An open label multicenter observational study of the efficacy, tolerability and safety of Amtolmetin Guacil – a non-steroidal anti-inflammatory drug, in patients with knee osteoarthritis and dyspepsia.

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Goal — to study the efficiency and tolerability of Amtolmetin Guacil (AMG; Niselat®, Dr. Reddy's Laboratories Ltd., India) in patients with knee osteoarthritis (OA) and signs of dyspepsia, compared with previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs).
Material and methods. The open observational study included 220 patients, ages 30–65 years, with OA of the knee-joint and intense pain, on the back of the therapy with NSAIDs and with symptoms of dyspepsia in the absence of contraindications to AMG. In general, following concomitant diseases occurred in 68 % of patients, among them hypertension (42 %), varicose veins of the lower extremities (6.4 %) and diabetes (6 %).
The therapy efficiency was assessed using the three scales of the WOMAC index (Western Ontario and McMaster Universities Osteoarthritis Index), pain intensity and overall health rating from the visual analog scale. Researchers used the SODA index (The Severity of Dyspepsia Assessment) to quantify dyspepsia.
Results and discussion. AMG has a pronounced analgesic effect, confirmed by pain reduction (by 40 % or more), which occurred in 72.5 % of patients. The high intensity of the AMG analgesic effect was reliably confirmed statistically ($p < 0.001$) by a significant decrease in the WOMAC index (pain and stiffness), and an increase in functional activity. The study established a significant decrease in the pain and other signs of dyspepsia, as well as the positive dynamics of the indicators "general assessment of the severity of dyspepsia" ($p < 0.001$) and "satisfaction with therapy". The overall assessment of therapy with AMG was decidedly positive: "Excellent" – in 33 % of patients, "good" – in 56 % and "satisfactory" – in 11 % of patients. Serious adverse reactions (AR) have not been reported. The severity of AR in 8 % of cases was average, and in 82 % of cases – mild. The AR were reported by 7.7 % of patients.
Conclusion. The obtained results confirm the good prospects of using AMG for treatment of knee-joint OA.
Key words: knee osteoarthritis; Amtolmetin Guacil; dyspepsia.
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AN OPEN-LABEL MULTICENTER OBSERVATIONAL STUDY OF THE EFFICACY, TOLERABILITY, AND SAFETY OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG AMTOLMETIN GUACIL IN PATIENTS WITH KNEE OSTEOARTHRITIS AND DYSPEPSIA

