1.1. Overview on anti-epileptic drugs and (generic) drug substitution

Introduction

Anti-epileptic drugs suppress seizures in *epilepsy* which are caused by an excessive discharge of neurons in the cerebral cortex. Their mode of action can be explained by two basic mechanisms. Firstly by the direct influence of the electrochemical transport through voltage-sensitive ion channels, such as blockade of sodium channels or calcium channels of various types. Secondly, by a strengthening of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), or a reduction of the excitatory glutamate transmission.
The prevalence of epilepsy treated with antiepileptic drugs is estimated to be 5:1000. The incidence in the Netherlands is 30:100,000 people aged 14 and older. In childhood the incidence is relatively high, then decreases and rises again in old age.
In addition to the treatment of epilepsy, anti-epileptic drugs are used in the treatment of *neuropathic pain*, *anxiety* and *bipolar disorders* [1]. See table in the addendum.

There has been discussion about whether generic substitution of anti-epileptic medicines with the same active moiety but from different manufacturers can safely take place. According to a position paper by the Dutch Medicines Evaluation Board (MEB) bioequivalence requirements are very strict and are the basis of therapeutic equivalence between innovators and generics. Therefore, switching to a generic anti-epileptic medicine appears to be safe based on pharmacokinetic grounds, and does not appear to provide a plausible pharmacological explanation for those cases where seizure frequency or seizure patterns change during antiepileptic treatment [2].

With generic substitution the effectiveness and safety of products should be equivalent. Upon registration of generics this be reviewed on the basis of bioequivalence studies. Generics be considered as bioequivalent if the 90% confidence interval of the AUC ratio and Cmax is within 80-125 % of the reference product. According to the KNMP Guideline on Drug Substitution, for drugs with a narrow therapeutic the 90 % confidence interval of the AUC ratio and Cmax (where relevant)must be within 90 to 111.11 % [3]. Classical anti-epileptic drugs (phenobarbital and other barbiturates, carbamazepine, ethosuximide, phenytoin, oxcarbazepine, sultiam, trimethadione, sodium valproate) are considered drugs with a narrow therapeutic width. Phenytoin also has non-linear kinetics [3].

The Netherlands Pharmacovigilance Centre Lareb has previously reported the number of drug-substitution cases to the MEB [2]. With this overview Lareb wished to update the MEB about the current number of reports on drug substitution for anti-epileptic drugs and the nature of those reports.

