# Tablet Clotam® (Tolfenamic Acid) Retard 300 mg *versus* Tablet Sandomigrin® (Pizotifen) 1.5 mg in Prophylactic Treatment of Migraine

**Antanas Vaitkus[1], Kristian Vinter Juul[2], Valius Pauza[1]**

*[1] Kaunas University of Medicine, Department of Neurology, Kaunas, Lithuania*
*[2] A/S GEA Farmaceutisk Fabrik, Frederiksberg, Denmark*

The aim of this study was to evaluate the efficacy and tolerability of tolfenamic acid *versus* pizotifen in migraine prophylaxis in a randomised, double-blind, single-centre trial. 192 patients with 4–8 moderate to severe migraine attacks per month were included in the study. The patients were treated for 12 weeks with a tolfenamic acid 300 mg long-acting tablet or a pizotifen 1.5 mg conventional tablet nocte, with a 4-week run-in period without medication.

A significant reduction in the frequency of attacks was seen for both drugs. The mean attack frequency per four weeks was 2.5 migraine days compared to 4.5 during the run-in period ($p < 0.001$). A significant difference in reducing the pain severity during migraine attacks was observed in favour of tolfenamic acid ($p = 0.04$). The main cause for dropout from the pizotifen group was weight gain, whereas tolfenamic acid was well tolerated.

Because of its high efficacy and excellent tolerability tolfenamic acid is an interesting drug for prophylactic treatment of migraine compared to the established prophylactic drug pizotifen.

**Key words:** tolfenamic acid, pizotifen, migraine, prophylactic treatment, randomised controlled trial

**Abbreviations**

NSAID – non-steroidal anti-inflammatory drug, GCP – Good Clinical Practice, HIS – International Headache Society, R-TA – tolfenamic acid retarded release, PI – pizotifen

## INTRODUCTION

Patients suffering from migraine need a continuum of clinical care, depending on their disability and response to treatment (1). The choice of therapy depends on the severity and frequency of the headache, the pattern of associated symptoms, comorbid illnesses, and the profile of the patient's treatment response. The pharmacological management of patients suffering from migraine with or without aura is concentrated on two approaches: treatment of the acute attack and long-term prophylactic therapy. In both cases, the choice of treatment depends on the efficacy and side effects.

Prophylactic treatment of migraine is often inefficient and unsatisfactory. The major objective of prophylactic therapy is to reduce the frequency, duration and intensity of attacks. Current therapy includes beta-blockers, serotonin (5-HT) re-uptake blockers, and 5-HT2 receptor antagonists such as pizotifen (2).

Tolfenamic acid and pizotifen act in different ways. Tolfenamic acid inhibits prostaglandin and leukotriene synthesis (3), whereas pizotifen is a 5HT-recpetor antagonist (4). However, both drugs have proven effective in prophylactic treatment of migraine. Clinical trials and clinical observations show that tolfenamic acid reduces the incidence of migraine attacks (5–7). A retard release formulation of tolfenamic acid (R-TA) has been developed for the prevention of migrainous headache and for treatment of dysmenorrhea. Pizotifen has been used as a reference compound in double-blind prophylactic migraine studies (8–14) and has proven to be as effec-

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Correspondence and reprints: Antanas Vaitkus, MD, Kaunas University of Medicine, Department of Neurology, Eiveniu 2, LT-3007 Kaunas, Lithuania. Tel/fax: +370-7 792 627. E-mail: neurpain@kmu.lt

tive as metoprolol, naproxen, flunarizine, and nimodipine.

## PATIENTS AND METHODS

### Patients

The study was carried out in accordance with the GCP guidelines. Prior to start, the study was reviewed and approved by local Ethics Committees and the National Pharmaceutical Committee. The patients were informed verbally and in writing about the study. The patients were informed about the possibility of stopping their participation in the study at any time without prejudice to their subsequent care. Signed informed consent was obtained from all patients. On May 28 1996, the first patients were recruited, and the clinical part of the trial was completed on May 14 1998.

Inclusion criteria for the study were that the patients of both sexes had to be aged 18–55 years and have a history of migraine with or without aura with 4–8 moderate to severe migraine attacks per month for more than one year. Migraine was defined by the criteria of the International Headache Society (IHS) (15).

