

Antiepileptic drugs and increased risk of suicidal behaviour and suicidal ideation

Introduction

Antiepileptic drugs (AEDs) are registered for the treatment of epilepsy. In addition, AEDs are used for psychiatric diseases and neuropathic pain. In the Netherlands the following antiepileptic drugs are available: carbamazepine (Tegretol[®]), clonazepam (Rivotril[®]), ethosuximide (Ethymal[®]), felbamate (Taloxa[®]), fenobarbital, phenytoin (Diphantione[®]), gabapentin (Neurontin[®]), lamotrigine (Lamictal[®]), levetiracetam (Keppra[®]), oxcarbazepine (Trileptal[®]), pregabalin (Lyrica[®]), primidone (Mysoline[®]), topiramate (Topamax[®]), valproic acid (Depakine[®]), vigabatrin (Sabril[®]) and zonisamide (Zonegran[®]).

On 31 January 2008 the FDA issued an alert for health care professionals concerning an association between an increased risk of suicidal behaviour and suicidal ideation and use of antiepileptic drugs. According to the FDA patients receiving antiepileptic drugs had approximately twice the risk of suicidal behaviour or ideation compared to patients receiving placebo. [1] In this context, we studied spontaneous reports in the Netherlands to see if the findings of the FDA were supported.

Reports

Up to March 6, 2008, Lareb received 15 reports of suicide, suicidal attempt or suicidal ideation in patients treated with anti-epileptic drugs (Table 1). Six patients had suicidal ideation, seven patients attempted to commit suicide without success and two patients attempted suicide successfully.

The following AEDs were involved: levetiracetam in six cases, pregabalin and carbamazepine in four cases, valproic acid in three cases, fenytoin in two cases and clonazepam, ethosuximide, lamotrigine and vigabatrin in one case. In some patients more than one antiepileptic drug was involved, as suspect drug or concomitant medication (see Table 1).

Table 1. Reports of patients with suicide-related adverse events (suicide, attempted suicide and suicidal ideation) associated with the use of antiepileptic drugs.

patient, sex, age, report number	drug, indication for use	concomitant medication	suspected adverse drug reaction, other reported side-effects	time to onset, action with drug, outcome, and remarks
A, F, 78 45310	levetiracetam, epilepsy	carbamazepin amoxicilin amlodipin	suicide	1 month, - death (suicide), patient was depressed when levetiracetam was started.
B M, 65 56934 (study)	valproic acid, not reported	sirolimus prednison	suicide	2 year - death (suicide)
C F, not rep. 29781	carbamazepine valproic acid vigabatrin, not reported		suicidal attempt, coma	not reported, unknown, recovered
D M, 22 34124 36100 (MAH)	levetiracetam, epilepsy	carbamazepine	suicidal attempt	not reported, levetiracetam was withdrawn, recovered, no psychiatric

patient, sex, age, report number	drug, indication for use	concomitant medication	suspected adverse drug reaction, other reported side-effects	time to onset, action with drug, outcome, and remarks
				history
E F,81, 52745	levetiracetam, auditory hallucinations	oxazepam paroxetin atorvastatin gliclazide carbasalate calcium risperidone insuline	suicidal attempt, aggression increased, hallucinations, paranoia	6 days, levetiracetam was gradually withdrawn, recovered
F F,14 37242 (MAH)	fenytoin carbamazepine paracetamol, not reported		suicidal attempt, coma	1 day, all drugs withdrawn, outcome unknown
G F,36 70045 (MAH)	pregabaline, not reported	zopiclon baclofen	suicidal attempt	not reported, not known if drug was withdrawn outcome unknown
H M,? 45012 (MAH)	levetiracetam, not reported	valproic acid oxazepam	suicidal attempt	4 weeks, unknown, recovering
I F,31 56595	levetiracetam, not reported	carbamazepine	suicidal attempt	10 months, both drugs continued, recovered
J F,9 50902	ethosiximide, ansences	not reported	suicidal ideation, anger	Several months, ethosuximide continued, outcome unknown
K F,38 35907	lamotrigine, Depressive episode	lithium	suicidal ideation	11 days, dose of lamotrigine not changed, not recovered
L F,56 59582 65017	pregabaline, neuropathic pain		suicidal ideation, depression, lack of effect	not reported, drug withdrawn, recovered, no history of psychiatric disorders
M M,59 62665	pregabaline, not reported	tramadol diazepam	suicidal ideation, nightmares mood swings	7 days, drug withdrawn, recovered
N F,61 38285, 39345	levetiracetam, epilepsy	fenytoin clonazepam amiloride/HCT	suicidal ideation, visual hallucinations, anxiety	2 days, levetiracetam was withdrawn, recovered, patient was depressed when levetiracetam was started.

