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Efficacy and Safety of Amtolmetin Guacyl in the Management of Knee Osteoarthritis and Associated Dyspepsia in Routine Clinic Setting: AGATA Study

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Abstract

Aim: To evaluate the efficacy and safety of amtolmetin guacyl in the management of osteoarthritis (OA) of knee and associated dyspepsia in routine clinic setting.

Methods: In an observational study conducted in the OA outpatients between February 2015 and December 2015, patients with knee joint (KJ) pain ≥ 40 mm on visual analogue scale (VAS) and dyspepsia were enrolled. Amtolmetin guacyl 600 mg tablets twice daily was administered for up to 28 days. Patients were evaluated at baseline, Day 14 ± 3, and at Day 28 ± 3 for severity of pain in "target" knee (VAS), Western Ontario and Mc master Universities Arthritis (WOMAC) pain and stiffness, and severity of dyspepsia assessment (SODA).

Results: Of the 219 OA patients, approximately 72.5% patients reported decrease in pain in the target KJ by ≥ 40% at the end of the study. Mean pain reduced from 65 mm at baseline to 27 mm at the end of the study. A significant decrease in WOMAC pain score, morning stiffness, and functional limitations were also observed (P<0.001). A significant decrease in severity of dyspepsia assessment (SODA) score and increase in satisfaction was observed. Amtolmetin tolerability was comparatively better than previously used NSAIDS.

Conclusion: Amtolmetin guacyl is effective and safe in OA patients with associated dyspepsia and has comparatively better tolerability than other NSAIDS. This trial is registered with http://clinicaltrials.gov, number NCT02865161.

Keywords: Osteoarthritis; Dyspepsia; Amtolmetin guacyl; Anti-Inflammatory agents; Non-steroidal

Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disorder which affects approximately 27 million people in the United States [1]. It causes considerable social and financial burden to the patients and health organizations by its impact on pain, disability, and quality of life, and its associated treatment costs [2].

Non-steroidal anti-inflammatory drugs (NSAIDS) remain the mainstay of therapy to reduce pain and disease activity. However, their impact on gastrointestinal (GI) safety is a major cause of concern which jeopardizes their therapeutic role. Elderly patients are the major population at risk for developing GI adverse events, from mild to severe dyspepsia or abdominal discomfort to life threatening complications. The annual incidence of dyspepsia is approximately 25% to 50% in patients taking non-specific NSAIDS [3]. The association of dyspepsia in arthritis patients using NSAIDS incur comparatively higher health care resource utilization and economic burden as compared to patients with non-dyspeptic symptoms.

Various treatment options have been adapted to overcome this concern such as the development of cyclooxygenase (COX-2) selective drugs or the use of gastro protective agents such as proton pump inhibitors, H2-blockers, misoprostol along with NSAIDS. These drugs have been able to prevent and treat gastro duodenal mucosal damage

in satisfactory proportion of patients. However the issues regarding their safety, compliance, and cost effectiveness are still unclear [1] which restrict the indiscriminate use of these drugs for long term prevention of the disease. Their use must be limited to only high risk patients.

There is an unmet medical need for analgesics or NSAIDS with a better GI tolerability profile for long term use in such conditions. Also a more stringent approach towards reducing the NSAID-associated systemic adverse events for the treatment of osteoarthritis is required. Therefore the pharmacological research is focussing on development of new NSAIDS that are clinically effective but devoid of any serious adverse effects.

Amtolmetin guacyl (AMG) is one such novel NSAID with good anti-inflammatory and analgesic properties combined with good gastrointestinal tolerability. It is derived from the condensation of tolmetin and guaiacol and glycine [4].

Previous studies have proven its comparable anti-inflammatory, analgesic, and antipyretic effects to reference NSAIDS [4,5]. Metaanalysis reports suggested the lower incidence of gastric side effects with AMG as compared to traditional NSAIDS [6].

