Valproic acid and prolonged QT: highlights from the FDA Adverse Event Reporting System (FAERS) database

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Abstract

Background. Several drugs can induce QT prolongation; however, the role of valproic acid played on the onset of this side effect has not been elucidated yet. Moreover, epilepsy itself represents a risk factor for the development of cardiovascular diseases; therefore, it is crucial to characterize the potential correlation between this drug and the occurrence of this cardiovascular complication.

Methods. We performed a descriptive analysis on the U.S. Food and Drug Administration Adverse Event Reporting System database, retrieving all adverse event reports involving valproic acid as suspect drug. After deduplication and data cleaning, we selected all cases reporting valproic acid as unique suspect and we analyzed those reporting the adverse event of interest, identified through the Standardized MedDRA Query “Torsade de pointes/QT prolongation”. Finally, we evaluated each case presenting other concomitant medications to explore potential drug-drug-interactions.

Results. Of 52,080 reports included in the analysis, 540 cases were referred to “Torsade de pointes/QT prolongation”. Loss of consciousness and syncope were the most reported events, included, respectively, in 241 (44.63%) and in 118 (21.85%) Individual Case Safety Reports. QT elongation and abnormal
electrocardiogram QT interval are reported only in 26 (0.1%) cases, ventricular arrhythmia only in 2 cases and the development of torsade de pointes has been recorded just in 1 case. Sudden death has been reported in 20 (0.1%) cases.

**Conclusions.** Our analysis revealed a very low number of cases reporting the adverse event of interest. The adverse event seems to be the consequence of multifactorial coexisting causes rather than imputable to the valproate alone.

**Key words**
QT prolongation, valproic acid, pharmacovigilance, FAERS, epilepsy

**Impact statement**
Our analysis evidences that valproic acid does not significantly influence QT elongation, which is the result of several coexisting factors.

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Introduction

The QT Interval indicates the period of ventricular depolarization and repolarization, defined as the time from the onset of ventricular depolarization to the end of repolarization.

A prolonged QT interval is suggestive of repolarization abnormalities; it can be associated with an increased risk of torsade de pointes (TdP), that can lead to ventricular fibrillation and sudden cardiac death (SCD) and it is considered a marker of arrhythmia [1–3].

The principal risk factors for QT prolongation are electrolyte imbalances, such as hypokalaemia, hypocalcaemia and hypomagnesemia, or medical conditions that can lead to electrolyte abnormalities, as renal dysfunction, diabetes, hypothyroidism, excess weight loss, malnutrition and obesity. Other risk factors are female gender, a positive family history for long QT syndrome, cardiovascular disorders and concomitant use of drugs that might inhibit the metabolism of another drug which causes QT elongation [4]. Underlying QT prolongation is often a functional impairment of ion channels within the cardiac muscle. Mutations of ionic channels or their dysregulation can affect both heart and brain functions, leading to a susceptibility to epilepsy and cardiac arrhythmias [5,6], such that long QT syndrome can also be congenital.

Several drugs can induce QT prolongation, including antiarrhythmic, antihistaminic, decongestant, diuretic, antibiotic and several psychotropic medications [4,7]. Indeed, some antipsychotics and antidepressants show a certain degree of blockade of potassium channels that could cause QT elongation [8]. The lengthening of the QT interval seems to be related to the inhibition of repolarizing potassium channels, which leads to an early after depolarization [9,10]. Epileptic seizures themselves could commonly lead to abnormalities of cardiac repolarization, largely found in people with chronic epilepsy [11]. Given that channelopathies play a role in the pathogenesis of cardiac disorders, caused by alterations in transmembrane potassium and sodium current, also major antiepileptic drugs, acting as sodium channels blockers, could be involved in this condition [7]. It is controversial if antiepileptic drugs are linked to QT prolongation syndrome, which may be underlying several cases of SUDEP (sudden unexpected death in epilepsy). Epileptic patients have an increased risk of premature death compared to the general population affecting about 1 in 1000 people with epilepsy and represents the most important directly epilepsy-related cause of death [12]. Since frequent seizures could constitute a major risk factor for SUDEP, the question arises on the role that treatment with antiepileptic drugs plays in it, especially of those drugs that are associated with occurrence of long QT syndromes [5,13]. Valproic
acid is widely used in epilepsy, bipolar disorders and other pathologies due to its diverse pharmacologic polymodal action. It exerts antiepileptic effects by suppressing the high-frequency neuronal firing by voltage-sensitive sodium, potassium and calcium channel blockade [14]. The association between valproate and prolonged QT interval is still not clear [1,6,7,15], so that in clinical practice pharmacological counselling is often requested on a possible involvement of valproic acid in the onset this side effect.

