Several classes of pharmacologically unrelated drugs are considered to be beneficial in the prevention of migraine headache [1]. In recent years sodium valproate has proved to be an effective prophylactic drug for migraine headaches [2–4]. It has given relief to patients whose response to other medication was poor and the benefit continues during long-term therapy [5, 6]. Although its mode of action in migraine is unclear [7], sodium valproate prolongs the effect of gamma-amino butyric acid (GABA) by inhibiting GABA-transferase, an enzyme responsible for its degradation [8]. Some new antiepileptic drugs with GABA-mimetic effects appear to have similar preventive effect in migraine [9]. Vigabatrin, a new-generation antiepileptic drug, inhibits the enzyme GABA-transferase like sodium valproate and potentiates the analgesic effects of other drugs [10–14]. The present paper describes a double-blind comparison of the effects of low-dose vigabatrin with matched placebo tablets in patients suffering from drug-resistant migraine.

A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache

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Abstract Twenty-three patients, aged 18–66 years and suffering from migraine with or without aura, were randomly selected to receive either vigabatrin or matched placebo tablets first for 12 weeks in a double-blind crossover study. Alternative treatment was given after a 4-week washout period. The dose of medication was titrated to a maximum of 4 tablets (2 g vigabatrin) daily according to patients' tolerance during the first six weeks of each treatment. No further dosage adjustment was made. Apart from rescue medication for migraine, no other drug was permitted. Four patients dropped out and four were excluded for non-compliance. Compared to placebo, vigabatrin decreased the frequency ($p=0.017$) and severity ($p=0.024$) of headache modestly. However, it reduced the duration ($p=0.019$) of headache and migraine index ($p=0.012$) considerably by 40% and 59%, respectively. No serious adverse effects were observed. Serum vigabatrin levels showed no correlation with the clinical effects.

Key words Compliance • Migraine • Prophylaxis • Vigabatrin

Patients and methods

Patients

Subjects were recruited from a public hospital headache clinic to which headache patients with complex problems are referred. Prior to attending the clinic the majority of patients showed poor response to most conventional prophylactic medication [1]. At the time of conducting this investigation, sodium valproate was less frequently prescribed for migraine by the general practitioners.
Patients who obtained no benefit from 2 or more preventive drugs (excluding sodium valproate) for migraine headaches were considered in this study as to be suffering from drug-resistant migraine. However, 15 patients previously received sodium valproate and 12 (80%) responded to this medication. Twenty two patients used sumatriptan during acute attacks but 4 patients had limited benefits and one never had any relief.

A total of 23 patients with migraine were recruited for study. Migraine was diagnosed according to the criteria of the International Headache Society [15]. The patients had no other clinically relevant physical or psychiatric disorder and all had normal computerised tomographic (CT) scan of the head. Electroencephalography (EEG) showed no evidence of epilepsy. The subjects were nonsmokers and none had a history of substance abuse, including analgesic or ergotamine overuse.

The local health authority’s ethics committee approved the study protocol and the participants gave written informed consent prior to entry. Patients retained the right to withdraw from the study at any time without jeopardising their further management at the headache clinic or at the local public hospital.

Study design

The investigation was carried out as a double-blind, randomised crossover study in which the prophylactic effect of vigabatrin in migraine headaches was compared with that of an identical placebo tablet. Following an initial 4-week pre-entry assessment period when all patients received placebo tablets as a single-blind treatment, the patients were randomly selected to receive either vigabatrin (n=12) or placebo (n=11) first for 12 weeks. They then received only placebo (single blind) for 4 weeks (wash out). Alternative trial medication was given after the wash out period for an additional 12 weeks. The investigation was performed as an outpatient study with the patients attending a research clinic following an overnight fast between 08.30 and 09.30 h for assessment at 2- to 6-week intervals.

