needed to take four tablets from four different bottles (including two placebo in paracetamol 1,000 mg SR tablet group) per day, which ultimately increase the complication in study drug administration and may also affect the study outcome if proper drug administration sequence is not maintained. Hence, simple open label, randomized, parallel group study design was selected to evaluate noninferiority of paracetamol 1,000 mg SR tablet in comparison to conventional paracetamol 500 mg tablet.

Paracetamol has pKa value of 9.5 [10] which means it remains unionized at all physiological pH ranges and get absorbed from the stomach as well as from the intestine. Paracetamol 1,000 mg SR formulation has been designed in such a way that 300 mg paracetamol immediately released into the stomach form IR layer to provide quick response and then SR layer may slowly and steady release 700 mg paracetamol into the intestine. In this way, a total of 12 hours therapeutic effect could be achieved with paracetamol 1,000 mg SR tablet which justifies the twice-daily administration.

The advantages of paracetamol 1,000 mg SR tablet is not only limited to patient compliance but it may also provide following advantages:
- Achieves lower level of peak plasma concentration (Cmax) and thereby minimize the risk of toxicity at higher therapeutic concentration.
- Maintain the minimum effective paracetamol concentration (i.e., 3 μg/mL) until 12 hours compared with conventional 500 mg paracetamol tablet, which is about 6 hours.
- Lessen the fluctuation in therapeutic plasma concentration and thereby reduces the chances of therapy failure or overdosage.

The limitation of the present study is that inclusion criteria related mild to moderate pain and/or fever was very general. Study evaluated noninferiority of paracetamol 1,000 mg SR tablet in many kinds clinical conditions associated mild to moderate pain and fever such as headache, body ache, malaria, various infections, osteoarthritis, etc. Hence, future studies showing specific applicability of paracetamol 1,000 mg SR is required.

Conclusion
Analgesic and antipyretic activity of paracetamol 1,000 mg SR tablet taken twice daily seems to be noninferior to conventional paracetamol 500 mg tablet taken four times daily, for 3 consecutive days. Paracetamol 1,000 mg SR tablet may has the potential to improve patient compliance as it reduces the administration frequency of oral paracetamol to half, and thereby, it may improve therapeutic efficacy of paracetamol as an analgesic and antipyretic.

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