Physical examinations and blood tests were performed at the start of the run-in period and after treatment were stopped. For each eligible patient, personal data, case history and findings from the medical examination were recorded and entered into a record form.

212 patients were included in the study. Of these, 20 patients discontinued the study, 3 due to pregnancy, 9 due to lack of effect, and 8 due to loss of contact. 192 sets of data were available for statistical analysis (97 patients were allocated to the R-TA group and 95 patients to the PI group). During the run-in period and the test period, 24 women on R-TA and 27 on PI reported at least 1 menstruation date. 3000 migraine attacks were reported. Of these attacks, 1149 occurred during the run-in period and 1851 during the test period.

### Study design

The study was designed as a randomised, double-blind, parallel group, single-centre trial. Each patient had to complete a run-in period of 1 month (4 weeks) followed by 3 months (12 weeks+5 days) of prophylactic treatment of migraine with R-TA or PI.

At the first visit, medical history and written consent were obtained, and the patient was instructed to record the migraine attacks in a diary for 1 month. The patients were not allowed to take any prophylactic migraine medicine during this period. At the second visit, the diary was reviewed, blood pressure, heart rate, and ECG were recorded and blood samples for routine haematology, liver function and electrolytes were taken. Patients who had filled in the run-in diary correctly were randomised to receive either PI tablets 1.5 mg (Sandomigrin®) or R-TA long-acting tablets 300 mg (Clotam Retard®) for 3 months + 5 days. A double-dummy blinding method was used. The patients were allowed to use escape medication to treat acute migraine attacks. A combination tablet consisting of paracetamol 500 mg + codeine 30 mg was used for this purpose. The patients were treated at home and had to visit the clinic at a final visit after completion of the trial. At the final visit, all examinations and tests were repeated.

### Evaluation of efficacy

The primary end-point was the frequency of attacks per 4 weeks. Attacks that ended or were interrupted by sleep and relapses within 24 hours were considered one attack. Other efficacy variables were: (1) duration of attack in hours; (2) intensity of migraine attack evaluated by a 4-point scale (0 = none, 1 = mild pain, 2 = moderate pain, 3 = severe pain); (3) need for escape medication during a migraine attack; (4) adverse events; (5) patient's global evaluation of the treatment (0 = no effect, 1 = little effect, 2 = moderate effect, 3 = good effect); (6) physician's global evaluation of the treatment (same 4-point scale); (7) difference in number of migraine days during the run-in period and during the 4-week treatment period; (8) duration of migraine attacks if the migraine occurred during menstruation; (9) difference in duration of menstrual-related migraine depending on treatment; (10) incapacitation due to migraine.

### Evaluation of safety

Adverse events of which the patient complained spontaneously were recorded along with response to a general health question. Severity was scored as mild, moderate or severe. Causal relationship to trial medication was recorded as unrelated, unlikely, possible, probable, or almost certain. Action taken could range from none to exclusion from the trial.

### Power calculations and randomisation

Calculation of the sample size was based on detecting a clinically significant difference of 25% in the reduction of attack frequency at a 5% significance level with a coefficient of variation of 55%. Based on the T-test approximation to the permutation test, power was calculated by an algorithm of the non-central T-distribution for the clinical significant dif-

ference. Minimum 150 patients were required to detect this difference with a power of 80%. 192 patients were actually included in the study.

A computer-generated randomisation code was used to assign patients in blocks of eight. In each block, four patients were assigned to the group given R-TA and four to the group given PI.

### Statistical methods

All statistical analyses were performed before the code was broken. All tests employed non-parametric methods:

1) the empirical frequency distributions of the absolute value and of the test value of relative change were tested for significant deviations from a normal distribution, employing the Kolgomorov–Smirnov test. The correlations between baseline values and changes were estimated applying the Spearmen rank correlation coefficient (R);

2) ordinal and continuous data were tested for treatment effects on medians (test values against baseline values) as related samples within study drugs, using the Wilcoxon matched pairs signed rank test;

3) test of differences between the study drugs and of drug-related differences in changes employed the Mann–Whitney test (16). Where the number of observations exceeded 25 in both treatment groups, the Mann–Whitney test employed the Z-statistics and otherwise the U-statistics;

4) nominal data were tested in contingency tables using the chi-square test without correction for continuity (17).