The patients received the trial medication starting with 250 mg (half tablet) at night for 2 days. This was then gradually increased to 500 mg twice daily by the end of week 2 of each treatment phase. The dose was further titrated up to a maximum of 1000 mg twice daily (4 tablets) at the beginning of weeks 5 and 6 in patients who had little or limited benefit at the lower doses and were able to tolerate the high dose. No further dosage adjustment was made after week 6. Patients were instructed to bring back all unused tablets in their original containers and a new supply of trial medication was given at each attendance. They were allowed to take rescue medications including triptans for acute attacks of migraine, but no other treatment was permitted (including herbal products or dietary supplements).

Assessments

Patients were assessed at the clinic according to a predetermined schedule: at 4 weeks prior to the entry to the study, at week 0 (pre-entry baseline assessment), and at weeks 2, 4, 6 and 12 of each treatment phase.

Assessment for safety

A physical examination was carried out at pre-entry state and at the ends of phases I and II. At each attendance the patients’ weight, blood pressure and pulse rates were recorded. Venous blood was taken for routine haematological and biochemical tests.

Assessment for side effects

A self-administered symptoms checklist, consisting of 13 common side effects of vigabatrin [10], was used to assess subjective side effects. The list included symptoms of nausea, vomiting, diarrhoea, loss of appetite, drowsiness, dizziness, double vision, forgetfulness, frequent confusion, somnolence, poor mental concentration and fatigue. Patients were also encouraged to list or report any other new problem or increase in the severity of an existing problem. Severity of each symptom was graded on a 3-point scale (1–3). The checklist was administered at baseline and at the ends of phases I and II. Corrected side effects scores were obtained by subtracting post-entry scores from the basal (0 week) score.

Assessment for efficacy

A standardised chart (migraine diary) was used to record details of each headache, associated symptoms and additional medications taken during an attack. The patients were instructed to indicate the duration (in hours) and severity (on a 3-point scale) of each symptom including aura for all migraine attacks. Migraine index (MI) was calculated by multiplying the frequency (F) of migraines per week with the mean duration (D) of attacks in hours and the mean severity (S) of attacks on a 3-point scale [16]. Therefore, MI=FxDxS.

Serum vigabatrin level monitoring

Venous blood was collected approximately 12 hours after the last dose at the end of weeks 2, 4, 8 and 12 during each treatment phase. Serum was immediately separated and frozen at –80° C. The serum samples were coded to ensure that the analysis of drug levels was performed blindly. Plasma levels were measured by a modification of a sensitive high pressure liquid chromatographic (HPLC) method [17]. Reproducibility of this measurement was checked in 28 pairs of duplicate samples.

Compliance

Tablet counting and serum drug level monitoring were used to assess compliance. In an attempt to ensure good compliance, a telephone follow-up was carried out at 2-week intervals, in addition to the usual assessment at the clinic.

Statistical analysis

We used analysis of variance (ANOVA) and multiple analysis of variance (MANOVA) to assess the difference between two treatments. The MANOVA test can assess the difference between means on both correlated and independent group data in a single analysis. MANOVA test was used with the paired t test between week 0 and week 12.

The frequency, severity and duration of attacks together with a migraine index (MI) were analysed by MANOVA with drug
phase and week as repeated measures factors and the drug of first treatment as a grouping factor. A paired t test (with square root transformation) was applied to the total number of headaches between the vigabatrin and placebo phases. Side effects were investigated using Wilcoxon’s nonparametric tests. To assess the relationship between serum levels and clinical effects, Spearman’s rank correlation coefficients were employed. The results given for all probability tests are two-tailed.

