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Reversible male infertility with valproate use: A review of the literature

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ABSTRACT

Sodium valproate is a broad spectrum anti-seizure medication useful in the treatment of both generalized and focal epilepsies. The association between valproate and female reproductive disorders is well understood and delineated. Male infertility however is an under-recognised adverse effect of Valproate therapy.

Previous case reports have detailed reversible male infertility secondary to valproate. One report demonstrated a relationship between valproate dose and abnormal sperm parameters. We submit a case report suggesting a dose dependent effect of valproate on sperm parameters and a possible relationship between the duration of valproate therapy and its deleterious effect on male fertility.

Men on valproate should be counselled about the possibility of progressive but reversible infertility. Valproate should be stopped and replaced by an alternative agent in those men who are infertile and where the couple are trying to conceive, particularly if there are associated abnormal sperm parameters while on the drug.

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Introduction

Fertility is lower in men with epilepsy compared to men without epilepsy. It has been shown that epilepsy itself results in subfertility; however it is also clear that anti-seizure medication (ASM) may play a role, particularly valproate (VPA).

The mechanism by which VPA exerts its effects on male fertility is poorly understood. There are several proposed pathways including altered serum sex hormone concentrations, direct effects on the gonads, oxidative stress and altered mitochondrial function.

There have been three previously published case studies detailing reversible infertility in male patients taking VPA for epilepsy.

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These men had abnormal sperm morphology, reduced motility and reduced sperm count. These changes corrected following cessation of VPA therapy and pregnancies were subsequently achieved. We submit another report of a patient on long term VPA treatment who had an abnormal semen analysis and ongoing infertility. His VPA was stopped, his sperm parameters improved, and a baby was conceived. When re-established on a lower dose of VPA his sperm morphology deteriorated over time.

VPA and infertility

VPA is used in the treatment of epilepsy as well as a mood stabilizer. Its precise mechanism of action in the treatment of these disorders remains unclear, although it has been shown to modulate GABA- ergic activity, have direct effects on ion channels, inhibit glycogen synthase kinase 3B, reduce myo-inositol levels and inhibit histone deacetylase [2–5].

The association of VPA therapy with female reproductive disorders is well documented. These disorders are characterized by hyperandrogenism and polycystic ovaries, potentially as a consequence of obesity and hyperinsulinaemia [6–8]. The effects of VPA on male fertility is less well explored, and less well appreciated in clinical practice.

It is known that fertility is lower in men with epilepsy compared to that of the general population with hyposexuality and reduced potency described in up to 71% of these patients [9]. A close electrophysiological and anatomical relationship between the temporo-limbic system and the hypothalamus has been demonstrated and clinical studies have shown that uncontrolled seizures can have an effect on the secretion of pituitary sex hormones [10]. Animal studies have replicated these findings showing that simulated focal amygdaloid seizures and simulated generalized seizures result in similar serum sex hormone alterations in the absence of anti-epileptic drug treatment [11].

There is also evidence, however, that implicates VPA treatment in male infertility independent of epilepsy-related subfertility. A study of 60 men noted an increased risk of sperm dysmotility and morphological abnormalities with VPA compared to controls [12]. Another group described high rates of sperm morphologic abnormalities in patients taking VPA compared to controls with no such abnormalities in sperm morphology in patients on levetiracetam therapy [13].

One report described a case of a male patient who received VPA for juvenile myoclonic epilepsy. As his VPA dose was increased consecutive semen analyses were undertaken demonstrating a decline in sperm count and sperm motility with increasing doses. When his VPA therapy was weaned and replaced with lamotrigine, his semen parameters normalized and a baby was conceived ([14]; Table 1).

Sperm motility determines the spermatozoa's ability to move through the reproductive tract to fertilise the female gamete. Morphological abnormalities adversely affect the ability of the spermatozoa to reach and fertilise the female gamete.

Motility: spermatozoa are categorised as progressively motile, non-progressively motile and immotile

Morphology: A morphologically normal sperm head can be defined as normal oval shaped with a smooth contour. Also considered as normal are sperm heads that are slightly tapered in the posterior region or spermatozoa with a slightly narrower heads and also forms with a slightly narrower heads combined with a slightly tapered post-acrosomal region [1,14]

Animal studies have further underscored this potential effect of VPA, with alterations in semen parameters following administration of VPA in non-epileptic rats [15] with spermatogenic arrest and reduced counts in the semniferous tubules of the treated rats in a dose-dependent and duration of treatment dependent pattern ([16], Table 2). Another group demonstrated a deterioration in sperm morphology correlating with both dose and duration of treatment with VPA [17] These findings are comparable to those found in human patients.

Two previously published case reports underline the idiosyncratic adverse effect of chronic VPA therapy in males. They describe patients with reduced sperm motility, abnormal sperm morphology, and a reduced sperm count while on VPA therapy for epilepsy. In both cases cessation of VPA therapy resulted in the normalization of these sperm parameters and successful conception ([18–19], Table 3). Our patient reported here is a further reminder of this potential adverse effect of VPA on male fertility, and the possibility of sperm normalization and a subsequent successful pregnancy following VPA cessation.

Mechanisms of VPA-associated infertility

Reproductive endocrine function

As previously stated epilepsy itself can have negative effects on reproductive hormone concentrations [10–11]. The prospect of ASM having an independent effect on neuroendocrine function has been investigated. Low dose VPA has been shown to increase prolactin and decrease luteinising hormone (LH) and follicular stimulating hormone (FSH) in male rats [20]. Human studies have shown that patients on VPA therapy have altered levels of serum androgens and gonadotrophins [21]. VPA-treated patients have high dehydroepiandrosterone (DHEAS) levels and lower FSH and LH concentrations compared to controls. There was no difference noted in serum testosterone or testosterone:sex-hormone binding globulin (SHBG) ratio and androstenedione levels, which may be expected in patients on enzyme-inducing ASDs [22]. Hypophyseal secretion of sex hormones is under the control of pulsatile release of GnRH. GABAergic neurons play a role in modulating noradrenergic inputs to these GnRH neurons. As previously noted, one of the putative anti-epileptic mechanisms of action of VPA is via modulation of GABAergic transmission [2]. This could be another potential mechanism by which VPA has an effect on sex hormone concentrations.

