Non-Fatal and Fatal Liver Failure Associated with Valproic Acid

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Key words
- valproic acid
- hepatotoxicity
- liver failure
- pharmacovigilance

Abstract

Introduction: Little is known about hepatotoxicity associated with valproic acid (VPA), a widely used substance in neuropsychiatry.

Methods: All reported cases to the German Federal Institute for Drugs and Medical Devices between 1993 and 2009 of VPA-induced serious hepatic side effects were evaluated.

Results: A total of 132 cases of serious VPA-associated liver failure were identified. Approximately one third (34.8%) occurred under VPA monotherapy, while the majority was seen with VPA plus co-medication, most frequently antiepileptics (34.8%) and benzodiazepines (16.7%). A subgroup of 34 cases (25.8%) had a fatal outcome, the largest number reported to date. Of these, 32.4% were under VPA monotherapy and 67.6% under VPA plus concomitant medication. Within the study period a significant increase in the total number of reported cases and the subgroup of fatal cases was found.

Discussion: This first pharmacovigilance study of VPA-associated liver failure indicates a higher rate of non-fatal and fatal liver failure when VPA is given with co-medication as compared to monotherapy. However, co-medication per se does not increase the risk of fatalities.

Introduction

Valproic acid (VPA, 2-propylvaleric acid) was first synthesised as an organic solvent by the US chemist Burton in 1881. Its anticonvulsant properties were recognised incidentally in seizure experiments with VPA as a vehicle [1]. VPA was first released in France in 1967 and has been approved by the US Food and Drug Administration for treatment of epilepsy, bipolar affective disorder [2] and migraine and cluster headaches [3]. Potentiation of GABA-ergic transmission by inhibition of GABA transaminase [4], direct effects on potassium channels [5], and attenuation of NMDA-receptor-mediated neural excitation [6] have all been assumed to play a role in the neurochemical activity of VPA, whereas the mood-stabilising function appears to be related to cellular inositol depletion.

VPA is considered to be safe when administered according to the well-established therapeutic serum drug level. Nonetheless, Sztajnkrycer described 373 cases of major toxicity and 16 deaths in the USA in the year 2000 after intentional and unintentional overdose (acute VPA intoxications) [7].

Within the normal dose range, VPA is often clinically administered in combination with other antiepileptic drugs, antidepressants or antipsychotics. Side effects typically evolve acutely, and most frequently observed side effects include fatigue, nausea, vomiting, haemorrhages, seizures, and ataxia. Liver failure, bleeding, and pancreatitis represent rare but life-threatening adverse events [8, 9]. The severity of hepatotoxicity can range from reversible hepatic dysfunction to irreversible liver failure [10]. Reports of fatal liver failure related to VPA monotherapy are anecdotal, and systematic analyses of these complications are scarce. Large pharmacovigilance studies specifically addressing VPA-associated hepatotoxicity with both fatal and non-fatal outcome covering children and adults are lacking. Bryant and Dreifuss focussed on VPA-associated fatalities in the U.S.A. and reported 29 deaths identified between 1987 and 1993 [11]. Koenig and co-workers performed a questionnaire-based study and reported 31 non-fatal and 9 fatal cases of VPA-associated hepatotoxicity in Germany between 1994 and 2003 [8]. There is only one large

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pharmacovigilance study that investigated drug-induced hepatic injury in children between 12 and 17 years of age [12].

We set out to study the frequency and risk factors of VPA-associated liver failure in a first pharmacovigilance study using data from the German federal authority, irrespective of VPA indication. We sought to determine the roles of the absence or presence of co-medications, gender and age.

Methods

To investigate VPA-associated liver failure, we analysed all reported cases of VPA-associated hepatopathy and liver failure in Germany that had been submitted to the responsible federal authority, the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM], UAW Datenbank, Germany), between 1993 and 2009. BfArM is responsible for the surveillance of risks due to medical products in Germany. Among other functions, BfArM records spontaneous reports about serious adverse events from clinicians and gains information through systematic studies of published reports from Germany. Each BfArM report is documented in a separate standard form filled out by the reporting clinician. Each case report about VPA-associated liver failure includes age, gender, co-medication, and outcome (fatal vs. non-fatal). Admittance to the data base of cases with VPA-associated hepatotoxicity requires causality classified by BfArM as either "suspected" or "possible". Cases in which a causal relationship between liver failure and VPA use was regarded unlikely were not evaluated because they are not recorded by the BfArM.

