Universiteit
Leiden
The Netherlands

Pharmacoresistance in epilepsy : modelling and prediction of disease progression

Liefaard, C.

Citation
Liefaard, C. (2008, September 17). *Pharmacoresistance in epilepsy : modelling and prediction of disease progression*. Retrieved from https://hdl.handle.net/1887/13102

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/13102

Note: To cite this publication please use the final published version (if applicable).

Pharmacoresistance in epilepsy

Modelling and prediction of disease progression

Pharmacoresistance in epilepsy

Modelling and prediction of disease progression

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 17 september 2008
klokke 13:45 uur

door

Cornelia Liefaard

geboren te Dordrecht
in 1977

Promotiecommissie

Promotores:	Prof. dr. M. Danhof
	Prof. dr. A.A. Lammertsma
Co-promotor:	Dr. R.A. Voskuyl
Referent:	Prof. H. Potschka
	(Ludwig-Maximilians-Universität München)
Overige Leden:	Prof. dr. E.R. de Kloet
	Prof. dr. J.M.A. van Gerven
	Prof. dr. A.P. IJzerman
	Prof. dr. W.J. Wadman

Coverdesign: Hans Stol

The research described in this thesis was supported by SEIN – Epilepsy Institutes of The Netherlands Foundation and the National Epilepsy Fund – "The Power of the Small".

The printing of this thesis was financially supported by:
SEIN – Epilepsy Institutes of The Netherlands Foundation
National Epilepsy Fund – "The Power of the Small"
UCB Pharma B.V.
Siemens Nederland N.V.
Leiden/Amsterdam Center for Drug Research

ISBN 978-90-9023252-2
Copyright © 2008 by C. Liefaard, Leiden

Table of contents

1 Scope and outline of the thesis 9

1.1 The problem of pharmacoresistance 9
1.2 Outline of the thesis 10

2 General introduction: Disease progression and pharmacoresistance in epilepsy 13

2.1 Introduction 13
2.2 Epilepsy and pharmacoresistance 13
Mesial temporal lobe epilepsy – Pharmacoresistance – Mechanisms underlying development of pharmacoresistance
2.3 GABAergic inhibition in epilepsy 17
Presynaptic processes – Postsynaptic processes – $GABA_A$ receptor subtypes
2.4 Animal models 20
Amygdala kindling – Post-status epilepticus animal model
2.5 Biomarkers for disease progression in epilepsy 22
Electroencephalography – Positron Emission Tomography – Electric cortical stimulation and behavioural analysis
2.6 Modelling and predicting disease progression in epilepsy 27
Models for description of pharmacokinetics, pharmacodynamics, and disease progression – Population or mixed effects modelling

3 Evaluation of the convulsive threshold as a marker for disease progression in the kainate post-SE model for temporal lobe epilepsy 39

3.1 Introduction 39
3.2 Methods 41
Animals – Experimental procedure – Implantation of electrodes for cortical stimulation – Induction of status epilepticus – Cortical stimulation procedure: Threshold measurements – Evaluation of the seizure pattern – Data analysis – Statistical analysis
3.3 Results 44
Threshold for localised seizures – Localised versus generalised seizures – Evaluation of the seizure pattern
3.4 Discussion 46
3.5 Conclusion 48

4 Quantitative EEG analysis: a biomarker for epileptogenesis 51

4.1 Introduction 52
4.2 Methods 53
Animals – Implantation of electrodes – Induction of status epilepticus – EEG-recording – Event synchronisation
4.3 Results 55
EEG during and after induction of status epilepticus – Time course of event rate and synchronisation during 4 weeks after status epilepticus
4.4 Discussion 62
4.5 Conclusion 65

5 Population pharmacokinetic analysis for simultaneous determination of B_{max} and K_D *in vivo* by positron emission tomography 69

5.1 Introduction 69
5.2 Methods 71
Production of [^{11}]flumazenil – Animals – Specific uptake of [^{11}C]flumazenil in rats – Scanning protocol – Image analysis – Drug analysis in blood – Data analysis
5.3 Results 76
5.4 Discussion 80
5.5 Conclusion 85

6 Changes in $GABA_A$ receptor properties in amygdala kindled animals: *in vivo* studies using [^{11}C]flumazenil and positron emission tomography 89

6.1 Introduction 89
6.2 Methods 91
Animals – Experimental setup – Kindling procedure – Production of [^{11}C]flumazenil – PET-scanning – Drug analysis in blood – Data analysis – Simulations – Statistical analysis
6.3 Results 97
6.4 Discussion 99
6.5 Conclusion 101

7 Decreased efficacy of $GABA_A$ receptor modulation by midazolam in the kainate model of temporal lobe epilepsy 105

7.1 Introduction 105
7.2 Methods 107
Animals – Experimental setup – Induction of status epilepticus – PK-PD experiment with midazolam – Drug analysis in plasma – Ex vivo binding studies with [^{3}H]flumazenil – Data analysis – Statistical analysis
7.3 Results 112
Pharmacokinetic analysis of midazolam concentration-time profiles – PK-PD analysis of midazolam effects: control experiments – Alterations in effect of midazolam after

induction of status epilepticus – Correlations between midazolam EEG-effect and ex vivo [^{3}H]flumazenil binding

7.4 Discussion 118

7.5 Conclusion 120

8 Modulation of GABAergic inhibition by tiagabine and alphaxalone is differentially affected in the kainate model of temporal lobe epilepsy 123

8.1 Introduction 123

8.2 Methods 125

Animals – Experimental setup – Induction of status epilepticus – Drugs and dosages – PK-PD experiment with tiagabine or alphaxalone – Drug analysis in plasma – Data analysis – Statistical analysis

8.3 Results 131

Pharmacokinetics of tiagabine and alphaxalone – Pharmacodynamics of tiagabine – Pharmacodynamics of alphaxalone

8.4 Discussion 135

8.5 Conclusion 137

9 Modelling and prediction of epilepsy progression and pharmacoresistance development: Summary, conclusions and perspectives 143

9.1 Introduction 143

9.2 Biomarkers of disease progression in epilepsy 143

Selection of biomarkers – Convulsive threshold in epileptic animals – Quantitative analysis of EEG in epileptic animals

9.3 The $GABA_A$ receptor in epilepsy 147

Quantification of receptor expression in vivo – Functionality of the receptor – Involvement of subunit alterations

9.4 Conclusions and future perspectives 149

Quantification of pharmacoresistance in epilepsy – Alterations in GABAergic inhibition – Extrapolation to clinical situation

Samenvatting 157

Nawoord 165

Curriculum Vitae 167

List of publications 167