The gastric sparing effect of AMG has been attributed to the presence of vanillic moiety, which causes calcitonin gene related peptide (CGRP) release through capsaicin receptors stimulation and increase in nitric oxide (NO) production. Therefore AMG is suggested to be administered on an empty stomach to enhance its gastro-protective property [7].

Despite the favourable properties of AMG, it has been underutilized in clinical practice owing to the availability of newer NSAIDS. Very few studies have been conducted so far which explores the efficacy and safety of AMG in osteoarthritis patients.

We had conducted the first patient reported outcome, questionnaire based study in the Russian Federation with an intent to obtain additional data on the efficacy and safety of amtolmetin guacyl in ambulatory patients with osteoarthritis of knee and associated dyspepsia in routine clinical practice. In addition to efficacy, we also included patient reported outcome measures for safety.

Methods

Participants and study design

This was an Open label, Observational, Post Registration study to evaluate efficacy, safety, and tolerability of amtolmetin guacyl treatment in patients with osteoarthritis of knee and symptoms of dyspepsia compared to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) in routine clinical settings. The study was conducted in the period between February 2015 and December 2015 in Russia. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). All patients provided signed informed consent prior to the start of the study in accordance with local regulations and standards of Bioethics.

Patients

Patients with 30-65 years of age referred to outpatient clinic and diagnosed with osteoarthritis of knee and associated pain syndrome (based on American College of Rheumatology [ACR], 1987 criteria) were included in the study. Only those presenting with pain in the investigated knee joint ≥ 40 mm on a 10 cm visual analogue scale (VAS) were enrolled. Patients with associated dyspeptic symptoms (according to severity of dyspepsia assessment [SODA] questionnaire) was another inclusion criteria. Patients with signs of renal or hepatic failure and systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg were excluded from the study. Patients with any condition which did not meet the protocol requirement or which in the opinion of the physician makes the patient unsuitable for inclusion, were excluded from the study.

Study design and treatment

This open label trial was carried out in seven Russian centres.

All patients with knee osteoarthritis who received various NSAIDs at maximum therapeutic dose prior to the enrolment in the study and observed dyspeptic symptoms, were administered with amtolmetin guacyl 600 mg tablets twice daily under fasting conditions for 28 days.

Assessments

Study participants were evaluated at baseline (Visit 1) and during the treatment visits on Day 14 ± 3 (Visit 2) and Day 28 ± 3 (Visit 3). The duration of study for each patient was 28 days.

A detailed history of all patients were taken prior to enrolment. Physical examination and blood pressure measurement was done at all visits. Severity of pain in the "target" knee by VAS scale; assessment of efficacy by Western Ontario and Mc master Universities Arthritis (WOMAC) index and assessment of safety and tolerability by severity of dyspepsia assessment (SODA) questionnaire were assessed at all the treatment visits.

Western ontario and Mc master universities arthritis (WOMAC) index: The WOMAC is used to assess pain, stiffness, and physical function in patients with knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items), stiffness (2 items), and physical function (17 items) [8]. In this study, we have used the 100 mm VAS format of WOMAC. Patients were administered with the questionnaire and were asked to fill it at all the treatment visits. For each item, the possible range of scores was 0-100 on VAS scale. Items were summed for each subscale, resulting in possible ranges as follows: pain=0-500, stiffness=0-200, physical function=0-1700. A total WOMAC score was created by summing the items for all three subscales.

Severity of dyspepsia assessment (SODA) questionnaire: The SODA questionnaire is used to measure dyspepsia related health and related changes over time. It evaluates three domains - Pain intensity (6 items), Non-pain symptoms (7 items), and Satisfaction with Dyspepsia-related Health (4 items). Greater symptom severity is indicated by higher scores on Pain intensity and Non-pain symptoms scales while greater satisfaction is indicated by higher scores on the Satisfaction scale [3]. Assessment of the overall effectiveness of therapy by physicians and patients and general state of the patient was also assessed by VAS scale on all the visits.