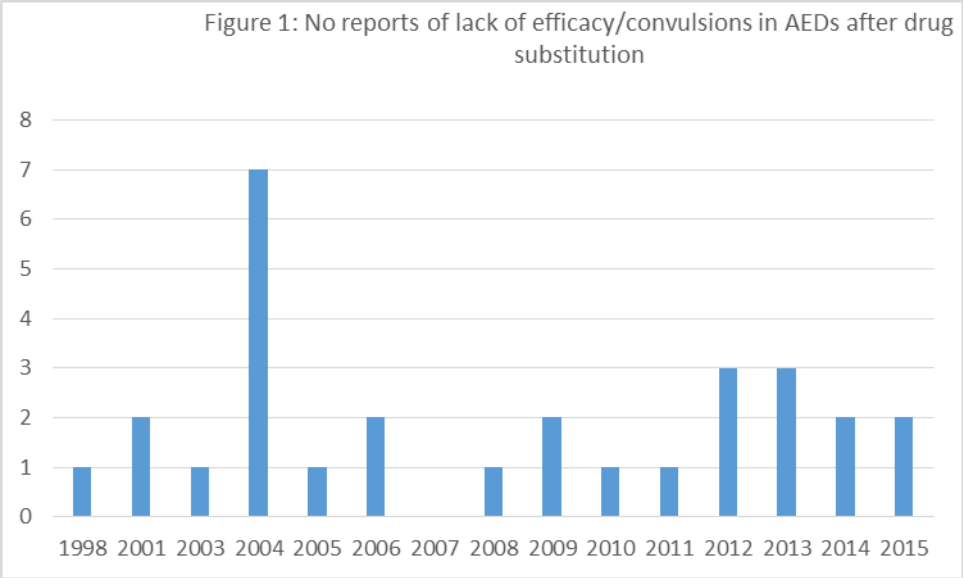
Reports

From 1998 until 1 March 2016 the Netherlands Pharmacovigilance Centre Lareb received 87 reports on anti-epileptic drugs (ATC N03A) and MedDRA Preferred Term (PT) ‘therapeutic response unexpected’. This term is used by Lareb to code reactions that occur after drug substitution between brands/generics. In one report there where 2 suspect drugs. These 87 reports consider all ADRs, including convulsion/possible lack of efficacy.
The drugs involved are: carbamazepine (n =22), clonazepam (n = 6), valproic acid (n =8), phenytoin (n=6), gabapentine (n=12), levetiracetam (n=10), lamotrigine (n =10), pregabaline (n=7), oxcarbazepine (n=3) and topiramate (n=4).

Of the 87 reports concerning the PT therapeutic response unexpected, 29 reports are associated with convulsion/possible lack of efficacy. These reports concern:

- Carbamazepine (n=15, with 5 reports originating from the same reporter; 43964,45970, 45968, 45972, 46293)
- Sodium valproate (n =4)
- Lamotrigine (n=4)
- Levetiracetam (n=4)
- Oxcarbazepine (n=2)

Figure 1 shows the number of reports per year concerning convulsions/lack of efficacy.



The 29 reports are summarized in the tables 1-5.

Table 1. Reports for convulsion/lackof drug effect in carbamazepine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome	Labvalues
A, 20643, F, 41-50, physician	Carbamazepine 100 mg, 2dd1.5, trigeminal neuralgia	Paracetamol, hydrochlorothiazide, omeprazole, simvastatin	Therapeutic response decreased, therapeutic response unexpected with drug substitution from Tegretol® to generic carbamazepine	1 day, switched back to Tegretol® and treatment with paracetamol, within 3 days improvement of pain	
B, 39507, F, 21-30, pharmacist	Carbamazepine apotex 200 mg, 2dd1, epilepsy		Convulsions, therapeutic response unexpected with drug substitution from Tegretol® to Katwijk farma	Unknown, switched back, recovered	
C, 43964, F, 31-40, physician	Carbamazepine Katwijk 400 mg, 2dd1, left temporal epilepsy	Topiramate	Drug ineffective, complex partial seizures, therapeutic response unexpected from Tegretol® to Katwijk	1 month, dosage increade from 800-1000 mg without effect, drug substituted to Tegretol®, recovered	17-01-2002 8.5microg/ml 30-01-2003 7.8 microg/ml on Tegretol® 15-04-2004 3.6 microg/ml (on Katwijk)
D, 45968, M, 11-20, physician	Carbamazepine Katwijk 400 mg, 1200mg/day, epilepsy	Methylphenidate	Status epilepticus (before sporadically 1-2 convulsions each year), therapeutic response	1 week, switched back, recovered	Blood levels on Novartis product: 6.3, 6.4, 5.4 microg/ml (mean 6.03) Spiegels Katwijk: 5.5,