In order to try to clarify the association between valproic acid and the occurrence of QT elongation, we conducted a descriptive analysis on the Food and Drug Administration Adverse Event Reporting System database (FAERS). Data mining of large pharmacovigilance databases is of great importance in the detection of the earliest possible signals: spontaneous reporting systems, such as the FAERS, represent a valuable source to obtain real-world data about the safety/efficacy profile of specific drugs, to compare therapeutic options, and gain insight on potential mechanisms of adverse drug reaction (ADR) [16–19].

**Materials And Methods**

We conducted a descriptive analysis on the FAERS database, the largest spontaneous pharmacovigilance system, that contains information related to post-marketing safety surveillance reports in the form of adverse events (AEs) submitted by healthcare professionals and consumers themselves. Adverse events were collected as Individual Case Safety Reports (ICSRs). ICSRs provide administrative information (country, type of report, qualification of the reporter), patient demographics (sex, age, weight), AEs characteristics (seriousness, date of onset, outcome), details about suspect drug therapy (drug name, exposure start and stop dates, time to onset, dose, route, indication, de-challenge and re-challenge) and information concerning any drug administered at the time of AE but not held responsible for its occurrence by the reporter, referred to as concomitant medication [20].

Data, recorded from 1976 to 2021, were obtained from the web-based tool FAERS Public Dashboard, updated to March 31st 2021.

We included in our analysis all the reports that presented, as a suspect drug, valproic acid or one of its derivatives (i.e. valproate, valproate bismuth, valproate calcium, valproate magnesium, valproate magnesium/valproic acid, valproate sodium, valpromide, bismuth/valproate sodium, divalproex sodium, divalproex sodium Dr, divalproex sodium Er, divalproex sodium/valproic acid).
Duplicate records were detected and deleted accordingly, using RStudio: we excluded all the duplicates for gender, age, event date, suspected product active ingredient and report country.

To perform our descriptive analysis, we evaluated the following fields: sex, age, seriousness and type of ADR. Reported events are coded according to the Medical Dictionary for Regulatory Activities, MedDRA, which includes broad System Organ Class, SOC, and specific event categories, e.g., Preferred Term (PT) [21]; to a single FAERS report is assigned one or more PTs, and each PT is included within a corresponding primary (and secondary, if applicable) SOC. Our analysis was based on MedDRA version 24.0.

We classified ADRs reported using both SOC and SMQ systems. A Standardised MedDRA Query, SMQ, is a group of MedDRA terms, ordinarily at the PT level that relates to a defined medical condition or area of interest. We used the SOC “Cardiac disease” (Supplementary Material S1) and the SMQ “Torsade de pointes/QT prolongation” (Supplementary Material S2).

In order to reduce the risk of bias, we also excluded all reports in which valproate was administered with other drugs referred as suspect.

Then we analysed the notoriety of the ADRs reported that were included in the “Torsade de pointes/QT prolongation” SMQ. We also focused on the reason for use of valproic acid; in particular, we evaluated if the drug was administrated for a psychiatric or nervous disease using the respectively SOC.

To explore potential drug-drug interactions (DDIs), each case presenting other concomitant medications was evaluated using international databases, i.e. Clinical Pharmacology and INTERCheck WEB, with the aim of identifying possible DDI related to adverse events.

**Results**

To March 31st, 2021, a total of 22,002,078 ICSRs was retrieved from the FAERS database. Of these, 69,842 involved valproic acid as a suspect drug. After data cleaning, 52,080 ICSRs were retained and included in the analysis (Figure 1).

