Author’s response to reviews

Title: Quantitative assessment of Vigabatrin-attributable visual field loss using semi-automated kinetic perimetry

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Author’s response to reviews: see over
Dear Editor of “BMC Ophthalmology”,

Thank you very much for reviewing the manuscript “Quantitative assessment of Vigabatrin-attributable visual field loss using semi-automated kinetic perimetry” by Katarzyna Nowomiejska, Marian Jedrych, Konrad Rejdak, Tomasz Zarnowski, Michael Koss, Katarzyna Ksiazek, Piotr Ksiazek, Anselm Juenemann, Ulrich Schiefer, Robert Rejdak

We would like to thank for the constructive comments of the associate editor and the reviewers. The manuscript is now corrected as suggested addressing all remarks included.

Reviewer 1 (Philip Griffiths)
No concerns.

Reviewer 2 (Miriam Conway)
• The authors report significant differences for both eyes between the area of isopters and consecutive visits. From the information shown in the Figures 1 to 6 however the significance does not appear to be obvious to the reader. If the authors reported the mean and standard deviation this might help to resolve the problem.

In the “results” chapter it is added:

For the right eye the mean area of III4e isopter was 13145.34 deg$^2$ (standard deviation [SD] 1695.16 deg$^2$) during the first examination and 11917.47 deg$^2$ (SD 2590.82 deg$^2$) during the fifth examination (fig. 1). The mean area of I4e isopter was 9863.88 deg$^2$ (SD 1874.24 deg$^2$) during the first examination and 8795.90 deg$^2$ (SD 2522.65 deg$^2$) during the fifth examination (fig. 2). The mean area of I2e isopter was 4120.17 deg$^2$ (SD 1244.25 deg$^2$) during the first examination and 3829.05 deg$^2$ (SD 1804.21 deg$^2$) during the fifth examination (fig. 3).

For the left eye the mean area of III4e isopter was 13445.71 deg$^2$ (SD 1575.41 deg$^2$) during the first examination and 12161.48 deg$^2$ (SD 2314.69 deg$^2$) during the fifth examination (fig. 4). The mean area of I4e isopter was 10217.37 deg$^2$ (SD 1762.10 deg$^2$) during the first examination and 8841.68 deg$^2$ (SD 2331.54 deg$^2$) during the fifth examination (fig. 5). The mean area of I2e isopter was 4152.29
$\text{deg}^2$ (SD 1044.73$\text{deg}^2$) during the first examination and 3853.79 $\text{deg}^2$ (SD 1552.76 $\text{deg}^2$) during the fifth examination (fig. 6).

Additionally SD abbreviation is explained at the end of the text.

- Significant differences were found for each isopter over time.

- A post hoc analysis to show between which visit was significant might also be useful

In the “statistical analysis” chapter it is added:

As post-hoc analysis nonparametric Wilcoxon test was used to show differences of isopters’ area between visits.

In the “results” chapter it is added:

For the right eye there were significant differences in area of III4e isopter between the first and second examination ($Z=1.98; p=0.05$) and the first and fourth examination ($Z=2.73; p=0.006$). For I4e isopter the differences were significant between the first and third examination ($Z=2.73; p=0.006$) and between the first and fourth examination ($Z=2.54; p=0.01$). For I2e isopter the differences were significant between the first and third examination ($Z=2.67; p=0.008$) and between the first and fourth examination ($Z=2.23; p=0.03$).

For the left eye there were significant differences in area of III4e isopter between the first and fourth examination ($Z=2.42; p=0.02$) and the first and fifth examination ($Z=2.10; p=0.04$). For I4e isopter the differences were significant between the second and fourth examination ($Z=2.54; p=0.01$) and between the second and fifth examination ($Z=2.10; p=0.04$). For I2e isopter the differences were significant between the third and fourth examination ($Z=2.79; p=0.005$).

- Also was a correction to adjust for multiple comparisons applied

Nonparametric Friedman’s ANOVA test has been already used for multiple comparisons.

In the “statistical methods” chapter it is now written:

Shapiro-Wilk test showed that the distribution of the data is not normal, thus nonparametric test Friedman $\chi^2$ ANOVA was used for multiple comparisons of each isopter area and RT during the follow-up.

Instead of:

Shapiro-Wilk test showed that the distribution of the data is not normal, thus the differences in each isopter area and RT between examinations were compared using the nonparametric test Friedman $\chi^2$ ANOVA.

These results have been already described.
• A correlation was found between cumulative dose and I2E and mean daily dose. This information is surprising as to my knowledge the vast majority of researchers report concentric constriction of the peripheral visual field. This means that you might also expect the outer isopters to be affected to a larger extent. In fact Kinirons et al., 2006 only used the III4e isopter to calculate the mean radial degrees. Further discussion is therefore required.