The cases were analysed irrespective of the indication for administration of VPA or diagnosis and they were studied systematically, regardless of whether they occurred with VPA monotherapy or under a regime of VPA plus comedication. In addition, the correlation between occurrence of VPA-associated hepatotoxicity and gender or age was assessed. In a second step we evaluated the subgroup of fatal VPA-associated liver failures among all cases of VPA-induced hepatotoxicity. We calculated the relative association (percentage) of VPA-associated liver failure for each substance used as a comedication with VPA to establish a rank order of risk for the entire set of cases and for the subgroup of fatal cases. Additionally, case-fatality rates were determined within the medication groups.

Finally, we evaluated the number of reported cases of VPA-associated liver failure between 1993 and 2009 and divided the results in 4 time periods (1993–1997, 1998–2001, 2002–2005, and 2006–2009) for all cases and for the fatal cases. The frequencies of reported cases across these 4 time intervals were compared with the chi^2 test assuming an equal distribution over time. Furthermore, the association between gender and outcome (non-fatal vs. fatal) was tested for significance using the chi^2 test. Age differences between the 2 outcome groups were tested with the the Mann-Whitney U test.

Results

A total of 132 cases of serious hepatic adverse effects associated with application of VPA were reported to the German federal authority (BfArM) between 1993 and 2009 (**Table 1**, left column); of these, 34 cases had a fatal outcome and this subgroup is further described below (**Table 1**, right column).

Table 1 All 132 cases of VPA-induced hepatic side effects and the sub-group of 34 fatalities (right column).

Co-medication	Total group (N = 132)	Sub-group with fatal outcome (N = 34)
none (VPA only)	**46 (34.8%)**	**11 (23.9%*)**
yes (VPA plus ...)	**86 (65.2%)**	**23 (26.7%*)**
– antiepileptics	46 (34.8%)	11 (23.9%*)
topiramate	13 (9.8%)	3 (23.1%*)
carbamazepine	11 (8.3%)	5 (45.5%*)
lamotrigine	10 (7.6%)	2 (20%*)
ethosuximide	7 (5.3%)	0 (0%*)
oxcarbazepine	6 (4.5%)	0 (0%*)
phenytoin	5 (3.8%)	2 (40%*)
– benzodiazepines	22 (16.7%)	8 (36%*)
– antipsychotics	9 (6.8%)	3 (30%*)
– diuretics	8 (6.0%)	5 (63%*)
– antidepressants	7 (5.3%)	2 (29%*)
– antibiotics	6 (4.5%)	3 (50%*)
– NSAID	5 (3.8%)	3 (60%*)
– proton pump inh.	5 (3.8%)	1 (20%*)
– other hypnotics	4 (3.0%)	2 (50%*)
– heparin	3 (2.3%)	2 (67%*)
– propofol	2 (1.5%)	2 (**100%***)

Multiple mentioning of listed medications allowed; nota bene: * reported percentages in the sub-group with fatal outcome (right column) are based on the total number of cases treated with the respective medication (as given in the left column)
Other co-medications reported in 3 cases or less: β-receptor antagonists, ACE inhibitors, angiotensin antagonists, aldosteron antagonists, corticosteroids, calcium antagonists, nitrates, oral anticoagulants, statins, thyroxine, acetylsalicylic acid, clopidogrel, anti-arrhythmics, biperiden, metoclopramide, levodopa, Iprazochrome, virostatics, alendronate, opioids, and muscle relaxants

The total sample of 132 cases consisted of 76 female and 54 male (gender not reported for 2) patients, resulting in a female-to-male ratio of 1.41–1. The median of age was 16.0 years (range 10 months to 86 years; age not reported for 11).

In 46 of the 132 cases, hepatic adverse effects were reported to have occurred under VPA monotherapy (34.8%), while in the majority of the reported cases, VPA was administered with other comedication (86 of 132 = 65.2%).