All tests were two-tailed with application of a 5% significance level. Statistical evaluation was performed using the SAS® system.

## RESULTS

### Attack frequency per 4 weeks

A significant reduction in attack frequency was observed for both treatment groups. During treatment with both active drugs, the number of days with migraine was 2.5 per 4 weeks compared to 4.5 during run-in, $p < 0.001$. No difference was found between the treatment groups as to frequency, $p = 0.669$ (Fig. 1).

Because prophylactic treatment was given for a limited time, it might be of interest to investigate whether a stable level of treatment effect was achieved at the end of the test period. Hence, the weekly attack rates were calculated during both study periods. The result appears from Fig. 2. A tendency towards a decreasing number of weekly migraine attacks was observed during prophylactic treatment. In addition, it seems evident that the weekly attack rate did not reach a stable level at the end of the study period as the number of attacks was still declining.

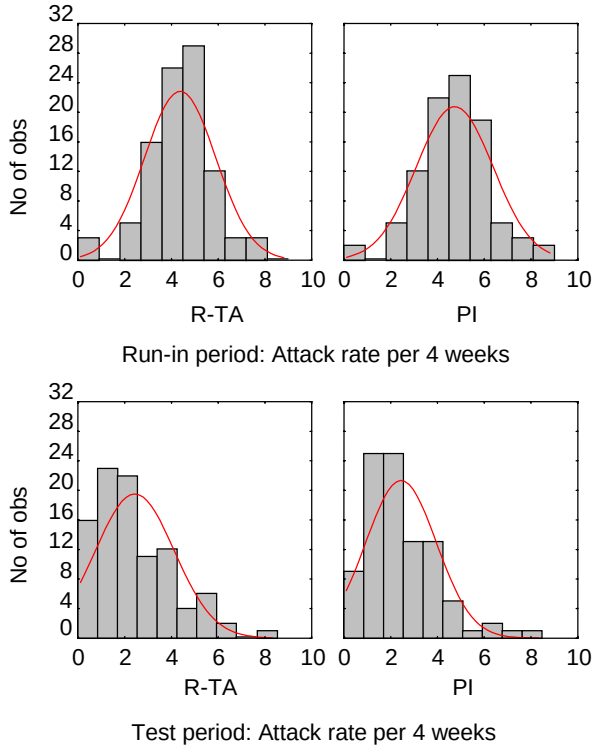


Fig. 1. Attack rate per 4 weeks: Frequency distribution of observations according to study period and treatment. Continuous lines indicate the theoretical distribution of a normal by distributed data set with identical means and standard deviations

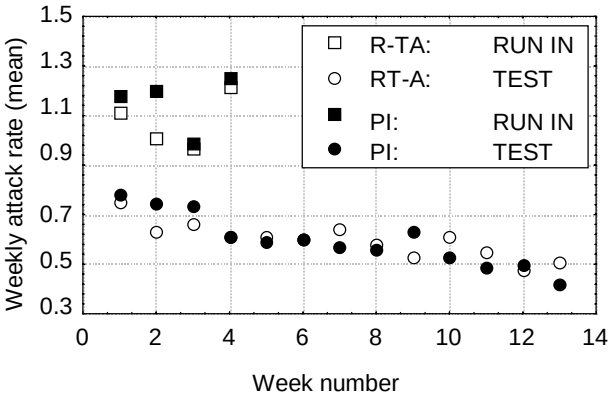


Fig. 2. Weekly attack rate according to study period and treatment

### Secondary efficacy variables

No difference was found between the groups in duration of attacks, $p = 0.194$ (Fig. 3), whereas R-TA was found superior to PI in reducing pain severity during migraine attacks, $p = 0.04$ (Fig. 4). Compared to the run-in period, patients treated with PI