Results

A total of 17 female and 6 male patients, aged 18–66 years, volunteered to participate in this study (Table 1). They were suffering from migraine with aura (n=10) or migraine without aura (n=13). Of the 23 patients, 8 had never tried sodium valproate as migraine prophylaxis, 3 previously had no response to sodium valproate, and 12 had experienced a

| Patient | Gender | Age, years | Migraine | Frequency, n/week | Previous response | Randomisation (first medication) | Comment |
|---------|--------|------------|----------|-------------------|-------------------|-------------------------------|---------|
|         |        |            |          |                   | Sumatriptan | Valproate |                           |         |
| 1       | M      | 38         | MA*      | 5.00              | Yes           | No     | Placebo | Trial completed |
| 2       | M      | 36         | MO       | 2.00              | Yes           | NT     | Vigabatrin | Trial completed |
| 3       | F      | 47         | MO       | 1.00              | Yes           | No     | Placebo | Trial completed; non-complier; excluded |
| 4       | F      | 46         | MA*      | 0.50              | Limited       | Yes    | Vigabatrin | Trial completed |
| 5       | F      | 44         | MA       | 0.50              | Yes           | Yes    | Vigabatrin | Trial completed |
| 6       | F      | 34         | MO       | 2.00              | NT            | NT     | Vigabatrin | Drop out at week 12; moved residence |
| 7       | M      | 66         | MO       | 0.75              | Yes           | NT     | Placebo | Trial completed |
| 8       | F      | 38         | MA*      | 5.00              | Limited       | Yes    | Placebo | Trial completed |
| 9       | F      | 55         | MO       | 1.00              | Limited       | Yes    | Vigabatrin | Trial completed |
| 10      | F      | 34         | MO       | 5.00              | No            | NT     | Vigabatrin | Trial completed |
| 11      | F      | 18         | MA       | 0.50              | No            | No     | Placebo | Drop out at week 2; poor motivation |
| 12      | F      | 39         | MO       | 5.00              | No            | No     | Placebo | Trial completed; non-complier; excluded |
| 13      | F      | 44         | MA*      | 0.75              | Yes           | NT     | Placebo | Trial completed; non-complier; excluded |
| 14      | F      | 42         | MA*      | 1.00              | Yes           | NT     | Placebo | Trial completed |
| 15      | M      | 63         | MO       | 3.50              | No            | Yes    | Vigabatrin | Drop out at week 3; preferred valproate |
| 16      | F      | 45         | MA*      | 2.00              | Yes           | Yes    | Vigabatrin | Trial completed |
| 17      | F      | 38         | MA*      | 4.00              | Yes           | Yes    | Vigabatrin | Trial completed |
| 18      | M      | 48         | MO       | 5.00              | Limited       | Yes    | Placebo | Trial completed |
| 19      | M      | 44         | MA*      | 1.00              | Yes           | Yes    | Placebo | Trial completed |
| 20      | F      | 28         | MO       | 0.50              | Yes           | NT     | Vigabatrin | Trial completed; non-complier; excluded |
| 21      | F      | 57         | MO       | 1.00              | Yes           | Yes    | Vigabatrin | Trial completed |
| 22      | F      | 44         | MO       | 0.75              | Yes           | Yes    | Vigabatrin | Trial completed |
| 23      | F      | 55         | MO       | 1.50              | Yes           | Yes    | Placebo | Drop out at week 4; side effects |

* Not all attacks are with aura

MA, migraine with aura; MO, migraine without aura; NT, never tried
beneficial effect from the drug but sought an alternative medication because of the weight gain associated with sodium valproate. The frequency of headaches varied between 0.25 and 5.0 attacks per week. As shown in Table 1, five patients reported 5 attacks of migraine per week, and the possibility of transition of migraine into chronic daily headache could not be excluded in these patients. However, as sodium valproate is also effective in chronic daily headache, it was decided to include these patients in the study.

All patients received a maximum daily dose of 2000 mg vigabatrin and 4 placebo tablets, as none of them became completely free from headaches. Of the 23 patients, 4 (3 women) did not complete the trial (Table 1). Two withdrew during the placebo phase for poor motivation and apparent side effects. Two dropped out at vigabatrin phase: one had no response and the other changed residence. Four other female patients were excluded from the study for evidence of poor compliance. They were also unreliable in completion of migraine diary. Poor compliance was suspected from tablet counting or no detectable serum vigabatrin levels on 2 or more occasions. Therefore, statistical analysis was performed on 10 female and 5 male patients.