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O F,62 73993	pregabalin, neuropathic pain	not reported	suicidal ideation	15 days, drug withdrawn. not recovered

In many cases diseases or symptoms that could also contribute to suicide-related adverse events were reported, such as depression, mood changes and symptoms associated with psychosis (hallucinations, paranoia). In two cases (patients D and L) it was mentioned explicitly that the patient was not known to have psychiatric illness before. In two cases the patient had not recovered at the time of report. In eight cases the patient recovered after the antiepileptic drug was withdrawn. The latency of the suicidal adverse events was between one day and two years.

Other sources of information

SmPC

In some Summary of Product Characteristics (SmPCs) of antiepileptic drugs registered in the Netherlands suicide or ideation of suicide is described as adverse event (levetiracetam, topiramate, vigabatrin and zonisamide), or as general warning (clonazepam). The SmPC of other AEDs - carbamazepin, felbamate, fenobarbital, fenytoin, gabapentin, lamotrigine, oxcarbazine, pregabalin, primidone and valproic acid - does not contain information on suicide, suicidal attempt and/or suicidal ideation as a possible adverse drug reaction.[2,3]

Literature

The FDA analysed data from 99 placebo-controlled clinical studies covering 11 different antiepileptic drugs studied for different indications. The pooled population included 27,863 patients treated with drugs and 16,029 patients who received placebo. The nature of this studies was not further specified. They found that suicidal behaviour or ideation occurred in 0.43% of patients in the antiepileptic drug treatment groups compared to 0.22% of patients in the placebo groups. The increased risk of suicidality was observed 1 week after starting an antiepileptic drug and continued to at least 24 weeks. When compared to placebo, results were generally consistent among the drugs and were seen in all demographic subgroups [4]. The FDA did not report details about the methodology and statistical analysis nor about the studies that were included in the meta-analysis. Epilepsy itself is associated with an increased risk of suicide, even if coexisting psychiatric illnesses, demographic characteristics and socio-economic factors are taken into account [5]. Some studies have found an increased risk of psychiatric adverse events during antiepileptic therapy [6]. Two studies specifically found an association between levetiracetam and behavioural effects [7], and suicidal ideation [4], two case-reports have been published on topiramate and suicide [8,9], and one case-report on zonisamide and suicidal ideation [10].

Databases

In the WHO-database, suicidal attempt (which includes suicide) was associated with various anti-epileptic drugs, with the exception of carbamazepine, phenytoin, pregabalin and primidone. The strongest associations were found for gabapentin (Reporting Odds Ratio 15.1 (95%CI 14.2-16.1)) clonazepam ROR12.4 (95%CI 11.2 – 13.7)) and levetiracetam ROR 8.1 (95%CI 6.7-9.9)).

Mechanism

It is not clear what mechanism causes suicide and suicidal ideation in patients using AEDs. Serotonergic mechanisms are involved in the pathogenesis of depression with suicidal behaviour, and serotonergic properties of AEDs could influence the risk of suicidality [11]. For example, the psychiatric adverse events of zonisamide may be related to the biphasic effect of zonisamide on the serotonin function [10]. However, these hypotheses are inconclusive, and further research on the mechanism of action is needed. It should be noted that in patients with (bipolar) depression – a risk factor for suicide – antiepileptic drugs can be prescribed [12].

Conclusion

In total, 15 cases of suicide, suicidal attempts or suicidal ideation associated with antiepileptic drugs were reported to Lareb. The suicidal adverse events were associated with different antiepileptic drugs, most frequently with levetiracetam. Several case-reports and data from the WHO database support the association.

References

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This signal has been raised on June 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).