Comedications grouped by substance classes are provided in **Table 1** (left column). They came from a wide range of substance groups. In descending order, they were antiepileptics (34.8%), benzodiazepines (16.7%), antipsychotics (6.8%), antidepressants (5.3%), diuretics (6%), antibiotics (4.5%), proton pump inhibitors (3.8%), non-steroidal anti-inflammatory drugs (NSAID) (3.8%), hypnotics (3%), heparin (2.3%) and propofol (1.5%). Among all licensed antiepileptics, topiramate, carbamazepine, lamotrigine, and ethosuximide showed the highest number of serious hepatic adverse effects with additional VPA medication.

Sub-group with *fatal* liver failure

34 out of the 132 patients with VPA-associated liver failure deceased during the further course, representing a fatality rate of 25.8% (**Table 1**, right column and **Table 2** for further clinical details). Of these, eleven (32.4% of all 34 fatal cases) were treated with VPA monotherapy, while the remaining 23 (67.6% of all 34 fatal cases) were treated with VPA and various comedications (see **Table 1** right column for details). The relative number of fatal cases was similar in patients with mono-therapy (11 out of 46 = 23.9%) or with combined medications (23 out of 86 = 26.7%). A disproportionally high rate of fatal outcomes was

Table 2 Subgroup of 34 fatal cases of VPA-associated liver failure.

N	Gen	Age	Indication for VPA	Concomitant illnesses	VPA since	Hepatic risk factors	Comedication
1	f	21 y	F-Epi	borrelia encephalitis	3 mo	no	clobazam, chloralhydrate, PHE, metoclopramide
2	f	1 y	Epi nos	acute virus infection	8 mo	no	aspirine, paracetamol, diazepam (after seizure)
3	m	23 y	F-Epi	status post meningoencephalitis	4 we	no	CBZ, phenobarbital, furosemide, vitamine k
4	f	75 y	Epi (first episode)	psychotic depression, hepatitis A	5 we	no	dibenzepin, melperon
5	m	36 y	F-Epi	infantile brain damage after meningitis, acute pneumonia	> 30 y	liver cirrhosis	CBZ, acute: penicillin, aminoglycoside, cephalosporine
6	m	86 y	F-Epi	cerebral infarct, urosepsis	6 days	no	clonazepam, L-Dopa, omeprazole, clopidogrel, furosemide, ciprofloxacine, diclofenac, heparin
7	f	24 y	grand mal Epi	mental retardation	> y	NR	lamotrigine (2 we before death), aspirine, primidon, amoxicillin, clindamycin, metamizol, paracetamol, metoclopramide, dimenhydrinat, etilefrine
8	m	73 y	S-Epi	bladder neoplasm, cerebral metastasis, cerebral infarct	7 days	no	diazepam, zolpidem, certoparin
9	f	9 y	grand mal Epi	mental retardation	3 mo	no	topiramate
10	f	49 y	F-Epi	traumatic intracerebral haematoma	1 y	no	lamotrigine (3 we before death)
11	f	25 y	S-Epi	NR	NR	NR	nos
12	m	NR	cluster headache	NR	int over	NR	nos
13	m	NR	NR	metabolic encephalopathy	NR	NR	nos
14	m	11 y	Epi nos	von Willebrands disease	NR	no	nos
15	f	10 y	absence Epi	von Willebrands disease, mental retardation, pancreatitis	NR	no	topiramate
16	m	54 y	Epi nos	perinatal hypoxic brain damage, acute pneumonia	20 y	no	isosorbide dinitrate, hydrochorothiazide, triamteren, thyroxine
17	f	14mo	recurrent S-Epi	developmental delay	NR	no	diazepam
18	m	6 y	myoclonic Epi, S-Epi	mental retardation, acute pneumonia	2 mo	no	phenobarbital (hypnotic), propofole
19	f	28 y	myoclonic Epi, S-Epi	MERRF	1 mo	no	nos
20	m	11 y	idiopath. generalized Epi	no	6 mo	hepatitis A	nos
21	f	21 y	symptomatic Epi	post infectious encephalitis	3 mo	no	CBZ, Clonazepam, PHE
22	m	12 y	symptomatic Epi, S-Epi	mental retardation	NR	hepatitis A	propofole
23	m	23 y	symptomatic Epi	post meningoencephalitis, mental retardation	1 mo	no	CBZ
24	m	30 y	Epi nos	no	NR	no	nos
25	m	29 y	F-Epi	mental retardation, Friedreichs Ataxia	2 mo	no	CBZ
26	f	10 y	pseudo Lennox Gastaut	mental retardation	3 mo	no	topiramate
27	m	54 y	symptomatic Epi	perinatal hypoxic brain damage, femur fracture operation	21 y	no	isoflurane, thiopental, triamteren, hydrochlorothiazide, thyroxine, isosorbide dinitrate
28	f	17 y	myoclonic Epi	Alpers disease	NR	NR	nos
29	f	10 y	myoclonic Epi	Alpers disease	NR	NR	nos
30	m	17 y	myoclonic Epi	Alpers disease	NR	NR	nos
31	m	8 y	S-Epi	NR	NR	NR	nos
32	f	52 y	impulse control disorder	schizophrenia, reduced intelligence	3 mo	no	thioridazine, levomepromazine
33	f	10 mo	S-Epi	Alpers disease	12 we	no	midazolam
34	f	58 y	bipolar depression	hypertonia	19 days	NR	duloxetine, risperidon, candesartan, lorazepam