Table 2 Effects of vigabatrin and placebo tablets on migraine attacks, corrected side effects, serum drug levels, systolic blood pressure and weight in 15 migraine patients

|                        | Vigabatrin period, weeks | Placebo period, weeks |
|------------------------|--------------------------|-----------------------|
|                        | 0 | 2 | 4 | 6 | 12 | 0 | 2 | 4 | 6 | 12 |
| **Attack frequency, n/week** | Mean | 2.77 | 2.20 | 2.43 | 2.43 | 2.40 | 2.87 | 2.93 | 2.77 | 2.70 | 2.82 |
|                        | SD | 1.97 | 1.96 | 1.84 | 2.03 | 1.80 | 1.88 | 1.64 | 1.89 | 1.96 | 2.00 |
|                        | SEM | 0.51 | 0.51 | 0.48 | 0.52 | 0.47 | 0.49 | 0.42 | 0.49 | 0.51 | 0.52 |
| **Severity**           | Mean | 1.75 | 1.41 | 1.49 | 1.41 | 1.57 | 1.82 | 1.89 | 1.83 | 1.84 | 1.79 |
|                        | SD | 0.53 | 0.66 | 0.66 | 0.57 | 0.55 | 0.56 | 0.59 | 0.66 | 0.67 | 0.61 |
|                        | SEM | 0.14 | 0.17 | 0.17 | 0.15 | 0.14 | 0.14 | 0.15 | 0.17 | 0.17 | 0.16 |
| **Duration, hours**    | Mean | 7.20 | 6.29 | 6.17 | 5.55 | 5.78 | 9.05 | 10.07 | 9.92 | 10.51 | 9.55 |
|                        | SD | 5.81 | 6.65 | 6.38 | 4.77 | 4.55 | 7.30 | 7.43 | 8.10 | 7.59 | 6.51 |
|                        | SEM | 1.61 | 1.84 | 1.77 | 1.32 | 1.26 | 2.02 | 2.06 | 2.25 | 2.11 | 1.81 |
| **Migraine index**     | Mean | 38.80 | 25.26 | 29.80 | 24.99 | 21.46 | 44.46 | 58.51 | 44.41 | 55.32 | 51.65 |
|                        | SD | 51.96 | 49.07 | 44.94 | 32.69 | 23.19 | 60.56 | 59.17 | 47.41 | 58.06 | 65.14 |
|                        | SEM | 17.19 | 13.61 | 12.46 | 9.07 | 6.43 | 16.80 | 16.41 | 13.15 | 16.10 | 18.07 |
| **Corrected side effects score** | Mean | 0 | -1.07 | -0.54 | -0.33 | -0.07 | 0 | -0.43 | 0.14 | -0.14 | -0.50 |
|                        | SD | 0 | 2.30 | 2.99 | 3.14 | 2.56 | 0 | 1.40 | 1.35 | 1.92 | 1.61 |
|                        | SEM | 0 | 0.62 | 0.83 | 0.91 | 0.68 | 0 | 0.37 | 0.36 | 0.51 | 0.43 |
| **Serum vigabatrin, mMol/l** | Mean | 0 | – | 8.07 | – | 18.36 | 0 | – | 0 | – | 0 |
|                        | SD | 0 | – | 3.56 | – | 10.10 | 0 | – | 0 | – | 0 |
|                        | SEM | 0 | – | 0.95 | – | 2.70 | 0 | – | 0 | – | 0 |
| **Systolic blood pressure, mmHg** | Mean | 120.00 | – | – | – | 117.00 | 117.64 | – | – | – | 117.00 |
|                        | SD | 23.00 | – | – | – | 15.29 | 15.32 | – | – | – | 18.97 |
|                        | SEM | 6.00 | – | – | – | 4.09 | 4.09 | – | – | – | 5.07 |
| **Weight, kg**         | Mean | 72.00 | – | – | – | 72.23 | 72.00 | – | – | – | 71.13 |
|                        | SD | 10.00 | – | – | – | 10.49 | 9.91 | – | – | – | 9.53 |
|                        | SEM | 3.00 | – | – | – | 2.80 | 2.65 | – | – | – | 2.55 |

