Evidence for sodium valproate toxicity in mitochondrial diseases: a systematic analysis

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ABSTRACT

Background We aimed to determine whether sodium valproate (VPA) should be contraindicated in all mitochondrial diseases, due to known VPA-induced severe hepatotoxicity in some mitochondrial diseases.

Methods We systematically reviewed the published literature for mitochondrial DNA (mtDNA) and common nuclear genotypes of mitochondrial diseases using PubMed, Ovid Embase, Ovid Medline and MitoPhen databases. We extracted patient-level data from peer-reviewed articles, published until July 2022, using the Human Phenotype Ontology to manually code clinical presentations for 156 patients with genetic diagnoses from 90 publications.

Results There were no fatal adverse drug reactions (ADRs) in the mtDNA disease group (35 patients), and only 1 out of 54 patients with a non-POLG mitochondrial disease developed acute liver failure. There were fatal outcomes in 53/102 (52%) POLG VPA-exposed patients who all harboured recessive mutations.

Conclusions Our findings confirm the high risk of severe ADRs in any patient with recessive POLG variants irrespective of the phenotype, and therefore recommend that VPA is contraindicated in this group. However, there was limited evidence of toxicity to support a similar recommendation in other genotypes of mitochondrial diseases.

BACKGROUND

Epilepsy often features in mitochondrial diseases, with myoclonic, generalised and focal onset seizure types. Sodium valproate (VPA) is effective in these seizure types in non-mitochondrial diseases, although not a first-line treatment for focal onset seizures. It is also used for migraines and bipolar disorder prophylaxis, which are found in mitochondrial diseases. However, it is important to note that VPA has known teratogenic effects and associations with neurodevelopmental disorders, leading to a lack of alternative options. While VPA may cause transient liver enzyme increases in 15% of patients, severe adverse drug reactions (ADRs) like hepatic failure are rarer (0.01% of all patients). POLG-related mitochondrial disease, typically Alpers syndrome presenting with developmental regression and intractable seizures, is an identified risk factor for VPA-induced hepatotoxicity. POLG disease can present at different ages with seizures commonly presenting in early-onset and juvenile to adult-onset forms. However, liver involvement is prevalent in early-onset POLG disease and is associated with worse survival including in phenotypes where epilepsy is not a feature. The severity of VPA-related ADRs in Alpers syndrome and the lack of systematic follow-up studies of VPA in other mitochondrial diseases have led clinicians to avoid VPA in all mitochondrial diseases without clear evidence, potentially
discarding an effective and cheap medicine. To bridge this gap, we assessed VPA effects across various mitochondrial diseases. MitoPhen,9 which contains published clinical data as human phenotype ontology (HPO) terms, was used to investigate whether there are any associated clinical features pre-empting VPA-related toxicity. Our aim was to evaluate the evidence base for VPA-induced toxicity in different mitochondrial diseases using published patient-level data.

**METHODS**

**Search strategy and study selection**

A systematic review of the literature, published up to July 2022, was conducted using PubMed, Ovid Embase, Ovid Medline and MitoPhen databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses10 (figure 1). Articles about mitochondrial diseases linked to migraine or seizures and VPA treatment were reviewed. We considered three groups: (1) POLG-related mitochondrial diseases, (2) mitochondrial DNA (mtDNA) diseases and (3) other nuclear causes of mitochondrial disease based on PanelApp genes.11 We supplemented the search with the ‘MitoPhen-Expanded’ data set which currently contains data on 89 pathogenic mtDNA variants,9 and common nuclear genotypes including POLG. Exclusion criteria were non-peer-reviewed articles, no documented VPA use, no genetic diagnosis and lacking patient-specific information. An ADR was defined as a noxious or unintended response to VPA, where the causal relationship between VPA use and the reaction was strongly suspected.12 ‘Symptom-control’ referred to reported seizure or symptom reduction with VPA. The search strategy and risk of bias assessment are detailed in online supplemental information.

**Survival analyses—POLG data set**

To investigate survival between patients who had and had not been exposed to VPA, we included the MitoPhen-Expanded POLG data set (publications up to 01 June 2022), where patients with seizure phenotypes and without documented VPA use were coded as ‘no VPA’. The survminer R package13 was used to create Kaplan-Meier plots and the log-rank p value was used for testing differences in survival between groups. ‘Event’ was defined as ‘death’ for survival analysis. Time in years was calculated by age at symptom onset until age at death or age at last follow-up.

**HPO-based analyses**

The OntologyX14 and gplots15 R packages were used to generate a matrix of phenotype similarity scores using the
Lin similarity measure, and a heatmap displaying the hier-
archically clustered scores per patient. Phenotype enrich-
ment was explored within the POLG data set by grouping
for VPA and no VPA exposure, and between POLG and
non-POLG data sets with VPA exposure, using one-sided
Fisher’s exact test adjusted with the Benjamini-Hochberg
procedure. HPO terms related to liver dysfunction were
excluded to avoid over-representation of VPA-related
toxicity.

Data availability
See online supplemental information. MitoPhen is acces-
sible at www.mitophen.org.

RESULTS
The search strategy revealed a total of 156 patients from
90 articles with mitochondrial diseases who had reported
VPA exposure (figure 1).