			unexpected with drug substitution from Tegretol® to Katwijk		5.2, 4.7 microg/ml (mean 5.13)
E, 45037, M, 41-50, physician	Carbamazepine apotex 400 mg, 2dd500mg, epilepsy		Drug ineffective (seizure free before substitution), therapeutic response unexpected with drug substitution from Tegretol® to Apotex®	Unknown, unknown	Bloodlevel on Tegretol® 9.0, blood level on generic 4.6
F, 45970, F, 11-20, physician#	Carbamazepine Genfarma 200mg, 900mg/day, epilepsy	Lamotrigine	Seizure, therapeutic response unexpected with drug substitution from Tegretol® to Genfarma®	Days, switched back after 2 weeks, recovered (recovery took several weeks)	
G, 45972, M, 31-40, physician	Carbamazepine apothecon 200 mg, 3dd1, epilepsy		Seizure, drug ineffective, therapeutic response unexpected with drug substitution from Tegretol® to Apothecon®	Unknown, First treated with lamotrigine,switched back, recovering but not seizure free on Tegretol®	
H, 46293, F, 41-50, physician	Carbamazepine 400 mg, unknown, epilepsy		Drug level decreased *without a change in convulsions*, therapeutic response unexpected with drug substitution from Tegretol® to unknown generic	Unknown, unknown	Blood level on Tegretol® 6.8, 6.7 microg/ml Blood level on unknown generic: 5.5, 6.1 microg/ml
I, 47266, F, 21-30, consumer	Carbamazepine 200 mg, 200-0-600 mg/day, epilepsy	Lamotrigine, topiramate	Therapeutic response decreased, headache, vision descresed, overall functioning descreased, therapeutic response unexpected with drug substitution from Tegretol® to unknown generic	2 weeks, switched back, recovered	
J, 56336, M, 31-40, physician	Carbamazepine 200 mg, 2dd300 mg, epilepsy		Patient had been seizure-free for years before substitution,	9 months, switched back, unknown	Bloodlevel on Tegretol® 7, Bloodlevel on generic 5 and bloodlevel did

			Therapeutic response unexpected with drug substitution from Tegretol® to unknown generic		not increase after dosage increase to 2dd400mg
K, 82362, M, 31-40, pharmacist	Carbamazepine Katwijk 400 mg, 2dd400 mg, unknown	Fusidic acid, artificial tears	Convulsions, dysgeusia, Therapeutic response unexpected with drug substitution from carbamazepine RP® to Katwijk®	Unknown	
L, 85732, F, 31-40, pharmacist	Carbamazepine apotex 400 mg, morning 400/evening 600 mg, epilepsy	Ethinyl estradiol/levonorgestrel	Therapeutic response unexpected with drug substitution, convulsion (patient had been seizure-free for 2 years before substitution), fatigue	3 weeks, unknown, recovered	
M, 87917, F, 31-40, pharmacist	Tegretol® 200 mg, 3dd1.5, epilepsy	Lamotrigine	Convulsions, Therapeutic response unexpected with drug substitution from carbamazepine PCH to Tegretol®*	13 days, switched back, recovered	
N, 120856, F, 51-60 pharmacist,	Carbamazepine apotex 200 mg, 2dd200 mg, epilepsy		Epileptic seizure (patient had been seizure-free for 10 years before substitution), Therapeutic response unexpected with drug substitution from Apothecon® to Apothex®	3 months, unknown	
O, 211084, M, 51-60, pharmacist	Carbamazepine apotex 200 mg, morning 600mg/evening 400 mg, epilepsy	fexofenadine, simvastin, macrogol/electrolytes	Therapeutic response unexpected with drug substitution, epileptic seizure, therapeutic response decreased from unknown brand to Apotex®	1 day, switched back, recovered	

#Patient is mentally disabled.
*Temporary drug substitution because of supply problems

Table 2. Reports for convulsion/lack of drug effect in sodium valproate

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 32322, M, 51-60, pharmacist	Depakine chrono 500 mg, morning 1000 mg/evening 1250 mg, epilepsy	atorvastatine, carbamazepine, acetylsalicylic acid / dipyridamol.	Convulsion aggravated (from 3 to 28), therapeutic response unexpected with drug substitution from Depakine® parallel product Depakine chrono®	15 days, switched back, recovered
B, 33494, M, 51-60, physician	Sodium valproate Katwijk 300 mg, 2dd1, epilepsy	-	Convulsions (after being seizure free for 9 years), therapeutic response unexpected with drug substitution from Depakine chrono® to sodium valproate Katwijk®	1 week, unknown, unknown
C, 137330, M, 51-60, pharmacist	Depakine chrono 500 mg, 3dd1, epilepsy	acipimox, codeine, azithromycin, metoprolol, propranolol, simvastatin.	absence seizure, abnormal vision, therapeutic response unexpected with drug substitution from Depakine chrono® to Depakine parallel product.	2 days, switched back, recovering
D, 167589, M, 71 and older, consumer	Sodium valproate 500 mg Ratiopharm, unknown, epilepsy		Epilepsy, therapeutic response unexpected with drug substitution from Depakine Chrono® to Ratiopharm®.	5 days, switched back, recovered