Estimated overall tolerability of therapy by patient on 4 point categorical scale: 1 - excellent 2 - good 3 - satisfactory 4 - bad was done at Day 14 ± 3 and Day 28 ± 3. All patients were administered daily diary to evaluate gastric tolerability. Overall tolerability was evaluated by recording adverse events and determining laboratory parameters.

Study endpoints

Primary endpoint: Proportion of patients with ≥ 40% decrease in the severity of pain manifestation according to VAS (0-100 mm) in the target KJ at Visit 3 vs. baseline (Visit 1).

Secondary endpoints:

1. Reduced WOMAC (according to pain, rigidity and function scales) by >20% vs. baseline.
2. Assessment of general condition (VAS, 0-100 mm).
3. Assessment of the overall effectiveness of therapy by the patient (VAS, 0-100 mm).
4. Assessment of the overall effectiveness of therapy by the physician (VAS, 0-100 mm).
5. Presence and severity of dyspepsia (SODA questionnaire).
6. Frequency and severity of any adverse effects.

Comparative evaluation of the tolerability of AMG in comparison with previous NSAIDS therapy was also done in the study.

Statistics

Only descriptive statistics (mean, standard deviation, median, minimum and maximum values, range, quartiles, number of valid cases for quantitative variables, absolute number, proportion and distribution for qualitative variables) was used in the present study. Statistical analysis was carried out in the patients who received at least one dose of study medication i.e., Intention to Treat (ITT) population.

Results

Data were collected from 219 osteoarthritis knee outpatients. There were 37 men and 182 women with a median age of 55.2 ± 6.9 years. Previous therapy before the study included both symptomatic slowly acting drug products (42%) and different NSAIDs. Patients were switched from NSAIDs to AMG without wash out period.

Baseline characteristics of OA patients are shown in Table 1.

Baseline characteristics	Amtolmetin Guacyl (n=219)
Gender: male/female	17% (37)/83% (182)
Age (Years)	55.2 ± 6.9
Body Mass Index (BMI) (kg/m^2)	31 ± 5.3
Target knee joint: Right/Left	55% (119)/45% (96)
Duration of OA of KJ (Years)	7 ± 5
Duration of current exacerbation (Weeks)	6.8 ± 5.9
OA of small joints of the hand	24.8% (53)
OA of hip joint	31% (67)
OA of backbone	46.8% (101)
OA of other joints	14.3% (29)
Smoking	20.7% (44)
Concomitant diseases	68.2% (150)
Obesity	3.6% (8)
Chronic gastritis	17.3% (38)
Essential hypertension	41.4% (91)
Diabetes mellitus	5.9% (13)
Lower extremity varicose vein disease	6.4% (14)
Concomitant therapy with chondroitin sulphate and glucosamine gastroprotectors	15.5% (34) 8.2% (18)

Table 1: Baseline characteristics of patients enrolled in the study with OA (n=219).

Efficacy analysis

Primary efficacy analysis: Amtolmetin guacyl had more evident analgesic effect approximately 72.5% patients who reported ≥ 40% decrease in pain according to VAS (0-100 mm) in the target KJ at Visit 3 vs. baseline (Visit 1) (Figure 1).

There was a significant decrease in mean KJ pain from 65 mm at baseline to 27 mm at Visit 3 (P<0.001) (Figure 2).

Analgesic effect of AMG was confirmed by decreased pain intensity according to dynamics of daily pain in the target KJ recorded by patients in their diaries.

Secondary efficacy analysis WOMAC index: There was a decrease in mean KJ pain score (from 239 to 120) (Figure 3), morning stiffness (from 100 to 58) (Figure 4), decrease in functional limitations in all the measured scales – I to IV, and total WOMAC score (from 1187 to 643). This decrease in all the domains of WOMAC questionnaire was statistically significant (P<0.001).