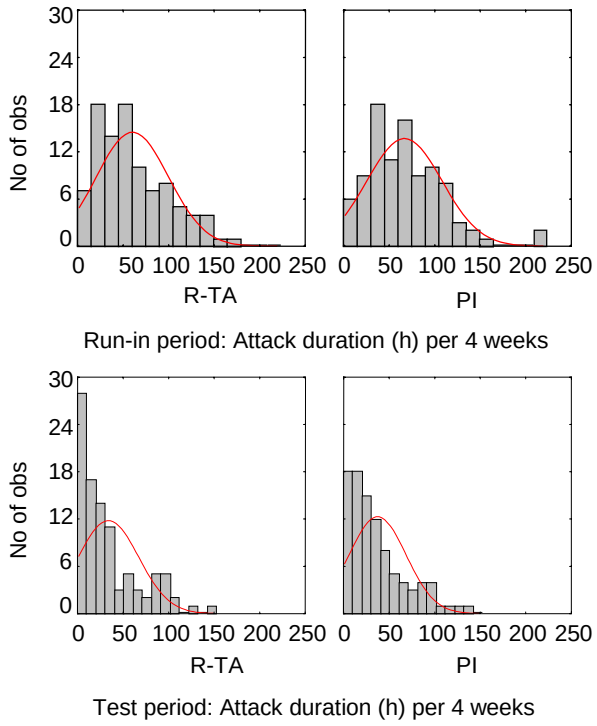


Fig. 3. Attack duration per 4 weeks: Frequency distributions of observed attack duration according to study period and treatment group. Continuous lines indicate the theoretical distribution of normally distributed data with identical means and standard deviations

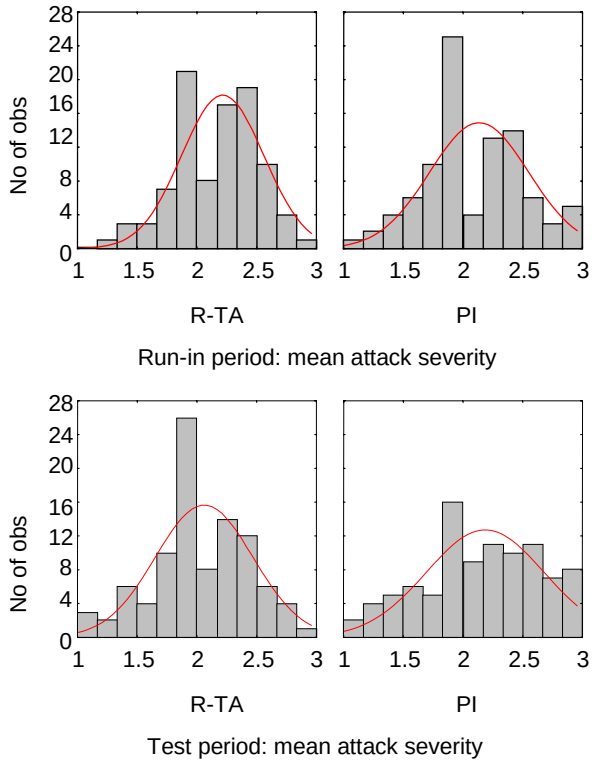


Fig. 4. Mean attack severity: Frequency distributions of observed mean attack severity according to study period and treatment group. Continuous lines indicate the theoretical distribution of a normally distributed data set with identical means and standard deviations

were in more need of escape medication ($p < 0.01$) than patients treated with R-TA, $p = 0.15$ (Fig. 5). This implies a strong tendency (although not significant in this study) to a need of a larger number of tablets per migraine attack in the patients treated with PI than in the patients treated with R-TA. For the patients treated with R-TA, the mean duration of menstruation-related attacks was 11.3 h *versus* 14.4 h for patients treated with PI, $p = 0.067$. Although not significant, this also implies a tendency to the duration of menstruation-related attacks being shorter for the patients treated with R-TA compared to the patients treated with PI.

For the remaining variables, the confidence limits of mean changes include the value 0, implying that the variables were unaffected by the kind of the drug used.