Table 3. Reports for convulsion/lack of drug effect in lamotrigine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 52395, M, 41-50, physician	Lamotrigine 50 mg Hexal, 1dd1, epilepsy	-	Convulsions, therapeutic response unexpected with drug substitution from Lamictal® to Hexal®*	Unknown, unknown, unknown
B, 58659, M, 21-30, pharmacist	Lamotrigine 100 mg, unknown, epilepsy	Sodium valproate	Epilepsy aggravated	Unknown, unknown, unknown

			(number of convusions increased tenfold, convulsion while swimming), therapeutic response unexpected with drug substitution from Lamictal® to generic	
C, 109402, F, 11-20, consumer	Lamotrigine 50 mg, 2dd1, epilepsy	-	Epilepsy aggravated, therapeutic response unexpected with drug substitution between unknown brands	2 weeks, switched back after 3 weeks, recovered
D, 144487, F, 11-20, pharmacist	Lamotrigine 100 mg Ratiopharm, 2dd1, epilepsy	levocetirizine, levonorgestrel/ ethinyl estradiol	Epileptic seizure, therapeutic response unexpected with drug substitution from Mylan® to Ratiopharm®#	2 days, switched back, recovered

* According to the reporter lamotrige Hexal® is made at the same production site as Lamictal® and the products are identical except for the packaging.
# Substitution due to supply problem

Table 4. Reports for convulsion/lack of drug effect in levetiracetam

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 147080, M, 21-30, pharmacist	Levetiracetam 250 mg, 2dd2, epilepsy	-	Seizures (n=3), therapeutic response unexpected with drug substitution from Keppra® to generic	7 days, unknown, unknown
B, 152623, F, 21-30, consumer	Levetiracetam 500 mg, 2dd1, epilepsy	-	Increase in number of blackouts, therapeutic response unexpected with drug substitution from Keppra® to generic	Days, no change, unknown
C, 163019, F, 51-60, consumer	Levetiracetam Aurobindo 250 mg, morning 500mg/evening 750 mg, epilepsy	-	Absence attacks, feeling down, dizziness, muscle cramps, therapeutic response unexpected with drug substitution from Keppra® to levetiracetam Aurobindo®	7 days, drug withdrawn, recovering
D, 176497. F, 21-30, consumer	Levetiracetam Aurobindo 500 mg, 3dd1, epilepsy	-	Epileptic seizure, migraine types headache, therapeutic response	2 days, switched back, not recovered

			unexpected with drug substitution from levetiracetam Accord® to Aurobindo®	

Table 5. Reports for convulsion/lack of drug effect in oxcarbazepine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 150068, M, 41-50, physician	Oxcarbazepine 600 mg, 1dd1/1dd1.5, epilepsy Sodium valproate 500 mg, 1dd1/1dd2, epilepsy		Epileptic seizure (before substitution no seizures for 8 years), therapeutic response unexpected with drug substitution from Trileptal® to generic and Depakine® to generic	1 week, unknown, recovered
B, 202848, F, 41-50, consumer	Oxcarbazepine 600 mg Sandoz, 2dd1, epilepsy	Amitriptyline	Multiple seizures, therapeutic response unexpected with drug substitution from Mylan® to Sandoz®	3 days, switched back, recovered

In addition, the 84 reports were screened on possible effects of toxicity after drug substitution. There were no reports where a PT mentioning ‘overdose’ was reported. There were no reports with laboratory values specifying overdose.