SD, standard deviation; SEM, standard error of the mean

a On a 3-point scale; b For 13 patients; c Subtracted from pre-entry values; d For 14 patients
At the dosage used, no serious clinical or laboratory adverse effects were observed. Compared to both baseline values and placebo treatment period, no significant changes in blood pressure, pulse rate or body weight were observed during vigabatrin treatment (Table 2). Corrected side effects scores showed no significant difference between vigabatrin and placebo treatments at week 12 (Wilcoxon’s test, Z=-0.85, p=0.4) (Tables 2 and 3).

Compared to placebo, total number of headaches were slightly but significantly less both at weeks 2 and 12 during vigabatrin treatment (Table 2). Analysis of variance showed no significant difference between using vigabatrin or placebo first. Compared to placebo treatment, MANOVA test demonstrated a decrease in the total number of headaches during the vigabatrin phase (F=7.49, df=1, 13; p=0.017) (Table 3). A paired t test on the total number of headaches in each period was also significantly less during vigabatrin treatment (t=2.86, df=14, p=0.013).

Likewise there was a significant reduction in the severity (F=6.49, df=1, 13; p=0.024) and duration (F=7.59, df=1,11; p=0.019) of migraine attacks during vigabatrin treatment (Table 3). Compared to placebo, there was a significant reduction in migraine index during the vigabatrin phase (F=9.09, df=1, 11; p=0.012) (Fig. 1). Vigabatrin reduced the duration of headache and migraine index by 40% and 59%, respectively, at week 12 (Table 2). In all tests there was no indication of any effect due to vigabatrin first prescribed.

Table 3 Statistical analysis on the comparison between the effects of vigabatrin and placebo treatments in migraine headaches. Compared to placebo, vigabatrin reduced the number, duration and severity of headaches, and migraine index

| Statistical analysis | Statistical test | p value |
|----------------------|------------------|---------|
| Corrected side effects at week 12 | Wilcoxon’s test, Z=-0.85, N=14 | p=0.4 |
| Total number of headaches during 12 weeks’ treatment | MANOVA, F=7.49, df=1 | p=0.017 |
| | Paired t test, t=2.86, df=14 | p=0.013 |
| Severity of headaches during 12 weeks’ treatment | MANOVA, F=6.49, df=1 | p=0.024 |
| Duration of headaches during 12 weeks’ treatment | MANOVA, F=7.59, df=1 | p=0.019 |
| Migraine index during 12 weeks’ treatment | MANOVA, F=9.09, df=1 | p=0.012 |

MANOVA, multiple analysis of variance

Fig. 1 Effect of vigabatrin and placebo on migraine index. Values are mean and standard error of the mean
Serum vigabatrin levels were analysed in coded samples. Due to an oversight, serum levels were not forwarded for analysis in one patient. The reproducibility of the analytical method was checked on 28 pairs of coded samples of which 16 pairs were blank. No vigabatrin was detected in any of the blank samples. Cronbach’s alpha reliability coefficient for the 12 non-blank pairs was 0.91. Spearman’s rank correlation coefficient of the two measurements was 0.79 (p=0.009).

There was a dose-related increase in serum vigabatrin concentrations as indicated from the levels at weeks 4 and 12 (Table 2). However, no drug level was detected in 4 patients on 2 or more consecutive occasions and they were excluded from the study. Correlation between the serum vigabatrin levels and the clinical effects were examined using Spearman’s rank correlation coefficients with the vigabatrin level being taken as the average in weeks 8 and 12. No relationship of vigabatrin serum levels with the frequency, severity and duration of headache, and migraine index or corrected side effects scores for the data at either week 2 or week 12 was detected.