Group 1: POLG-related mitochondrial diseases
Data collated from 46 articles on 102 patients with POLG-
disease and VPA exposure (figure 1) showed ADRs in 91
patients (89%), with 87 patients (85%) reported to have
hepatotoxicity. There were no reported ADRs in seven
and ADR status was unknown in four patients. There was
no pre-existing liver disease in 92/102 patients (90%).
There were fatal outcomes in 53/102 patients (52%),
with 8 being unrelated to VPA such as intractable seizures.
Liver transplant was required in 15 patients, and 6 (40%)
died post-transplant. Age at onset was available for 98/102
patients (96%). Survival between male and female patients
was similar (p=0.7), but the lower age at onset group
(0–4 years) had a lower survival compared with onset in
later childhood: 5–18 years (p=0.05). All patients exposed
to VPA with reported genotypes (97/102) had recessive
POLG variants. Compound heterozygous variants were
associated with worse outcomes compared with homozygous variants (p<0.01) (figure 2A).

There were 280 patients from 66 articles with recessive POLG variants, without documented VPA exposure included in the MitoPhen-Expanded data set. There was a lower survival in the VPA exposure group compared with no VPA use (p<0.0001, figure 2B).

**Group 2: mtDNA diseases**

In the mtDNA disease group, 28 articles mentioned VPA use in 35 patients without any documented fatal ADRs. Seizure control was reported to be effective in 10/13 (77%) patients with m.8344A>G and presentations of myoclonic epilepsy and ragged red fibres (MERRF syndrome). Seizures were exacerbated in 3/8 (38%) m.3243A>G patients who had features suggestive of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS syndrome) (figure 2C, online supplemental table S1). Patients with generalised myoclonic seizures, and/or focal myoclonic seizures, had reported good symptom control with VPA (figure 2D). There was one report of VPA being instigated for migraine in a patient successfully, although it was a dominant symptom in five published patients. There were 3/35 (9%) cases with non-fatal hepatotoxic effects including pancreatitis (online supplemental table S1).

**Group 3: other nuclear-encoded mitochondrial diseases**

The search strategy for 227 nuclear genotypes of mitochondrial diseases resulted in 16 articles documenting 19 patients (figure 1). Four patients (21%) had VPA hepatotoxicity: one patient with a severe encephalopathy and epilepsy due to WARS2 variants developed acute liver failure after commencing VPA, two patients with recessive TWNK variants and one with biallelic PAR2 variants had transient elevations in hepatic transaminases. Three patients had transient symptoms where VPA was thought to be a contributing factor, however, a causal relationship was not clear. Therefore, 15/19 (79%) patients in this group had no definite VPA-induced ADRs (online supplemental table S2).

According to the Clopper-Pearson exact method, ADRs could not be predicted by phenotypic profiles in other mitochondrial diseases. Hierarchical clustering of all 156 patients exposed to VPA using phenotype similarity scores showed that patients with non-POLG diagnoses clustered together (online supplemental figure S1A). Patients with early onset POLG disease had a lower survival compared with other clusters (p<0.05, online supplemental figure S1B). The clusters resemble clinically defined phenotypic groups relating to genotypes (online supplemental figure S1C). Status epilepticus was more frequent in POLG disease (online supplemental figure S2), explaining why VPA was used in these patients.

**DISCUSSION**

This comprehensive systematic review used several search engines, and MitoPhen-Expanded data sets. We assessed 228 nuclear genes and 27 mtDNA genes linked to mitochondrial diseases, incorporating patient-level data for 436 patients. No published patients with dominant POLG variants exposed to VPA were found. Data confirm the significant risk in recessive POLG disease (figure 2), with fatal outcomes in 52% and ADRs in 89% of 102 patients, aligning with previous findings. In mtDNA diseases, 10/13 patients with m.8344A>G-induced seizures responded well to VPA with no reported ADRs. Non-POLG genotypes without mtDNA depletion, including m.7472_7473insC, TWNK and PAR2 variants, showed hepatic transaminase increases in 4/54 patients, comparable to rates in non-mitochondrial diseases. The lack of natural history data on rarer genotypes meant it was difficult to attribute VPA toxicity to the fatal neurological decline of a patient with a WARS2 diagnosis, following the resolution of their VPA-induced liver failure. The reasons for significantly different VPA-induced hepatotoxicity proportions between POLG (87/102) and non-POLG mitochondrial diseases (7/54) (p<0.0001), remain unclear.

A limitation of this review is publication bias favouring POLG disease data, attributed to higher status epilepticus frequency in the POLG group (online supplemental figure S2), necessitating additional antiseizure medications like VPA. Also, publication bias would factor in reporting of ADRs related to VPA over non-events, thereby giving a likely overestimate of ADRs. Some authors changed VPA due to perceived ADR risks in non-POLG disease. This contributes to uncertainty in the clinical management of mitochondrial epilepsy due to the lack of longer-term follow-up in non-POLG mitochondrial diseases with VPA exposure. Additionally, there were unclear causal relationships between VPA and clinical features which could be explained by the natural progression of the mitochondrial disease. Despite variability in reporting VPA dosage and time to ADR, consistent documentation of clinical features enabled survival analyses using HPO-driven clusters, revealing significantly different survival between POLG and non-POLG diseases (online supplemental figure S1). ADRs could not be predicted by phenotypic profiles in POLG disease.

**CONCLUSIONS**

The data showed a significantly lower proportion of hepatotoxicity with VPA in non-POLG versus POLG mitochondrial
diseases. Additionally, VPA resulted in reported symptom control particularly in patients with \( m.8344A>G \) disease, with no reported ADRs. Longer-term follow-up studies are required to define the natural history of rare nuclear genotypes of mitochondrial diseases and the role of VPA in treating patients with non-POLG mitochondrial diseases. We recommend VPA is contraindicated in patients carrying recessive POLG variants.

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