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Objective: to investigate the efficacy and tolerability of amtolmetin guacil (AMG; Niselat®, Dr. Reddy's Laboratories Ltd, India) versus previous therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with knee osteoarthritis (OA) and signs of dyspepsia.
Subjects and methods. The open-label observational study included 220 patients aged 30—65 years who suffered from knee OA and intense pain during NSAID intake and had symptoms of dyspepsia in the absence of contraindications to the use of AMG. Among the comorbidities that generally occurred in 68 % of the patients, there was a preponderance of hypertension (42 %), lower extremity varicose veins (6.4 %), and diabetes mellitus (6 %). Treatment efficacy was evaluated using three domains of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), by also taking into account pain intensity and general health assessment on the visual analogue scale. A Severity of Dyspepsia Assessment (SODA) scale was used to rate dyspepsia.
Results and discussion. AMG had a marked analgesic effect confirmed by 40 % or more pain reduction that occurred in 72.5 % of the patients. The high analgesic effect of AMG was confirmed by a statistically significant ($p < 0.001$) reduction in the WOMAC index (pain and stiffness) and by an increase in functional activity. There was a significant decrease in painless and painful signs of dyspepsia, as well as positive changes in the measures "overall assessment of dyspepsia severity" ($p < 0.001$) and "satisfaction with treatment". Overall assessment of AMG tolerability was only positive: excellent (33 %), good (56 %), and satisfactory (11 %). There were no serious adverse events (AE). AE were graded as moderate and mild in 8 and 82 % of cases, respectively. AE were recorded in 7.7 % of the patients.
Conclusion. The findings suggest that AMG offers good prospects for knee OA treatment.
Key words: knee osteoarthritis; amtolmetin guacil; dyspepsia.
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the efficacy, tolerability, and safety of the nonsteroidal anti-inflammatory drug amtolmetin guacil in patients with knee osteoarthritis and dyspepsia. Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice. 2016;54(6):654-659 (In Russ.).
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Osteoarthritis (OA) is a heterogeneous group of diseases of various etiologies with similar biological, morphological, clinical manifestations and outcome, which is based on the destruction of all components of the joint, primarily cartilage, as well as subchondral bone, synovial membrane, ligaments, capsule and periarticular muscles [1]. OA is the most common joint disease affecting 10 % of men and 18 % of women aged 60 years and older [2]. According to the Russian epidemiological study, OA with predominant lesion of the knee (KJ) and/or hip joints (HJ) is detected in 13 % of the population [3, 4]. In the outpatient practice OA affects 75 % of patients coming to see a rheumatologist [4]. The leading clinical symptom of OA is pain in the affected joint that can be reduced with the most effective use of non-steroidal anti-inflammatory drugs (NSAIDs), according to current clinical recommendations [5–9]. However, Adverse Effects (AE) present an important obstacle to the use of NSAIDs; the most frequent and dangerous AE include gastrointestinal ulcer (GIU) and cardiovascular complications. They are primarily associated with the main action mechanism of NSAIDs – inhibition of cyclooxygenase 1 (COX1) and COX2 enzymes that regulate the synthesis of prostaglandins, which not only participate in the development of pain and inflammation but also have gastroprotective and antithrombotic effects [10, 11]. Among AE arising on the back of NSAIDs, symptoms of dyspepsia (abdominal pain, epigastric distention, heartburn, nausea, etc.) are of special clinical and pharmaco-economic importance and occur 10–12 times more often (8–12 %) [12] than severe complications caused by ulcerative necrotic lesions of the gastrointestinal mucosa (1–2 %) [13, 14]. It is noteworthy that selective inhibitors of COX2 (coxibs) induce dyspepsia development more often than nonselective NSAIDs administered in combination with proton pump inhibitors [15].

One of the new relatively safe NSAIDs is Amtolmetin Guacil (AMG; Naizilat®, Dr. Reddy's Laboratories Ltd., India), a combination of NSAID tolmetine with guaicol and glycine. AMG belongs to the nonselective NSAIDs with a selectivity ratio to COX2 / COX1 equal to 4.4 [16]. Evidence shows that AMG has similar efficacy as other NSAIDs nonselective to COX, and a selective COX2 inhibitor by celecoxib, but better tolerability from the gastrointestinal tract [16–20]. It is believed that this favorable effect of AMG is due to the presence of vanillin residues in the molecule structure, that stimulate capsaicin receptors and the formation of a peptide associated with the calcitonin gene, which in turn promotes the formation of nitric oxide with "gastroprotective" activity [21, 22]. It is believed that the activation of capsaicin receptors occurs after direct contact of the drug with the gastric mucosa, therefore, to ensure the maximum "gastroprotective" activity, AMG should be taken on an empty stomach.

Nevertheless, the data on the efficacy and safety of AMG in therapy of rheumatic diseases is limited, and requires further research.

After oral administration, AMG almost completely (99 %) binds to plasma proteins. The half-life in adults is equal to about 5 hours. Within 24 hours the drug is almost completely eliminated from the body in the form of glucuronides (80 % – with urine, and 20 % – with bile).

The aim of the open-label observation study of AGATA (**A**mtolmetin **G**uacil in patients with osteoarthritis of knee joints), conducted on a specially selected pool of patients, was to evaluate the efficacy and tolerability of AMG therapy in patients with knee OA and signs of dyspepsia, and compare it with previous NSAID therapy.

Material and methods

The study involved 220 patients aged 30–65 years, suffering from OA (which manifested clinically with significant pain in knee joints), receiving NSAIDs and having symptoms of dyspepsia. The general clinical characteristics of patients are presented in Table. 1. The study group was mostly dominated by middle-aged women, with a prescription of about 7 years, a prolonged exacerbation (6.8 ± 5.9 weeks) in the "target" knee joint, overweight (mean BMI – 31.5 kg/m^2), and OA of other joint groups: small joints of the hands (24.8 %), hips (31 %). In general, following concomitant diseases occurred in 68 % of patients, among them hypertension (42 %), varicose veins of the lower extremities (6.4 %) and diabetes (6 %).