Discussion

This investigation was carried out in a small but clearly defined group of patients whose progress was closely monitored during the 32-week study period. The patients were suffering from migraine with aura or migraine without aura for several years, and most recorded a family history of migraine. They derived no significant benefit from most conventional prophylactic agents and were categorised to be suffering from drug-resistant migraine. However, 15 of them had received sodium valproate in the past, and 12 (80%) benefited [5].

Vigabatrin was well tolerated by most patients who suffered from no clinical, biochemical or haematological abnormalities during the study period. No significant changes in blood pressure, heart rate and body weight were found, and none of them experienced any psychiatric or visual symptoms. A low dosage regimen of maximum 2 g per day for 12 weeks was used and this may account for the low incidence of side effects. No significant difference in the corrected side effect scores was observed between the two treatments.

Serum drug level measurements were reproducible and vigabatrin concentrations were related to dose. Drug level determination was helpful in verifying 4 non-compliers who were excluded from the study. In other 14 patients serum vigabatrin measurement indicated that compliance with treatment was good.

Compared with placebo phase, vigabatrin therapy was associated with slight but significant reduction in the number (p=0.017) and severity (p=0.024) of migraine headaches. Compared to baseline values and placebo phase, greater reductions in the duration of attacks (p=0.019) and migraine index (p=0.012) were observed during vigabatrin therapy. Compared to placebo, vigabatrin therapy reduced the duration of headache and migraine index by 40% and 59%, respectively, at week 12.

The investigation was carried out as a double-blind study in which patients were randomly selected to receive either placebo or vigabatrin first; this probably accounted for the slight but significantly lower baseline values for the duration of attacks at the vigabatrin phase. It can be argued that this difference might have magnified the beneficial effect of vigabatrin. However, migraine index improved progressively during the vigabatrin phase, whereas there was a persistent deterioration in the migraine index during the placebo period.

No relationship was demonstrated between the serum vigabatrin levels and clinical benefits or side effects. There are several possible reasons for this lack of correlation. First, vigabatrin has a short plasma half-life of 5–7 hours and there are inter-individual variations in drug levels. The levels are likely to be influenced by gender, age, and renal functions [18]. In this study venous blood was taken approximately 12–14 hours after the last dose, i.e. the trough vigabatrin levels were measured in a group of male and female patients with a wide age range. It is less likely to demonstrate any relationship of drug level with clinical effects in a physiologically heterogeneous group of patients. Second, serum drug level measurement may not reflect the concentrations of drug at the neuronal site [19, 20]. Third, vigabatrin increases the GABA levels by inhibiting GABA-transferase, i.e. an indirect pharmacological effect on GABA [8]. It may not have a simple relationship with serum drug levels. Fourth, GABA-mimetic drugs may produce a non-specific effect by reducing the pain threshold or may have some other complex beneficial effect in migraine [21, 22]. While it is difficult to demonstrate a simple relationship between clinical effects and serum vigabatrin levels, in view of the high incidence of non-compliance among migraineurs, drug level monitoring should be included in all studies aimed to evaluate the efficacy of a new agent.

In conclusion, vigabatrin appeared to have a modest beneficial effect in the reduction of migraine headaches. We would like to emphasise that the patients enrolled in this study were referred to a headache clinic for poor response to conventional preventive drugs, such as a beta blocker, pizotifen and amitriptyline, but derived some benefit from vigabatrin. Although 12 patients who completed the study previously responded to sodium valproate, in view of the intra-individual variability of migraine attacks, it is difficult to draw any comparison between the two drugs without car-
rying out a controlled study. Vigabatrin potentiates the effect of GABA similar to sodium valproate. The latter is now an established preventive agent for migraine headaches [2, 6]. Another new GABA-mimetic antiepileptic drug, gabapentin, has been reported to have prophylactic effects in migraine [9]. The possible mechanism of GABA-mimetic drug in the prevention of migraine headache is unclear. Unlike sodium valproate, vigabatrin, in the dosage used, was not associated with weight gain. No visual abnormality was observed. However, further long-term studies are necessary to assess its efficacy and adverse effects in migraine patients.