Among 52,080 ICSRs, the median age was 38.10 ± 22.16 years; of these, 8,848 (17.0%) cases occurred in paediatric patients, 28,561 (54.8%) in adults and 6,121 (11.8%) in patients older than 65 years of age; while in 8,545 (16.4%) age was not available.
Female was the most recorded sex with 24,450 (47.0%) cases; 23,523 (45.2%) cases were male and in 4,107 (7.9%) the gender was not available. Above all cases, 48,200 (92.6%) were serious.

“Cardiac disease” was reported in 6,612 (12.7%) ICSRs and "Torsade de pointes/QT prolongation” events in 2,642 (5.1%) (Table I).

In 19,025 (36.5%) cases, valproic acid was the only suspect drug. Of these, 1,815 (9.5%) reported the SOC “Cardiac disease” and 540 (2.8%) the SMQ “Torsade de pointes/QT prolongation” (Table I).

4,751 (25.0%) ICSRs were referred to paediatrics patients, 10,373 (54.6%) ICSRs to adults and 1,948 (10.2%) to over 65 years of age; in 1,953 (10.3%) cases, age was not available. Female cases were 9,420 (49.6%) and male 8,749 (46.0%).

About 540 “Torsade de pointes/QT prolongation” cases, 297 ICSRs reported, as reason for use, one of the SOC “nervous system disorders” PTs (Table III).

The median age was 32.95 ± 22.28 years; of these, 125 (23.2%) were in paediatrics patients, 296 (54.8%) in adults and 60 (11.1%) were in over 65 years old.

The gender distribution was 265 (49.1%) cases for female and 259 (48.0%) cases for male and in 16 (3.0%) the gender was not available. 531 (98.3%) cases were serious.

Loss of consciousness and syncope were the most reported ICSRs, included, respectively, in 241 (44.63%) ICSRs and in 118 (21.85%) (Table IV).

QT elongation and electrocardiogram QT interval abnormal are reported only in 26 ICSRs (0.1%), ventricular arrhythmia only in 2 cases and the development of TdP has been recorded just in 1 case. Sudden death has been reported in 20 ICSRs (0.1%).

From the notoriety analysis, most of the ADRs resulted unknown; in particular, PTs are reported in order of frequency in Table IV.

The potential DDIs found were increase serum concentration (92 ICSRs); decrease serum concentration (74 ICSRs); additive sedative, CNS, and/or respiratory-depressant effects (59 ICSRs); unpredictable effect (32 ICSRs); alter pharmacokinetics (21 ICSRs); increase potential side effects (21 ICSRs); reduce effect (5 ICSRs); increase effect (4 ICSRs); additive cardiac conduction effects (1 ICSR).

About the SMQ of interest, the principal DDIs that may alter valproic acid pharmacokinetic and pharmacodynamics were, in order of frequency, decrease serum concentration (59 ICSRs, 10.9%); increase...
serum concentration (30 ICSRs, 5.6%); alter pharmacokinetics (11 ICSRs, 2.0%); increase potential side effects (10 ICSRs, 1.9%); increase effect (2 ICSRs, 0.4%); additive cardiac conduction effects (1 ICSR, 0.2%). These DDIs mechanisms and relative drugs involved are reported in Figure 2.

Discussion

This is, to our knowledge, the first study exploring the potential association between valproic acid and the occurrence of QT elongation syndrome using data extracted from FAERS, one of the largest spontaneous pharmacovigilance surveillance system.

Some studies reported that ADRs of the SMQ “Torsade de pointes/QT prolongation” are more present when valproate is administered together with others drugs, confirming the evidence that other co-administered drugs are involved in the onset of QT elongation than valproic acid [4,8,22]. Consistently with this, the analysis we conducted on reports with valproic acid as unique suspect drug revealed that only 3% of cases involves ADRs of the SMQ of interest; of these, loss of consciousness and syncope are the most reported events, even if sometimes they could be caused by seizure itself [5].

Another study underlines that there is no correlation between seizures frequency and electrocardiogram alterations, except for a slight increase in QTcd in patients taking valproate [15].