In the study of Kinirons I4e and III4e isopters were measured but only III4e was used for calculation of mean radial degree, but the reason is not explained in this publication.

In the discussion chapter it is added: However in the study of Kinirions [18] no correlation was found between the mean radial degree of III4e isopter and either the maximum dose of VGB taken, the duration of drug exposure or the cumulative dose.

This publication of Kinirions [18] was cited more times in the discussion chapter:

In the study of Kinirions [18] 152 patients were initially identified, but finally 93 were analysed. Forty-six patients were unsuitable for VF assessment because of moderate or severe learning disability and 11 patients had VFs that were thought to be unreliable.

• It is probably quite important to understand how the isopters fluctuate over a 2 year period (using SKP) in a normal population as static visual field loss is routinely adjusted for age.

Differences in isopters area in different ages are shown in the study:


However longitudinal follow-up was not performed.

Additionally, would the authors expect cognitive impairment over the 2 year period have an effect on reaction time or visual field size. Is another cohort of patients with epilepsy not receiving VGB required?

As we examined 6 patients not receiving VGB, but other antiepileptic drugs, we included these results into the study:

In the abstract it is added:

Additionally, six epilepsy patients on other antiepileptic drugs were examined five times with SKP as a control.
In epilepsy patients who were not receiving VGB, there were no significance differences in isopters’ area during follow-up.

In the “methods” chapter it is added:

Additionally, six patients never exposed to VGB treated with other antiepileptic drugs were examined five times as a control group. Median visual acuity was 1.0, mean age was 38 years (range 26-51 years). Patients from the control group received CBZ 67%, CLZ (33%) or gabapentinum (17%). For the control group the examination duration was 12 min for both eyes (range 9-15 minutes).

In the “results” chapter it is added:

In epilepsy patients who were not receiving VGB, there were no significance differences (p>0.05) in III4e, I4e and I2e isopters’ area between examinations during follow-up period.

- The authors conclude that SKP is a new diagnostic tool for monitoring VAFL however they have not compared SKP against any other investigative techniques to determine if it more or less useful. Instead the main finding appears not to be the technique used (SKP) but how the visual field loss alters with time or how it is correlated with cumulative dose. If this is what they consider to be their main findings then perhaps their title and introduction might also need to alter.

The title has been changed into: “Relationship between the area of isopters and Vigabatrin dosage during two years of observation”.

Instead of: “Quantitative assessment of Vigabatrin-attributable visual field loss using semi-automated kinetic perimetry”.

In abstract it is now written: There was a significant decrease of I2e, I4e and III4e three isopters’ area between examinations during the follow-up of two years. Correlation was found between the I2e isopter’s area and both cumulative dose and mean daily dose of VGB.

RT, the cumulative dose and the mean daily dose of VGB influenced isopters’ area obtained with SKP during two-years follow-up.

In abstract the background is changed into:

The aim of the study was to evaluate the relationship between the area of isopters obtained using semi-automated kinetic perimetry (SKP) and Vigabatrin dosage in epilepsy patients with pretreatment baseline examination during 2-years of the follow-up.

Instead of:

The aim of the study is to evaluate prospectively Vigabatrin (VGB)-attributable visual field loss (VAVFL) using semi-automated kinetic perimetry (SKP) in patients with pretreatment baseline examination during 2-years of the follow-up.
The aim of the study in introduction chapter is as follows:

The aim of this prospective study was to evaluate the relationship between the area of isopters obtained using SKP and Vigabatrin dosage quantitatively VAVFL using SKP in a prospective study during a 2-years follow-up period in patients with pretreatment baseline examination.

Instead of:

The aim of this study was to evaluate quantitatively VAVFL using SKP in a prospective study during a 2-years follow-up period in patients with pretreatment baseline examination.

One conclusion is added:

In our study there was attenuation of area of III4e, I4e and I2e isopters during a period of 2 years.

Instead of:

SKP seems to be a new diagnostic tool in detecting and monitoring VAVFL adding quantitative information of the visual function in epilepsy patients.

• What was the accuracy of the visual field testing (what were the reliability criteria?). The interweaving of isopters suggests that there may have been some short-term fluctuations not attributed to vigabatrin. It may also have been useful to repeat one of the visual fields tests within the same week to determine how repeatable each visual field test was.

It is difficult to assess the reliability of kinetic visual field examination. In the following study:


patients with advanced visual field loss were examined with SKP 4 times during one day. It was concluded that RT is the most important factor influencing the variability of the response and fatigue during SKP and can be used as a reliability indictor.

In “abstract” it is added:

With increasing RT, there was decreasing of all isopters’ area in patients receiving VGB.

In our study additional information regarding RT was added at the end of the ‘results’ chapter:

There was a correlation found between RT and area of III 4e (R=-0,46) , I4e (R=-0,52) and I2e (R=-0,52) isopters. Thus, the longer RT, the smaller isopter’s area.