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References
1. Silberstein SD (1997) Preventive treatment of migraine: an overview. Cephalalgia 17(2):67–72
2. Sorenson, KV (1988) Valproate: A new drug in migraine prophylaxis. Acta Neurol Scand 78:346–348
3. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double blind study versus placebo. Cephalalgia 12:81–84
4. Ghose K (1994) Valproate in the prophylaxis of migraine: a pilot study. NZ Med J 107(987):409
5. Ghose K, Niven B (1998) Prophylactic sodium valproate therapy in patients with drug resistant migraine. Meth Findings 20(4):353–359
6. Ghose K (1999) Long term efficacy and safety of sodium valproate in patients with drug resistant migraine. Headache Q 10(2):127–113
7. Cutrer FM, Limmroth V, Moskowitz MA (1997) Possible mechanisms of valproate in migraine prophylaxis. Cephalalgia 17(2):93–100
8. Godin Y, Heiner L, Mark J, Mandel P (1969) Effects of di-n-propylacetate, an anticonvulsive compound, on GABA metabolism. J Neurochem 16:869–873
9. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadän N, Stacey B, Tepper S (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41(2):119–128
10. Mumford JP, Dam M (1989) Meta-analysis of European placebo controlled studies of vigabatrin in drug resistant epilepsy. Br J Clin Pharmacol 27:101–107
11. Jung MJ, Lippert B, Metcalf BW, Bohlen P, Schechter PJ (1977) Gamma-Vinyl GABA (4-amino-hex-5-enoic acid), a new selective irreversible inhibitor of GABA-T: effects on brain GABA metabolism in mice. J Neurochem 29:797–802
12. Buckett WR (1980) Irreversible inhibitors of GABA-transaminase induce antinociceptive effects and potentiate morphine. Neuropharmacology 19:715–722
13. Sawynok J, LaBella FS (1982) On the involvement of GABA in the analgesia produced by baclofen, muscimol and morphine. Neuropharmacology 21:397–403
14. DeFeudis FV (1983) GABA-ergic systems and analgesia. Drug Dev Res 3:1–5
15. – (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Headache Classification Committee of the International Headache Society (IHS). Cephalalgia 8(Suppl 7):1–96
16. Ghose K, Coppen A, Carroll D (1977) Intravenous tyramine response in migraine before and during treatment with indoramin. Br Med J 1:1191–1193
17. Tsaacitis L, M, Wicks J, Williams J Richens A (1991) Determination of vigabatrin in plasma by reversed-phase high-performance liquid chromatography. Ther Drug Monit 13:251–253
18. Haegele KD, Huebert ND, Ebel M, Tell GP, Schechter PJ (1988) Pharmacokinetics of vigabatrin: implications of creatinine clearance. Clin Pharmacol Ther 44:558–565
19. Bohlen P, Huot S, Palfreyman MG (1979) The relationship between GABA concentrations in brain and cerebrospinal fluid. Brain Res 167:279–305
20. Ben-Menachem E, Persson L, Schechter PJ, Haegele KD, Huebert N, Hardenberg J, Dahlgren L, Mumford JP (1988) Effect of single doses of vigabatrin on CSF concentrations of GABA, homocarnosine, homovanillic acid, 5-hydroxyindoleacetic acid in patients with complex partial epilepsy. Epilepsy Res 2:96–101
21. Hout S, Robin M, Palfreyman MG (1981) Effect of γ-vinyl GABA alone or associated with diazepam on a conflict test in the rat. In: DeFeudis FV, Mandel P (eds) Amino acid neurotransmitters, advances in biochemical psychopharmacology. Raven Press, New York, pp 45–52
22. Rasmussen KJ, Schneider HH, Petersen EN (1981) Sodium valproate exerts anti-conflict activity in rats without any concomitant rise in forebrain GABA level. Life Sci 29:2163–2170