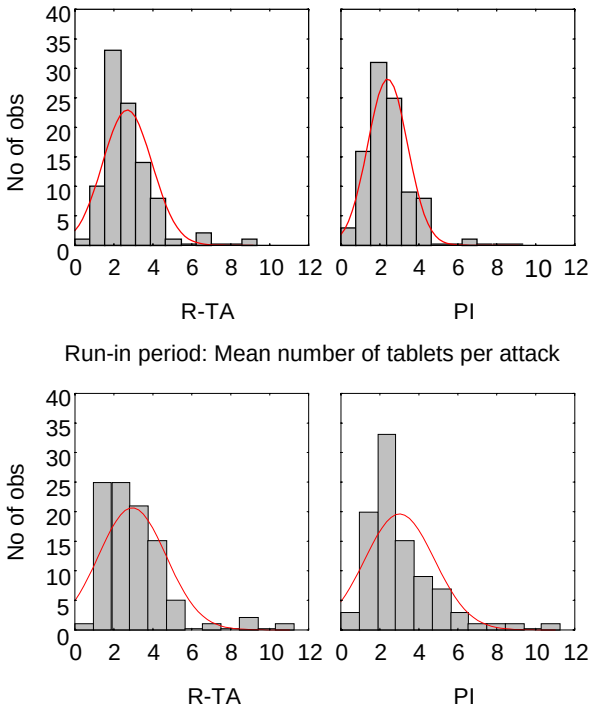


Fig. 5. Mean number of tablets per attack: Frequency distributions of observed mean number of tablets per attack according to study period and treatment group. Continuous lines indicate the theoretical distribution of normally distributed data with identical means and standard deviations

## Safety

Seven patients in the R-TA group reported adverse events such as irritable stomach and other gastrointestinal symptoms. Fourteen patients in the PI-group reported increased appetite, weight gain, and daytime drowsiness. No serious adverse events were observed. There was no statistical difference between

the two treatment groups regarding the severity of adverse effects.

The patients treated with PI experienced a weight gain of 2.56 kg (95% confidence interval, 1.89–3.25). A weight gain of 0.63 kg was seen in patients treated with R-TA (95% confidence interval, 0.13–1.13).

## DISCUSSION

In clinical practice, it may be difficult to find the optimal treatment for migraine attacks, because the condition is often debilitating and may prove refractory to therapy (18). Obviously, many patients with migraine obtain a sufficient degree of headache control when using agents like the triptans. This treatment will normally not provide a lasting improvement for individuals suffering from frequent severe headaches, and they may require stabilisation by effective prophylactic therapy. Unfortunately, the number of agents for prophylactic treatment of migraine does not increase as rapidly as the number of abortive medications. Therefore, the majority of clinicians and patients only have a small number of drugs for this purpose (19). For each individual patient, the choice of prophylactic treatment has to be based on evaluation of contraindications and availability of the drug. Prophylactic medication is usually given daily for months or years, but no commonly chosen migraine prophylactic agents have shown absolute effective for prevention of migraine. Furthermore, the benefit for these patients did not exceed 50% as compared to placebo (20).

This trial showed significantly fewer attacks for both active drugs when compared to the run-in period. The major additional benefit of R-TA is that it was superior to PI in reducing pain severity during those migraine attacks that none the less occurred, making the burden of the disease lighter for the patients.

Weight gain was observed in both active drugs. During a 3-month-period, the average weight gain was 2.6 kg in patients treated with PI and 0.6 kg in patients treated with R-TA. In none of the treatment groups, the confidence interval of weight-differences included the value 0. In addition, a drug-related difference in weight change was implied by the fact that the confidence intervals of the mean changes in each treatment group did not overlap. Considering these results, it can be concluded that the reason why the patients experienced weight gain was due to the prophylactic treatment. Weight gain was more pronounced in patients treated with PI than in patients treated with R-TA. Weight gain may limit the use of PI in clinical practice (21).

Levels of sex hormones fluctuate throughout the female life cycle, and these fluctuations may trigger, intensify or alleviate migraine (22). A tendency, although not significant, to a shorter duration of menstruation-related attacks were seen in women treated with R-TA compared to women treated with PI. This makes R-TA an interesting option for use in both prophylactic and therapeutic treatment of headache resulting from such fluctuations.