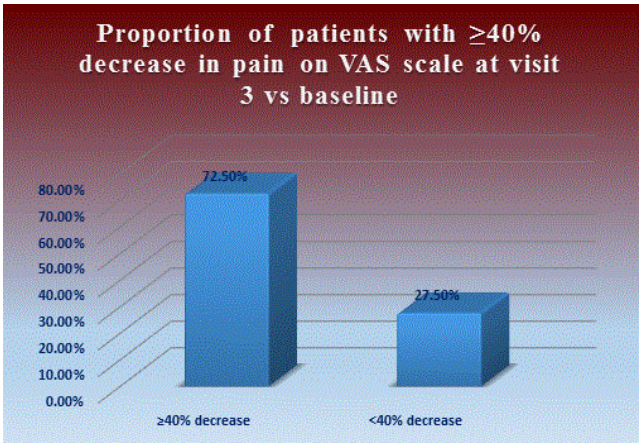

Figure 1: Proportion of patients with ≥ 40% decrease in pain manifestation according to visual analogous scale (VAS) (0-100 mm) in the target knee joint at visit 3 vs. baseline (visit 1).

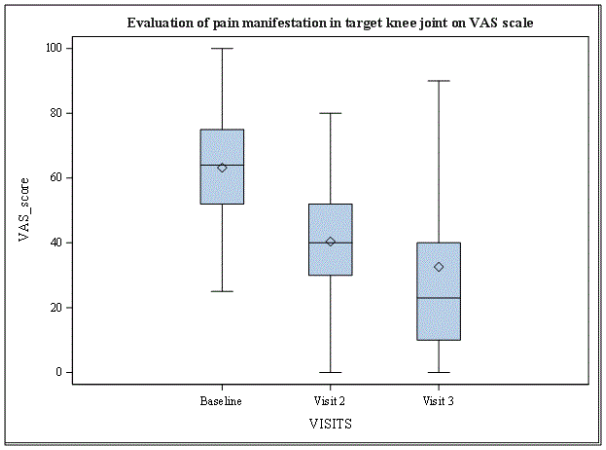

Figure 2: Evaluation of pain manifestation in the target knee joint according to VAS (0-100 mm).

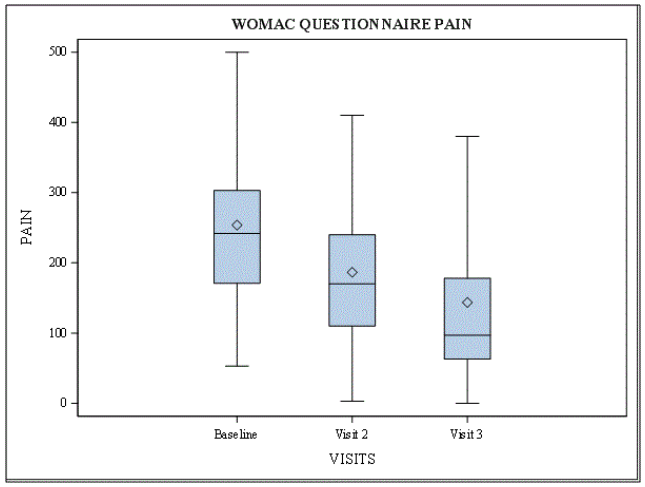

Figure 3: Decrease in pain according to WOMAC questionnaire.

Safety analysis: Safety was assessed using SODA questionnaire. There was a decrease in SODA score from baseline to end of the study: from 16 to 12 for non-pain signs, from 24 to 17 for pain signs, and an increase in satisfaction with treatment (SODA score from 12 to 14). The observed changes were statistically significant (P<0.001). A decrease in overall evaluation of dyspepsia was observed from 87 to 63.

Overall general condition of the patient improved significantly (P<0.001) – from 52 to 71 mm according to VAS. According to evaluation by patients and physicians, AMG was significantly (P<0.001) effective. After 14 days of AMG administration, 26%, 57%, 14% and 3% of patients evaluated tolerance as excellent, good, satisfactory and poor, respectively. Final tolerance evaluation observed excellent tolerability in 33%, good in 56% and satisfactory in 11% of patients.