Other sources of information

Literature

There are many articles available on bio-equivalence of brand and generic anti-epileptic drugs and the effects of drug-substitution.
Yamada et al. systematically reviewed the literature on generic antiepileptic drugs (AEDs), evaluated the efficacy and safety of generic AED substitution, and performed a pharmacokinetic (PK) analysis using the American Academy of Neurology (AAN) scheme to classify evidence. They concluded that there is inconsistency between retrospective and prospective studies of generic AED substitution. The highest levels of evidence indicated that there should not be a problem with generic substitution, although some patients are more prone to problems with the generic products. Some evidence suggests that switches between multiple generic AED products in certain individuals may be problematic [4].
Kesselheim et al. evaluated studies comparing brand-name and generic AEDs and determined whether evidence existed of superiority of the brand-name version in maintaining seizure control. Seven RCTs were included in the meta-analysis. The aggregate odds ratio (n=204) was 1.0 (95% confidence interval: 0.7–1.4), indicating no difference in the odds of uncontrolled seizure for patients on generic medications compared to patients on brand-name medications. In contrast, the observational studies identified trends in drug or health services utilization that the authors attributed to changes in seizure control. According to the authors the observational study data may be explained by factors such as undue concern from patients or physicians about the effectiveness of generic AEDs after a recent switch [5].

Gagne et al. estimated the risk of seizure-related events associated with refilling prescriptions for antiepileptic drugs (AEDs) and to estimate the effect of switching between brand-name and generic drugs or between two generic versions of the same drug. They conducted a case-crossover study using health-care databases from British Columbia, Canada. Refilling the same AED prescription was associated with an elevated risk of seizure-related events whether or not the refill involved switching from a brand-name to a generic product [6].
Polard et al. assessed the association between brand to generic anti-epileptic substitution and seizure-related hospitalization in a case crossover using the French National Health Insurance Database. Eight thousand three hundred seventy nine patients were analysed. Brand-to-generic AED substitution was not associated with an elevated risk of seizure-related hospitalization [7].
Privitera et al. assessed US Food and Drug Administration (FDA) bioequivalence standards by studying the effects of switching between two disparate generic immediate-release lamotrigine products in patients with epilepsy. The Equivalence among Generic Antiepileptic Drugs (EQUIGEN) chronic-dose study was a randomised, double-blind, crossover study that enrolled adults (aged ≥18 years) with epilepsy from six epilepsy centres at academic institutions across the USA who were receiving immediate-release lamotrigine dosed at 100 mg, 200 mg, 300 mg, or 400 mg twice daily. Eligible patients were randomly allocated (1:1) to one of two treatment sequences (sequence 1 or sequence 2), comprising four study periods of 14 days each. During each 14-day treatment period, patients received balanced doses of an oral generic lamotrigine product every 12 h (200-800 mg total, identical to lamotrigine dose prior to study enrolment); after each 14-day period, patients were crossed over to receive the other generic product. 35 eligible patients were enrolled and randomly assigned to treatment sequence 1 (n=15) or treatment sequence 2 (n=20). 33 patients completed all four treatment periods and were included in the primary outcome analysis. The 90% CIs of the ratios of both Cmax and AUC were within equivalence limits (AUC 90% CI 98-103, Cmax 90% CI 99-105), showing that lamotrigine exposures were equivalent between the generic products. No significant changes in seizure frequency or adverse events were recorded [8].

Prescription data

Table 6. Number of patients using the anti-epileptics highlighted in this report, in the Netherlands between 2010 and 2014 [9].

Drug	2010	2011	2012	2013	2014
Carbamazepine	47,075	44,949	44,104	42,223	41,271
Sodium valproate	62,749	61,960	61,647	60,702	60,008
Lamotrigine	17,237	17,752	18,506	19,150	19,871
Levetiracetam	21,666	23,943	26,197	28,320	30,948
Oxcarbazepine	5,594	5,358	5,155	5,086	5,161