On the contrary, Kwon et al. suggest that antiepileptic drugs, or even polytherapy of antiepileptic drugs, may not lengthen the QT interval. They also suggest that some traditional antiepileptic drugs are known to shorten the QT interval with an unclear mechanism, so sodium channel blockers may be used in an attempt to normalize the QT interval [7].

This is in contrast with other studies that support the increased risk of QT elongation in patients treated with antiepileptic drugs and, in particular, with valproic acid. Asoğlu et al. demonstrate that QT dispersion, QTcd (QT interval corrected for heart rate dispersion) and Pd (atrial depolarization dispersion) values are significantly higher in epileptic patients using carbamazepine and valproic acid than in the healthy control group. They also report that female patients using carbamazepine and male patients using valproic acid have QTcd values significantly higher compared to female population in valproic acid or male patients on carbamazepine [1].
The study conducted by Altun et al., valproic acid group shows a significant increase in Tp-e interval, Tp-e/QT and Tp-e/QTc values after three months of treatment, suggesting that valproic acid increases ventricular repolarization [6].

The relationship between valproic acid and the onset of QT prolongation is therefore not completely clarified; the results presented here indicate that valproic acid does not significantly influence QT elongation, which is the result of several coexisting factors.

Multiple mechanisms may be implicated in the QT prolongation and cardiac arrhythmias are more likely to occur if drug-induced QT prolongation coexists with other risk factors, such as inherited long QT syndrome, electrolyte imbalance, cardiac or hepatic diseases [7]. In epileptic patients, significantly longer QTmaxc and QTcd intervals are observed than in healthy controls, increased age being associated with longer QTcd intervals but not with the duration of the disease, etiology of the seizures, mono- or polytherapy treatment regimens [23].

Interactions between antiepileptics and other drugs known to prolong QT may also be clinically important. From our analysis emerged that no less than 17.0% of ICSRs reported valproic acid being co-administered with medications that could alter drugs pharmacokinetic profile. Certain drugs that prolong QT are metabolized by CYP3A4 and, when administrated together CYP3A4 inhibitors, such as valproic acid, may raise their levels such that the occurrence of ventricular tachyarrhythmia is increased [5,7].

The use of a spontaneous reporting system database has some important intrinsic limitations because reporting might be influenced by factors including no definitive proof of the causal relationship between exposure to the product and the reported event, notoriety bias, selection bias, under-reporting, stimulated reporting and other confounding factors [24].

Furthermore, neither the incidence of ADRs nor the absolute measures of risk can be computed from the FAERS analysis due to the lack of a denominator (number of patients prescribed the product). Despite these critical aspects, our study highlights the clinical relevance of post-marketing spontaneous reporting, since this kind of analysis are based on real-world data derived from clinical practice and, so, they provide a very large amount of cases about heterogeneous groups of patients that generally are not included in clinical trials. It is worth mentioning that real-world data sources give us a general overview of the drug utilization, letting us
better evaluate the safety/effectiveness of drugs in clinical practice, including the long-term impact of therapies.

Conclusions

In conclusion, the current findings seem to be relatively reassuring. Our analysis revealed a very low number of ICSRs reporting the adverse event of interest and most studies did not report a significant increased risk in QT prolongation associated to valproic acid itself. The adverse event seems to be the consequence of multifactorial coexisting causes rather than imputable to the valproate alone. However, evidence is not conclusive due to the design of the descriptive analysis and the limited number of available studies. Even if major antiepileptic drugs don’t seem to cause QT prolongation themselves, patients remain at risk for cardiac arrhythmia for many possible coexisting factors such as electrolyte imbalance, hepatic or renal impairment and co-medication with other drugs. For this reason, epileptic patients need to be actively screened for QT prolongation due to the increased risk of SUDEP.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Figures

Figure 1. Study flowchart
Figure 2. Principal DDIs of interest

Supplementary Materials

Supplementary Material S1. SOC “Cardiac disease” PTs.

Supplementary Material S2. SMQ “Torsade de pointes/QT prolongation” PTs.

References

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