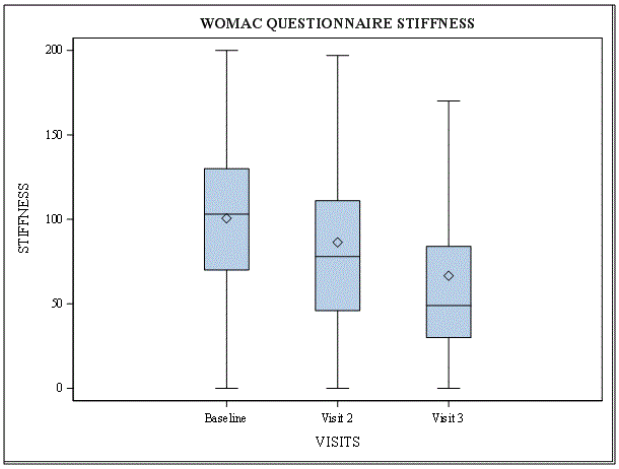

Figure 4: Decrease in stiffness according to WOMAC questionnaire.

As far as comparative evaluation of tolerability of AMG in comparison with previous NSAIDS therapy is concerned, AMG tolerance, according to evaluation by patients, was comparatively better than previous NSAIDS (Table 2). After the end of study, 90% patients wished to continue treatment with AMG.

Tolerability of Amtolmetin vs Other NSAIDS:	Frequency	Percentage
Nimesulide	49	21.21%
Ibuprofen	14	6.06%
Meloxicam	54	23.38%
Ketoprofen	15	6.49%
Diclofenac	61	26.40%
Naproxen	4	1.73%
Indomethacin	3	1.29%
Aceclofenac	16	6.93%
Celecoxib	2	0.87%
Etoricoxib	7	3.03%
Tenoxicam	1	0.43%
Nurofen	1	0.43%
Ibuprofen + Paracetamol	3	1.29%
Diacerein	1	0.43%

Table 2: Comparative tolerability of amtolmetin guacyl (patient assessment).

No statistically significant changes in the laboratory parameters or major side effects were reported on the use of AMG during the study.

Discussion

We conducted the first observational study in Russia to study the efficacy and safety of amtolmetin guacyl in OA outpatients with associated dyspepsia in routine clinic settings.

Osteoarthritis is associated with systemic adverse events due to the ubiquitous use of NSAIDS. Strategies to diminish these systemic side effects are considered by the clinicians in the management of OA. As per the American College of Rheumatology (ACR) recommendations, acetaminophen is the first line treatment of knee OA as they are considered safer than NSAIDS. However, in a metaanalysis report by Zhang and colleagues, NSAIDS were more effective than acetaminophen with regard to pain relief, clinical response rate, and symptom relief by WOMAC or the patients' preference. Therefore NSAIDS with gastroprotective potential and no cardiac or renal toxicity is the preferable option for OA treatment [9]. Amtolmetin is known to have the gastric sparing effect and therefore the treatment choice in our study. Also it does not impair renal function [10] and seems to be safer than selective COX-2 inhibitors in patients with CV risk due to its comparable antiplatelet activity with that of aspirin [7,11].

In our study, amtolmetin decreased pain in the target knee joint by ≥ 40% from baseline to the end of the study in more than 70% of patients. The observed decrease in mean pain VAS score was significant (P<0.001). Additionally, AMG reduced stiffness and functional disability, therefore proven to be clinically effective. Additionally, amtolmetin was found to be safer with a decrease in SODA score (pain and non-pain signs) and a significant increase in satisfaction score. Its tolerability was comparatively better than previous NSAIDS and preferred by majority of patients post study.

Our study findings are consistent with the previously conducted studies. The efficacy results of a four weeks study (AMG vs. piroxicam) showed significant improvement from baseline to the end of the study in pain on active movement (from 71.8 ± 12.3 mm to 45.8 ± 12.3 mm); pain at rest (from 59.2 ± 7.8 mm to 37.9 ± 7.8 mm) and disease activity (from 61.4 ± 10.7 mm to 42.8 ± 10.7 mm) (P<0.01) by the use of AMG [5].

