# Effectiveness of verapamil in patients with carbamazepine-resistant epilepsy

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Evaluation of the efficacy and tolerability of adding verapamil to the antiepileptic drug regimen in patients who did not become seizure free on carbamazepine.

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Seizures (incl subtypes) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON36793

**Source**
ToetsingOnline

**Brief title**
Verapamil in epilepsy patients

### Condition

- Seizures (incl subtypes)

**Synonym**
epilepsy; falling sickness

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Stichting Epilepsie Instellingen Nederland
**Source(s) of monetary or material Support:** Own funds

### Intervention

**Keyword:** carbamazepine, epilepsy, verapamil

## Outcome measures

### Primary outcome

Percentage of patients with more than 50% reduction in seizure frequency during

the maintenance period compared to the baseline seizure frequency

### Secondary outcome

- number of patients withdrawing from the study due to adverse effects

- MDR1 expression in peripheral blood mononuclear cells prior and following

verapamil administration

# Study description

### Background summary

A significant proportion of patients with epilepsy does not enter long-term remission despite pharmacotherapy (Shorvon & Luciano 2007). Although there is no single definition of pharmacoresistant (also known as refractory) epilepsy, two criteria commonly used to identify patients with pharmaco-resistant epilepsy are persisting seizures despite the use of two or more adequately selected antiepileptic drugs (AEDs) and the absence of a significant seizure free period (Berg & Kelly, 2006). In two hospital based-studies approximately 35% of patients were diagnosed to have pharmacoresistant epilepsy (Kwan & brodie, 2000; Dlugos et al., 2001).
The underlying mechanisms for pharmacoresistance are often not known: it is unclear why patients with similar seizure types and/or etiology respond differently to AEDs. One popular hypothesis is that AEDs inadequately penetrate across the blood-brain barrier due to multidrug transporters (also known as the *transporter hypothesis*) (Kahane et al., 2008)). P-glycoprotein (P-gp) is the drug transporter which is most relevant in this respect. P-gp is the encoded product of the human multidrug-resistance-1(MDR1) gene. It is an ATP- and Ca2+-dependent detoxifying pump that extrudes potentially toxic compounds out of cells, located in gut, blood, kidney, liver and endothelial cells of the blood brain barrier (6). Many drugs, including cancer drugs and several AEDs, are substrates of P-gp. Overexpression of P-gp and other drug transporters has been found in endothelial cells and brain tissue of patients with refractory epilepsy, removed during epilepsy surgery (Lazarowski et al., 2007; Kwan & Brodie 2005). Two case reports have been published in which the administration of the P-gp inhibitor verapamil led to significant improvement

in seizure control (Summers et al. 2004; Ianetti et al., 2005).
Based on these findings, a pilot study was performed in China recently to evaluate the efficacy of verapamil in 42 patients who did not become seizure free with carbamazepine (in monotherapy or in combination with another AED). Thirty-eight patients completed the six month treatment period with verapamil: 4 of these patients became seizure free, 7 experienced a seizure reduction of 75-99% and in 8 patients seizure frequency was reduced by 50-74%. The remaining patients that completed the trial did not experience a significant seizure reduction. Two patients withdrew from the study because of adverse effects (diplopia) and two patients were lost to follow-up. These results are very promising, but need to be replicated before they can be submitted for publication, and therefore a similar study will now be carried out in the Netherlands.

## Study objective

Evaluation of the efficacy and tolerability of adding verapamil to the antiepileptic drug regimen in patients who did not become seizure free on carbamazepine.

## Study design

The study will be conducted at the outpatient department of SEIN in Zwolle. Eligible patients are identified by their treating physician. Verapamil will be added to AED regimen in a stepwise fashion: first week 120 mg/day; second week 240 mg/day; fourth week 360 mg/day; sixth week: 420-480 mg/day. The daily dosage will be administered in three divided dosages. The baseline seizure frequency will be determined during a three month baseline period (retrospectively if possible; prospectively otherwise). During the study. seizure frequency will be recorded using seizure calendars and adverse effects will be recorded by use of a questionnaire (10) the titration period and the six month maintenance period. Before the start of verapamil treatment and at the end of the titration and maintenance periods, AED serum levels, and blood counts, liver function tests, kidney function tests will be measured. EKGs will be recorded and EKGs will be performed. Blood pressure will be measured at visits to the outpatient clinic. In case of adverse effects, verapamil dosage can be decreased during the study.
In addition the following data will be recorded per patient:
- Demographics: age, gender.
- Epilepsy characteristics: epilepsy type, duration of epilepsy, etiology.
- Medication: type and number of AEDs used before enrolment.
Outcome analysis
In this mirror-image analysis, patients serve as their own control group in the assessment of verapamil effectiveness. Treatment with verapamil will be considered effective if a reduction in seizure frequency of at least 50% is accomplished during the maintenance period compared the seizure frequency

during the baseline period and if verapamil is continued throughout the treatment period without dose increases of the AEDs or addition of another AED. Patients will be classified as seizure free if treatment with verapamil led to the absence of any type of seizures during the maintenance period.

### Intervention

Addition of verapamil to the epilepsy medciation of patients.

### Study burden and risks

The use of Pgp inhbitors has been evaluated in oncology and withdrawal rates due to adverse effects were high in these exploratory studies (Kwan & Brodie 2005). In the abovementioned pilot study in Chinese epilepsy patients, only 5% of patients withdrew due to adverse effects. The proposed study will be carried out in patients with pharmacoresistant epilepsy; these patients experience a high burden of disease and often are highly motivated to try new therapies. The intervention in this study consists of adding verapamil to the antiepileptic drug regimen of patients. Verapamil is a registered drug in the Netherlands, which implies the risks of participating in such a study are not disproportionate.

## Contacts

**Public**
Stichting Epilepsie Instellingen Nederland (SEIN)

Postbus 563
8000 AN Zwolle
NL
**Scientific**
Stichting Epilepsie Instellingen Nederland (SEIN)

Postbus 563
8000 AN Zwolle
NL

## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- patients aged 18 years and older with a history of localization-related epilepsy of at least 2 years;
- epilepsy not controlled despite the (previous) use of two or more antiepileptic drugs;
- current use of carbamazepine as an antiepileptic drug, with the possible addition of no more than one other antiepileptic drug;
- seizure frequency of at least 2 seizures per month;
- AED serum levels in therapeutic range

## Exclusion criteria

- There was no or an uncertain diagnosis of epilepsy, based on clinical history, seizure description and/or EEG registration.
- progressive neurological disease
- cardiac disease (heart failure; 2nd or 3rd degree atrioventricular block; sick sinus syndrome; Wolf-Parkinson-White syndrome; sinus bradycardia)
- hypotension (defined as lower systolic pressure than 100 mm Hg and/or lower diastolic prerssure than 70 mm Hg)
- pregnancy

# Study design

## Design

**Study type:** Interventional

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-12-2010 |
| Enrollment: | 40 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Isoptin |
| Generic name: | Verapamil |
| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 24-05-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-020102-15-NL |
| CCMO | NL32301.029.10 |