Discussion and conclusion

Multiple studies have shown that on a population level in epidemiological studies generic switching of anti-epileptic drugs does not equal a loss of seizure control [4-8]. Although on a population level generic products and brand products may be bioequivalent, it is possible that the differences in AUC within the same person vary significantly [3]. Unfortunately, most reports Lareb received do not mention the patient's blood levels before and after the switch to different brands/generics. Only for carbamazepine, five reports with blood levels are available. In these reports higher blood levels for Tegretol® are mentioned. In the past, further pharmacokinetic and clinical investigations were conducted on behalf of the Dutch Regulatory Agency, in which the 'older' carbamazepine generic medicines were compared with the branded Tegretol®. Results from these investigations demonstrated that pharmacokinetics of carbamazepine and its metabolites were not clinically significantly different for Tegretol® and its generics. Moreover, no difference in subjective complaints and cognitive functions was noted between patients using any of these medicines [2].
Also, in the treatment of epilepsy compliance is a critical factor. For anti-epileptics drugs changes in pill colour, that may occur after drug substitution, significantly increase the odds of non-persistence; this may have important clinical implications [10]. Gagne et al. found that antiepileptic drug refilling itself may be associated with an elevated risk of seizure-related outcomes. One possible explanation is that refilling behaviour may result in lapses in pharmacotherapy continuity which may lead to breakthrough seizures [6].

Although (generic) substitution of anti-epileptic drugs is not recommended by the KNMP [3], this does occur in clinical practice. In some reports the preference policy of health insurance companies is mentioned as a motive for this substitution. In addition, supply issues can cause certain drugs to be (temporarily) out of stock and patients have to be switched to a different brand subsequently. On February 22 2016, the KNMP has issues a notice that carbamazepine 200 mg generic tablets may presently not be provided by various manufacturers because of production problems. Carbamazepine retard tablets of 200 and 400 mg are available in reduced quantities because one of the manufacturers has production problems and some other manufactures have decided to stop the supply of these tablets.
The Netherlands Pharmacovigilance Centre Lareb will be vigilant of any issues related to possible switched to different brands because of this supply issue and will update the MEB accordingly.

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Table addendum : Overview on the most commonly used anti-epileptic drugs in the Netherlands and their indications [1]

Drug	Indications
Barbituraten	
phenobarbital	Third choice drug for generalised and localisation bound epilepsy; in new-borns phenobarbital is first choice
primidon	
Benzodiazepinen	
clonazepam	status epilepticus; treatment attack exacerbation; Third choice drug for generalised and localisation bound epilepsy
diazepam	status epilepticus; treatment attack exacerbation
clobazam	Second choice drug for generalised and localisation bound epilepsy
nitrazepam	West's syndrome and Lennox'syndrome
Other anti-epileptics	
carbamazepine	First choice drug for localisation bound epilepsy, second choice drug for primary GTCA* (except in patients also suffering from generalised absences)
ethosuximide	Gegeneralised absences; symptomatic form of van generalised epilepsy
felbamate	Last choice drug, adjuvant drug for Lennox-Gastautsyndrome
phenytoin	Second choice drug for localisation bound epilepsy and for primary GTCA* (except in patients also suffering from generalised absences)
gabapentine	Second choice, add on therapy for localisation bound epilepsy
pregabaline	Second choice, add on therapy for localisation bound epilepsy
lamotrigine	First choice drug for localisation bound epilepsy/second choice drug for generalised epilepsy and adjuvant drug for Lennox-Gastautsyndrome
lacosamide	'add-on'-drug for localisation bound epilepsy
levetiracetam	Second choice and 'add-on'-localisation bound epilepys/ GTCA*
oxcarbazepine	Second choice drug for localisation bound epilepsy and for primary GTCA* (except in patients also suffering from generalised absences)
perampanel	'add-on'-drug for localisation bound therapy
retigabine (= ezogabine)	Last choice 'add-on'-drug for localisation bound therapy
rufinamide	2–3rd choice, adjuvant drug for Lennox-Gastautsyndrome
stiripentol	GTCA* in severe juvenile myoclonic epilepsy (Dravet's syndrom) as 'add-on' treatment with clobazam and sodium valproate
sodium valproate	First choice drug generalised and localisation bound epilepsy (incl. absences)
vigabatrine	First choice drug for West's syndrome, last choice drug for localisation bound epilepsy
topiramate	Second choice drug for localisation bound en generalised epilepsy and as adjuvant for Lennox-Gastautsyndrome
zonisamide	Second choice, 'add-on'-drug for lokalisation bound epilepsy
*** gegeneralised tonic-clonic attacks**	