Table 1 Clinical characteristics of the patients with OA (n=220)

Indicator	Meaning
Sex. n (%):	
men	37 (17)
women	182 (83)
Age, years, M±S	55.2±6.9
Disability, n (%)	26 (12)
Duration of the disease, years, M ± S	7±5
Smoker, n (%)	44 (20.7)
Body weight, kg, M±S	85±16
BMI, kg/m2, M±й	31±5.3
Pain in the knee joint, n (%):	
right	119 (55)
left	96 (45)
The duration of the current exacerbation, weeks, M±S	6.8±5.9
Pain in other joints, n (%):	
small joints of the hands	53 (24.8)
Hips	67 (31)
other joints	29 (14.3)
Comorbid diseases, n (%):	150 (68.2)
Obesity	8 (3.6)
hypertension	91 (41.4)
diabetes	13 (5.9)
Varicose disease of the lower extremities	14 (6.4)

Note. BMI – body mass index.

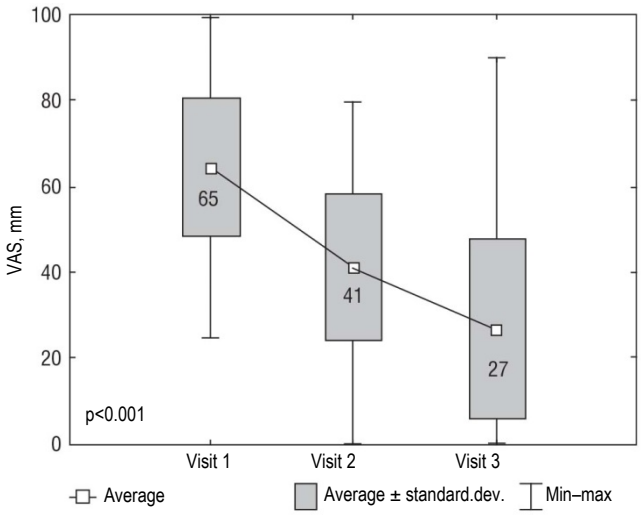

Figure 1. Assessment of the severity of pain in the "target" knee joint by VAS (0–100 mm)

The therapy efficiency was assessed using the three scales of the WOMAC index (Western Ontario and McMaster Universities Osteoarthritis Index), pain intensity and overall health rating from the visual analog scale VAS, and efficiency according to the doctor and the patient. Researchers used the SODA index (The Severity of Dyspepsia Assessment) to quantify dyspepsia [23].

According to the protocol, the therapy of concomitant diseases during the study period was stable. Before joining the study, patients received various NSAIDs: diclofenac – 92 (41.8 %), ketoprofen – 31 (14.9 %), aceclofenac – 35 (15.9 %), meloxicam – 78 (35.5 %), nimesulide – 70 (31.8 %), Ibuprofen – 13 (5.9 %) of the patients. The replacement of NSAIDs with AMG occurred without a "washout" period.

Since the study was descriptive, it was not planned to check the statistical hypotheses when processing the results; the pool size for this study was given beforehand.

Results

Efficacy. It was found that AMG has a pronounced analgesic effect, confirmed by pain reduction (≥40 %), which occurred in 72.5 % of patients. In dynamics, the intensity of pain (according to the VAS) in the "target" KJ significantly decreased ($p < 0.001$). Moreover, the significant decrease was noted after 14 days of AMG administration (Fig. 1). The presence of a pronounced analgesic effect of AMG (Table 2) was confirmed by a decrease in the intensity of pain in the opinion of patients who rated it daily according to VAS (diary of the patient). When analyzing the dynamics of WOMAC parameters, a statistically significant ($p < 0.001$) reduction in pain, stiffness, functional limitations and total score was established. Against the backdrop of AMG treatment, a positive trend in the overall assessment of patients' health was observed ($p < 0.001$). In general, AMG therapy was regarded as effective, in the opinion of both the doctor and the patient (Figure 2).

Tolerance. The tolerance of AMG from the gastrointestinal tract was assessed by the SODA index (Table 3). A significant decrease in non-pain and pain signs of dyspepsia was established. In addition, the positive dynamics of the indicators "general assessment of severity of dyspepsia" ($p < 0.001$) and "satisfaction with treatment" was noted.