In a double blind study by Telhag et al, tolmetin sodium twice a day showed greater improvement in pain at rest and on motion than naproxen assessed on a 5 point rating scale in patients with osteoarthritis of knee or hip at 4 weeks. The observed difference was significant in mean values for pain on motion at 4 and 12 weeks (P<0.05). Number of patients with pain reduction after 12 weeks of treatment were significantly greater in the tolmetin sodium group as compared to naproxen group (P<0.05) [12].

Our study shows similar results to other studies with regard to safety and tolerability. Gastric tolerability was better in the AMG group as compared to piroxicam group. In the AMG group, two of the 49 patients withdrew due to side effects vs nine of the 50 patients in the piroxicam group. There were no serious side effects with AMG as compared to three cases in the piroxicam group. Epigastric and abdominal pain were more frequently observed side effects with piroxicam [5].

In a metaanalysis by Marcolongo et al. it was shown that gastric tolerability of AMG as compared to other NSAIDS was higher. The odds ratio of AMG adverse effects vs all other NSAIDS was 0.2 (95% CI: 0.1 to 0.3); the odds ratio for severe gastric mucosal lesions at endoscopic evaluation was 0.3 (95% CI: 0.1 to 0.7) [7].

A healthy volunteer study showed the significant difference in the gastrointestinal safety of AMG vs piroxicam. Amtolmetin treated volunteers had the post treatment endoscopy gastric injury score of 1 vs. 3 in piroxicam treated volunteers. About 71% patients in AMG group vs 57% patients in the piroxicam group reported adverse reactions [13].

In another study, gastric tolerability and safety was significantly higher with AMG group. There was a significant difference in the normal gastroduodenal findings in both the groups (50% in AMG group vs. 25% in diclofenac group; P<0.05). Gastric ulcers were observed in 3% of the patients in AMG group as compared to 25% in the diclofenac group (P<0.05). Also a recurrence of gastric damage was observed in 18% of patients in AMG group vs. 53% of patients in diclofenac group (P<0.05) [4].

In a recent study, it was shown that AMG reduced pain intensity (WOMAC) significantly by 30 days as compared to diclofenac in 55% and 29% of patients respectively. Improvement in functional abilities was also comparatively better with AMG than diclofenac (35% and 24% by day 20 and 50% and 30% by day 30 respectively) [14].

We have administered the study drug on empty stomach. It has been studied earlier in osteoarthritis patients that amtolmetin guacyl is much more efficient when administered on empty stomach the reduction in global symptom score was -4.05 (95% CI: -4.82 to -3.28) in AMG administered on empty stomach vs. -2.77 (95% CI: -3.55 to -2.00) in full stomach group (P=0.023). Also there was a significant difference between groups in improvement in pain on motion (P=0.012) [15].

Dyspepsia is an important factor to determine patient's quality of life, withdrawal from the clinical trial, or noncompliance, however it is not necessarily an accurate predictor of mucosal injury or any other GI complications. In a Celecoxib Long-term Arthritis Safety (CLASS) study [16], dyspepsia was reported by 39.4% of patients of which 7% withdrew from the study [3].

We used SODA questionnaire in our study and found that AMG successfully reduced overall dyspepsia and patients experienced greater satisfaction with the treatment. Also we could not find any changes in clinical and biochemical parameters pertaining to renal or cardiovascular function.

Conclusion

Our study results suggest the effectiveness of AMG with very limited toxicity as compared to other NSAIDS in the management of osteoarthritis with associated dyspepsia. The drug might prove to be a valid option to current therapies if these findings are confirmed on a wider scale. It is imperative to study the effect of AMG in longer duration trials and also to evaluate its efficacy and safety by conducting comparative studies with other available drugs in future.

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