In the ‘discussion’ chapter it was added:

Moreover, RT has been found to be the most important factor influencing the variability of the response and fatigue during SKP and can be used as a reliability indictor [28]. As in our study RT is
prolonged in patients receiving VGB and there is correlation with decreasing isopters' area, we can presume that there may be high variability of response and fatigue in VGB patients performing SKP. Additionally, the historical study dealing with kinetic perimetry and reaction time was included:


• Was the learning effect and the fatigue effect accounted for?

The learning effect and fatigue effect were not evaluated in the current study.

The fatigue effect (the difference of isopter area between the first and four subsequent sessions) has already been evaluated in regard to patients suffering from glaucoma, retinitis pigmentosa and hemianopia in the study:


This reference has been already added to the list.

RT may be an indicator of the learning effect in SKP. This information has been already included.

• There appears to be significant discussion about the advantages of SKP without any discussion about its disadvantages. This is probably a little biased as it was not compared against another testing techniques to determine for example whether manual Goldmann may have enabled more of the 29 patients to have been reviewed as a human perimetrist can often adjust to the patients needs. In the NHS many hospitals maintain Goldmann’s for paediatric visual field testing as they find that an experienced perimetrist can acquire a field test more easily using the manual form (SKP).

During SKP examination examiner can also cooperate with the patient, but the speed of the stimulus is standardized and not guided by hand.

In the discussion chapter it is added:

SKP is also preferred by patients more than manual Goldmann kinetic perimetry. In the study comparing SKP with manual Goldmann perimetry in patients with advanced VF loss [12] a questionnaire was given to assess the preference of the patients. SKP was preferred by 52%, Goldmann was preferred by 32%, 16% had no preference. SKP was mostly preferred among patients with concentric constriction of the VF due to retinitis pigmentosa.

SKP has been already compared with static automated perimetry in patients with bilateral optic nerve head drusen in the study:

This publication has been included in the references section.

It was cited in the introduction section:

Results of SKP have been shown to be comparable to those of Goldmann manual kinetic perimetry [12] and static automated perimetry [13].

• I think that the Kinirons study may have reported on 93 patients (not 14) over a 10 year period and found no correlation with drug dose. The fact that this group of researchers carried out larger numbers over a longer period and found the opposite results needs a further more detailed discussion.

In the retrospective study of Kinirions the mean number of assessments was two (range, 1–6). Of patients having more than one assessment (n = 65), the mean follow-up time was 2.4 years (range, 0.7–5.6 years), 28 patients had only one VF assessment.

• Was the daily dose of VGB constant over the 2 year period as this may have affected cumulative dose.

The daily dose of VGB was not constant, but in assessing the cumulative dose, we took it into account.

• There was no discussion about how maximum VGB dose might also be correlated to VGB attributed field loss (Conway et al., 2008). Maximum VGB dose and cumulative dose are linked therefore some of the power might be due to maximum dose.

We considered the cumulative dose and mean daily dose as in most of the papers: 3,4,17,19,23.

In the discussion chapter the references were added:


In the discussion chapter the sentences were added:

However, in the studies of Kalviainen [15], Kinirions [19] and Newman [3] no correlation was found between VF loss and either, the duration of VGB exposure or the cumulative dose. In the study performed by Conway and colleagues [25] maximum daily VGB dose was taken as an independent
variable and was found as the most reliable indicator to exhibit VF defects. However, in this investigation only central VF was examined with automated static perimetry.

- Not sure why only 14% of the population has a defect. A discussion suggesting possible reasons in relation to other research findings might be useful. Again I think Kinirons may have suggested that most of the damage occurs early on.

In the study of Kinirons it is written that as the majority of patients had been taking the drug for a number of years before testing, little data was available on how quickly constriction develops. Moreover none of the patients in this study was examined before therapy.

In the “discussion” chapter it is added:

Kininron and colleagues observed concentric constriction in 52.7% of the cohort [19], Newman in 20% of examined patients [3] but they used mean radial degree of III4e [19] or I4e [3] as an indicator.

Minor

V-A is on average 1.00 in the table 0.1 in the text

In the text it is written:

The mean of the best-corrected visual acuity of right eye was 0.97 (range 0.7-1.0) and 0.99 (range 0.9-1.0) of the left eye.

Did the reading correction vary with the central isopter over the 2 year period (particularly for the presbyopes)?

There were 7 presbyopes in the cohort. The reading correction was adjusted for age and did not vary during the follow-up period.

In the discussion spelling mistake in the Royal College of Ophthalmologists. It has been corrected.

Additionally, dr Michael Koss from Heidelberg in Germany, who contributed in the revision of the manuscript and analysis of the data, was added to the list of authors.

Kind regards,

Katarzyna Nowomiejska