Gen = Gender; f = female; m = male; NR = not reported; y = years; mo = months; we = week; Epi = epilepsy; F-Epi = focal epilepsy; S-Epi = status epilepticus; nos = not otherwise specified; int over = intentional overdose

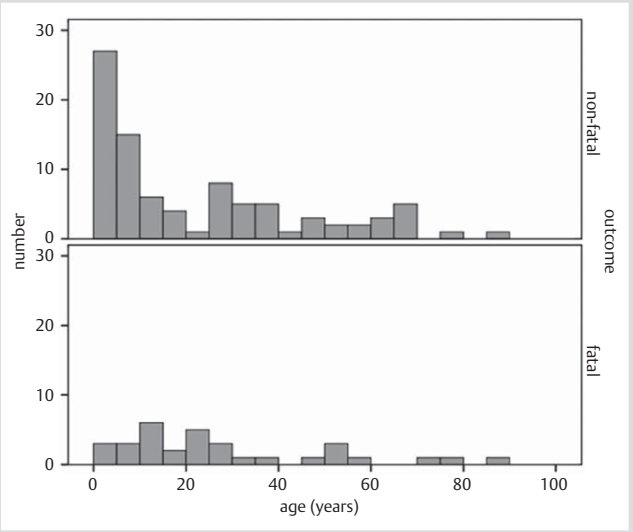

Fig. 1 Age distribution for cases with severe hepatic side effects (non-fatal) and for cases with fatal liver failure.

found for propofol (2 out of 2 = 100 %), heparin (2 out of 3 = 66.7 %), diuretics (5 out of 8 = 62.5 %), antibiotics (3 out of 6 = 50 %), carbamazepine (5 out of 11 = 45.5 %), and phenytoin (2 out of 5 = 40 %) (**Table 1**).

In contrast to a preponderance of female patients in the total number of cases, no differences in the number of fatal cases were found for men and women (17 vs. 17). However, the association between gender and outcome (fatal vs. non-fatal) was not statistically significant ($chi^2 = 1.36$, df = 1, p = 0.244). Regarding age, there was no overall significant difference between the groups (fatal and non-fatal liver failure) (z = −1.61, p = 0.106) (age not reported for 2 of the fatal cases). When inspecting the age distribution of the 2 groups (**Fig. 1**), there seemed to be an increased occurrence of serious hepatic side effects in children under 11 (0–10) years while the number of fatalities seemed equally distributed. An exploratory post hoc test of significance revealed that children under 11 have a lower risk of fatality (9 out of 54 = 17 %) as compared to patients with higher age (23 out of 67 = 34 %) ($chi^2 = 4.79$, df = 1, p = 0.029).