After 14 days of therapy, 26 % of patients evaluated the tolerance of AMG as "excellent", 57 % – as "good", 13 % – as "satisfactory", and only 3 % – as "bad". At the same time, after the completion of the study, the assessment of tolerance of AMG therapy was only positive: "Excellent" – in 33 % of patients, "good" – in 56 % and "satisfactory" – in 11 % of patients. In general, patients tolerated AMG better than NSAIDs that they received in the past (Figure 3).

Table 2 Dynamics of clinical parameters, VAS, mm, Me [25th; 75th percentile]

Indicators	Prior to therapy	After 14±3 days	After 28±3 days
Pain, WOMAC	242 [171; 303]	170 [110; 240]	96.5 [62; 177]
Stiffness, WOMAC	102.5 [69.5; 129.5]	77.5 [46; 111]	49 [30; 83.5]
Total index, WOMAC	1199 [841; 1495]	865[583; 1202]	549.5 [336.5; 891.5]
Pain intensity in the target joint	64 [52; 75]	40 [30; 52]	22.5 [10; 39]
General health assessment	52 [40; 66.5]	60 [50; 70]	72 [64; 85]
The effectiveness of therapy according to the patient	-	60 [50; 69]	78 [70; 87]
The effectiveness of therapy according to the doctor's evaluation	-	62 [50; 72]	77.5 [67; 87]

AE were registered with 7.7 % of the patients. The severity of AE in 18 % of cases was average, and in 82 % of cases – mild. No abnormal changes in hemoglobin levels, transaminases, leukocyte numbers and blood pressure were noted. No serious AE were registered. According to doctors, the "probable" connection of AEs with AMG was noted in 76.4 %, "possible" – in 11.8 % and "definite" – in 11.8 % of patients. Early termination of therapy was chosen by 11 patients, and AE caused the termination of AMG therapy in only 1.4 % of cases. At the end of the study, the vast majority (90 %) of patients expressed the desire to continue therapy with AMG.

Discussion

There is evidence that nitric oxide (NO) has a gastroprotective effect due to an increased blood flow in the mucosa of the gastrointestinal tract, which contributes to the production of mucus, bicarbonate secretion and reduced adhesion of neutrophils to the vascular endothelium [24–26]. This led to creation of a new class of NSAIDs that are capable of local release of NO, which, with analgesic and anti-inflammatory effects, do not cause damage to the gastrointestinal tract caused by NSAID-induced suppression of prostaglandin synthesis [27, 28].

Among AEs associated with the intake of NSAIDs, dyspepsia attracts specific attention – a frequent pathological condition, occurring in about 25 % of the world's population [29]. It can be associated with many causes, including intake of NSAIDs, or is functional in the absence of structural changes in the gastrointestinal tract [29, 30]. Since dyspepsia occurs more often than ulcerative necrotic lesions of the gastrointestinal tract against the background of treatment with NSAIDs, it is believed that, from the pharmaco-economic point of view, its prevention is essential, as we as the prevention of severe complications from the gastrointestinal tract [13]. It should be noted that the SODA questionnaire [23] used in our study is recommended for assessing the severity of dyspepsia in patients taking NSAIDs [31].

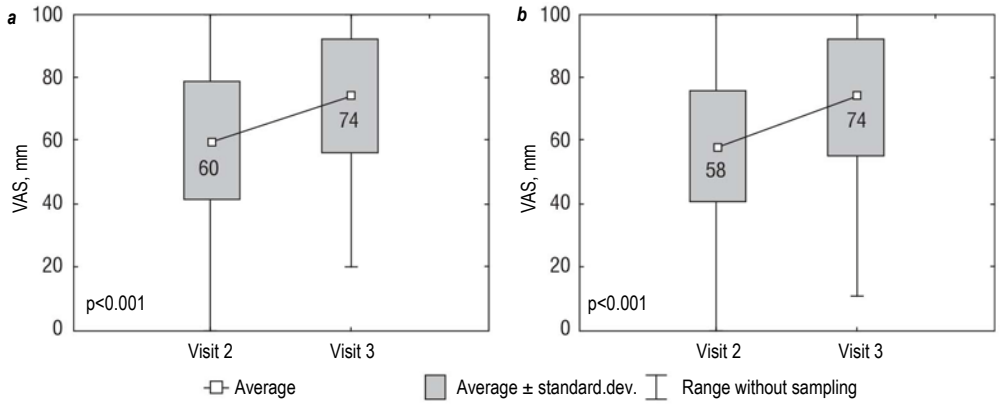

Figure 2. Evaluation of the overall effectiveness of therapy according to VAS, by physician (a) and patient (b)