## CONCLUSION

It can be concluded that tolfenamic acid as a migraine-prophylactic medication is equipotent to pizotifen regarding the frequency and duration of attacks and superior in terms of reducing pain severity. Furthermore, tolfenamic acid has a less impact on weight gain than pizotifen. Therefore, tolfenamic acid is an interesting drug for prophylactic treatment of migraine compared to the established prophylactic drug pizotifen.

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Statistician: MSc, PhD Mogens Bildsųe, KLIFO A/S, Copenhagen Science Park Symbion, Denmark.

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**A. Vaitkus, K. V. Juul, V. Pauza**

**PROFILAKTINIS MIGRENOS PRIEPUOLIŲ GYDYMAS LYGINANT CLOTAM RETARD® (TOLFENAMINĖ RŪGŠTIS) SU SANDOMIGRIN® (PIZOTIFEN)**

S a n t r a u k a

Profilaktinio migrenos priepuolių gydymo tikslas – sumažinti galvos skausmų dažnį, intensyvumą ir neleisti sutrikdyti darbingumą. Migrenos priepuoliai prevenciškai gydomi skirtingų farmakologinių grupių medikamentais, galinčiais sumažinti centrinio ar periferinio skausmo aktyvinimo smegenyse slenkstį. Vartojamų medikamentų arsenalą sudaro kalcio kanalų blokatoriai, antikonvulsantai, beta receptorių blokatoriai, serotonino receptorių antagonistai, nesteroidiniai vaistai nuo uždegimo ir kt. Dauguma šių vaistų pirmiausia vartojami kitokioms ligoms gydyti, tačiau kai kuriems turi patvirtinta indikacija migrenos priepuoliams profilaktiškai gydyti. Kasmet atliekamos 5–6 klinikinės studijos, kuriose vertinami šie vaistai lyginant juos su praktikoje paplitusiais medikamentai. Tolfenaminė rūgštis priskiriama nesteroidinių vaistų nuo uždegimo grupei. Ji pradėta taikyti migrenos priepuolių profilaktikai Skandinavijos šalyse, kurį laiką buvo primiršta, kaip ir klasikiniai profilaktiniai medikamentai metisergidas ir pizotifenas, tačiau sukurtos naujos vaistų formos, geruųjų tolerancija vėl sukėlė tyrėjų susidomėjimą šiais medikamentais. Lietuvoje pirmą kartą atliktas migrenos profilaktinio gydymo tyrimas, kurio pagrindinis tikslas buvo įvertinti 300 mg tolfenaminės rūgšties efektyvumą. Migrenos profilaktikai buvo vartojama 300 mg tolfenaminės rūgšties, palyginti su 1,5 mg pizotifeno. Atlikta dvigubai akla paralelinių grupių studija. Į tyrimą įtraukta 214 ligonių, kurie atitiko Tarptautinės galvos skausmų asociacijos (TGSA) migrenai keliamus reikalavimus. 192 ligonių baigtas tyrimas. Galutiniu pirminio veiksmingumno kriterijumi buvo laikomas priepuolių, įvykusių per 4 savaites, dažnumo sumažėjimas. Buvo įvertintas migrenos priepuolių intensyvumo bei trukmės sumažėjimas 12 savaičių gydymo pabaigoje, jį lyginant su pradinio laikotarpio duomenimis. Buvo tiriamos dvi ligonių grupės, kurių viena vartojo Clotam retard su placebo, o antra – Sandomigrin su placebo. Abiejose grupėse pastebėtas didelis priepuolių dažnio sumažėjimas ($p < 0,001$). Tolfenaminė rūgštis daugiau negu pizotifenas sumažino skausmo aštrumą ($p = 0,009$). Ligoniai, vartoję pizotifeną, daugiau vartojo gretutinių vaistų negu tolfenaminę rūgštį vartojusiųjų grupė ($p < 0,01$). Šalutinis poveikis, t. y. svorio padidėjimas, mažiau pastebimas vartojusiųjų tolfenaminę rūgštį nei kitos grupės. Buvo įrodyta, kad gydymas abiem medikamentais yra efektyvus ir gerai toleruojamas.

**Raktažodžiai**: migreniniai galvos skausmai, tolfenaminė rūgštis, pizotifenas, profilaktinis gydymas