Frequency of reported liver failure cases (1993–2009)

The number of reported cases of VPA-associated liver failure between 1993 and 2009 was evaluated. Therefore, all cases and fatal cases were subdivided according to the date of report in 4 time periods: 1993–1997, 1998–2001, 2002–2005, and 2006–2009. There were 14 reports from 1993 to 1997, 12 reports from 1998 to 2001, 29 reports from 2002 to 2005, and 111 reports from 2006 to 2009. 4 fatal cases were reported between 1993 and 1997, 2 from 1998 to 2001, 6 from 2002 to 2005, and 22 cases from 2006 to 2009. The chi^2 test indicated a significant increase in both, in all cases ($chi^2 = 159.3$, df = 3, p < 0.001) and the subgroup of the fatal cases ($chi^2 = 29.5$, df = 3, p < 0.001).

Discussion

This is the first pharmacovigilance study that evaluated all cases of VPA-associated liver failure with fatal or non-fatal outcome irrespective of the indication of VPA covering all ages (children and adults). Within a total sample of 132 cases of VPA-associated liver failure 34 fatalities occurred, representing the largest published sample of fatal liver failure to date [11]. As compared with available studies, our pharmacovigilance study based on reported data to the German federal authority between 1993 and 2009 has a comparatively long observation period of 17 years (e.g., 7 years in [11]).

Considering the total number of cases with serious hepatic adverse effects a preponderance of female patients was observed resulting in a female-to-male ratio of 1.41–1. Regarding comedication, one third of the hepatic adverse effects were reported to have occurred under VPA monotherapy, while in the majority of the reported cases, VPA was administered with other comedication, most frequently substances with extensive hepatic metabolism such as antiepileptics, benzodiazepines, antipsychotics, diuretics, antidepressants and antibiotics. Approximately one quarter of patients who developed serious hepatic adverse effects due to VPA-treatment deceased in the further course (fatal VPA-associated hepatotoxicity). This observation showed no statistically significant difference regarding gender and age of affected patients. While children under the 11 years of age seem to be particularly at risk for developing any serious hepatic AE related to VPA this age group might feature a lower risk of fatal liver failure. Of the reported fatal cases one third were treated with VPA monotherapy, while two thirds received comedication in addition to VPA. The relative number of fatal cases was similar in patients with monotherapy or with combined medications (about a quarter).

To put our results in a larger perspective, Binek and colleagues estimated a risk of 1:5000 to 1:10000 of fatal liver failure with VPA in adults [13]. Dreifuss et al. found this risk to be approximately 1 in 37000 in adults with VPA monotherapy [14]; as for children between 0 and 2 years old receiving valproate as polytherapy, they found a much higher risk of fatalities (1 out of 500 cases). A particularly high risk for fatal hepatotoxicity under VPA was described for patients on additional antiepileptic drugs, with congenital metabolic disorders, with severe epileptic seizures in mental retardation or children, especially those under the age of 2 years (Box Warning [15]). Thus, the risk of VPA-induced hepatotoxicity in adults without these additional risk factors was thought to be definitely lower. This is in contrast with the study by Koenig et al. who counted 9 fatalities resulting from VPA-induced hepatopathy in Germany from 1994 to 2003 from questionnaires sent to all members of the German section of the League against Epilepsy [8]. They found that 5 out of 9 reported fatalities occurred in adults and 3 out of 9 patients had VPA monotherapy. Hence, this study was not in line with the generally accepted concept that VPA-induced hepatopathy occurs only in children or adults with risk factors such as polypharmacy [11]. Bauer et al. even reported a case of fatal fulminant liver failure under VPA monotherapy in a patient with bipolar affective disorder without any comorbidity [16].

The present study supports the view that VPA hepatotoxicity is not restricted to specific risk constellations except for age and comedication. We found a slightly higher occurrence of non-fatal hepatic injury in children younger than 11 years while the risk of a fatal outcome was about 2 times lower than in older patients. Otherwise no effect of age was observed. The majority of VPA-induced liver failure occurs in patients with VPA plus comedication. This finding is consistent with the earlier assumption that polypharmacy is still an important factor in VPA-induced hepatotoxicity. If comedication was present, substances that are extensively metabolised in the liver were found to be

common (see **Table 1** for details), so that in the presence of such substances liver function should be monitored even closer than in VPA monotherapy. The observed increase of registered cases of serious and fatal hepatic side effects over time might be explained by either changes in prescription practise or increased reporting to the BfArM pharmacovigilance data base.