Table 3 Dynamics of SODA questionnaire indicators, points, Me [25th; 75th percentile]

Parameters	Prior to therapy	Day 14	Day 28
Pain intensity	23.4 [20; 27]	21 [18; 23]	16 [12; 22]
Non-pain signs	16.5 [14; 18]	15 [12; 17]	13 [10; 15]
Satisfaction with therapy	11 [10; 13]	12 [11; 14]	14 [12; 17]

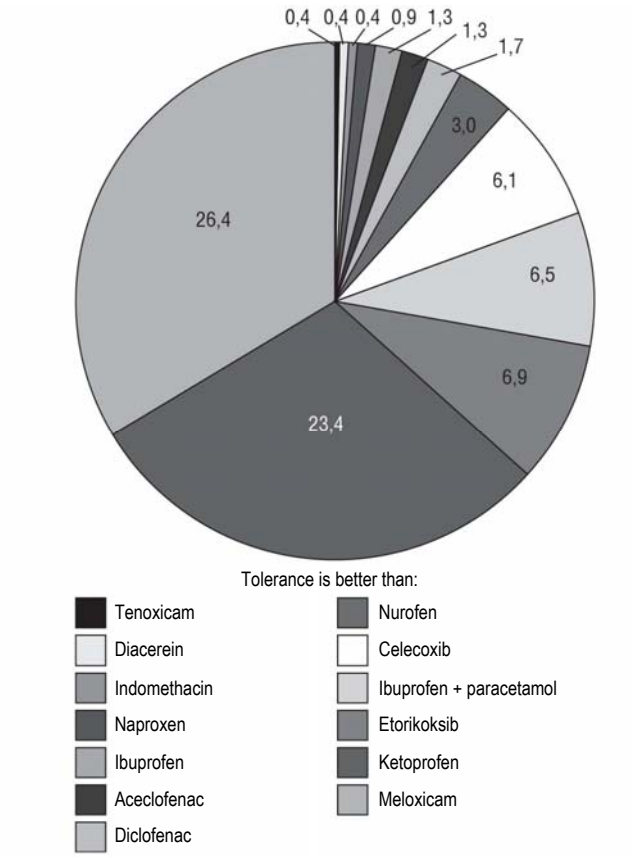

Figure 3. Conclusions on the comparative tolerability of AMG therapy (according to patients' responses, n = 231)

The study confirmed the high efficacy and very good tolerability of AMG in patients with knee OA, when the effective analgesic therapy is not acceptable due to dyspepsia. Previous studies have found that its frequency in patients who took AMG does not differ from that in patients treated with diclofenac [19] and celecoxib [16] with rheumatoid arthritis and piroxicam [18] – with OA. However, the frequency of ulcerative-necrotic lesions (gastric and duodenal ulcers, high endoscopic count) when using AMG was not lower than in the case of therapy with other NSAIDs ($p < 0.05$). It is noteworthy that the severe AE that led to the therapy cancellation developed significantly less frequently ($p < 0.05$) against the background of AMG treatment [20]. Moreover, our data indicate a good subjective (SODA questionnaire) tolerability of therapy in patients with OA and dyspepsia after substitution of standard NSAIDs with AMG. This may be important to consider then selecting the proper NSAID and in increasing commitment to treatment. At the same time, it should be emphasized that the presence of severe lesions of the gastrointestinal tract is not always accompanied by appropriate clinical manifestations [32]. Thus, according to a prospective study, gastric bleeding was observed in the absence of symptoms of dyspepsia (or pain in the epigastric region) in more than 80 % of patients [33]. This indicates the need for careful monitoring of patients who have a high risk of complications from the gastrointestinal tract when taking NSAIDs.

Nevertheless, on the whole, the obtained results indicate good prospects for the use of AMG in treatment of OA.

Study transparency

The study did not have sponsorship support. The authors bear full responsibility for providing the final version of the manuscript to the press.

Declaration on financial and other relationships

All authors took part in the development of the concept of the article and in writing the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive a fee for the article.

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