We are aware of some limitations of our study. As a pharmacovigilance study, it is retrospective and fully depends on the physicians' reporting discipline (leaving room for an unknown number of unreported cases) as well as the quality of the data provided. We cannot explain whether the observed increase in the occurrence of VPA-associated liver failure depends on a better reporting practice or the increased use of VPA in general. Further, it appears to be possible that comedication was not reported in every case, leading to an overestimation of hepatotoxicity in VPA monotherapy. Our study does not allow for drawing either general causality conclusions or aetiological considerations about VPA-related fatalities and fully relies on the factors reported to the federal authority such as age, gender and comedication. We cannot provide any information regarding the time interval between onset of VPA treatment and the development of liver failure because the BfArM data base does not contain usable information for this important question. In addition, our German data cannot be generalised for other countries. Thus, similar studies in other countries would be desirable.

Across countries the recommended laboratory function tests before and after starting VPA therapy differ significantly. In Germany, the summary of product characteristics recommends several baseline tests (coagulation parameters including fibrinogen, total protein, whole blood cell count, bilirubin, transaminases, gamma-glutamyl-transferase, lipase and amylase, and serum glucose) and monthly clinical and laboratory controls (transaminases, bilirubin, coagulation parameters and amylase) for half a year; in case of pathologies after 4 weeks, 3 further controls with a maximum delay of 2 weeks each and subsequent monthly controls until 6 months after initiating VPA treatment should be performed [17]. In children, additional safety measures are recommended (laboratory controls at every second clinical appointment and parent education about signs of liver dysfunction) [17]. For the United States, the manufacturer recommends that "liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months" (without providing details about the tests and the intervals) [15]. Some authors highlighted that severe VPA-associated hepatotoxicity usually manifests within the first 90 days after treatment initiation [18] and thus, in addition to abovementioned controls recommended by the manufacturers particular attention to clinical and laboratory signs of liver dysfunction should be paid for the first 3 months.

Management of VPA-associated hepatoxicity is largely supportive, and the prognosis for patients with acute liver failure due to idiosyncratic drug reactions is poor, with a 60–80% mortality rate without liver transplantation [19]. In 2001, Bohan et al. proposed the intravenous use of carnitine because carnitine deficiency, either as a pre-existing condition or induced by VPA therapy, appears to promote VPA-induced liver failure [20]. Carnitine is well tolerated and has been shown to reduce fatal outcomes if supplementation therapy was initiated early in severe VPA-induced hepatic dysfunction, especially in children [9,21,22]. However, further investigation is needed to evaluate its clinical value and the appropriate dosage.

Conclusion

Our study indicates a higher rate of both non-fatal and fatal liver failure associated with VPA plus comedication as compared to VPA monotherapy. However, comedication per se does not increase the risk of fatalities, but is reported in the majority of non-fatal and fatal cases. Particular attention to liver function should be paid when co-medications with extensive hepatic breakdown, e.g.. other antiepileptics (topiramate, carbamazepine, or lamotrigine in particular), benzodiazepines and antipsychotics, are used with VPA. Some comedications such as propofol or heparin appear to have a disproportionally high risk of fatal liver failure when used with VPA.

Considering the growing number of reported cases of VPA-induced hepatic failure greater focus on the early detection of VPA-related hepatotoxicity is warranted. From a patient's perspective, detailed knowledge of possible VPA side effects is indispensable and patients need sufficient information about early clinical signs. While patients on VPA should be instructed to immediately seek medical help if gastrointestinal symptoms, general weakness, gait ataxia, or elevated temperature occur, future advances in proteomics, metabonomics and genomics will hopefully pave the way to personalised medications in which the beneficial effect of VPA is maximised and its toxicity minimised.

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Conflict of interest

None. MMS, RWF, and CSL designed and performed the research, analysed the data, and wrote the manuscript. FK, BJC, CH, MG, WK, and MF analysed the data and wrote the paper.

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