Gonadal effects

It remains unclear whether fertility is affected as a result of altered levels of gonadotrophins or whether direct effects of ASDs on the gonads has a more significant impact. The possibility of

Table 1
Sperm analyses related to VPA therapy and dosage in a patient with epilepsy.

	Lower reference limit	500 mg VPA	1000 mg VPA	1500 mg VPA	9 months post cessation VPA
Duration of VPA treatment (years)		6	0.3	2	
Sperm concentration	15mill/ml	87	2	5,1	91,2
Total motility	32%	42	10	10	60
Progressive motility		25	5	5	35
Normal morphology	4%	8	1	0	28

Table 2
Sperm analysis relating deteriorating parameters to dose and duration of dose in rats [16].

		4 weeks	7 weeks	10 weeks
Motility (% of motile sperm)	Control	80	87	86
	VPA 250 mg/kg	80	88	87
	VPA 500 mg/kg	81	72	72
Sperm count: No. of sperm heads ($x10^8$/epididymis)	Control	1.27	1.31	1.40
	VPA 250 mg/kg	1.27	1.23	1.29
	VPA 500 mg/kg	1.088	1.023	0.975

Table 3
Sperm analyses measured on VPA therapy and several months after its cessation on carbamazepine monotherapy in an patient with epilepsy. [18]

	Lower reference limit	2250 mg/day VPA	Off VPA
Sperm count (mill/ml)	20	18.4	157.5
Motility (%)	50	4–8.4%	65
Morphology (%)	>60 oval morphology	4–5%	34%

direct inhibition of testicular endocrine function by ASDs including VPA was first investigated in animal models by exposing Leydig cells to VPA and maximally stimulating concentrations of hCG or cAMP. Testosterone formation by the Leydig cells was reduced by 50% [23]. Another group looked at the *in vitro* and *in vivo* effects of ASDs, including VPA, on sperm motility. Sperm motility was measured following incubation with VPA and found to be half that of controls. This finding was replicated *in vivo* in patients on long term VPA therapy [24]. The frequency of any sperm abnormality, including poor motility and low concentration, is higher in men on VPA treatment. This may be also associated with small testicular size [12,9].

Oxidative stress

Another potential mechanism by which VPA affects male fertility is via oxidative stress. *In vitro* studies initially implicated VPA in creating reactive oxygen species (ROS) which mediated cell damage via destruction of DNA and cellular proteins and lipids [25–26]. ROS can alter signal transduction cascades in gene translation. At therapeutic concentrations VPA acts as a histone deacetylase inhibitor resulting in hyperacetylation of histones [5]. This alters histone to protamine transition which is an important part of spermatogenesis, protamine being a component nuclear protein [27]. Furthermore protection has been demonstrated against alteration of sperm motility in long-term VPA treated rats with the co-administration of the anti-oxidant, resveratrol. A decrease in sperm motility correlating with an increase in oxidative damage to cellular proteins and fats in the presence of VPA was shown. When VPA was administered with resveratrol these changes were not observed, implicating oxidative stress as a potential mediator of VPA related infertility [28].

Mitochondrial dysfunction

Carnitine is a nutrient present in the diet, synthesized from dietary amino acids. VPA is associated with a decrease in carnitine levels [29] Carnitine allows for the transport of long-chain fatty acids across the inner mitochondrial membrance for beta-oxidation. It also allows for the removal of the toxic acyl-coenzyme-A metabolites from the mitochondria. L-carnitine is derived from carnitine, taken up by the spermatozoa, and is involved in their maturation and motility [30]. Low carnitine levels reduce fatty acid concentration within mitochondria leading to decreased energy production and decreased sperm motility [31]. Studies have shown a correlation between abnormal sperm count, motility, morphology, testicular volume and carnitine levels in a VPA dose-dependent and duration-dependent pattern [30]. This offers, yet another, potential mechanism by which VPA exerts deleterious effects of male fertility.

Case report

Our patient is a 36-year-old man who has had drug-resistant, non-lesional frontal lobe epilepsy since the age of 12. He has suffered with frequent nocturnal seizures which had been best controlled on dual ASM therapy with lamotrigine, 150 mg in the a.m. and 200 mg in the p.m. and controlled release VPA 500 mg in the a.m. and 1200 mg in the p.m. with an average of one seizure per month. These seizures generally occured within 20 minutes of the onset of sleep. They would wake him, he would feel dazed and then lose awareness. His wife described grunting noises followed by whole-body rigidity, flailing of both arms and flickering of the eyes. They had a duration of up to one minute.

He had been on this ASM regime for 16 years when he and his partner began to try to conceive a baby without success for six months. They had both been investigated for infertility, and our patient had been found to have a low sperm count with poor morphology and motility (Table 4). His partner did not have any abnormalities associated with female infertility. The decision was made to wean the VPA to zero while introducing levetiracetam in addition to his baseline lamotrigine therapy. This change resulted in a marked increase in seizure frequency with nightly seizures reported. Levetiracetam was stopped and clobazam was introduced.

Another sperm analysis was performed three months following the cessation of VPA therapy (Table 4) showing improved sperm morphology, concentration and motility. Eight months following the cessation of VPA therapy a baby was conceived, and a healthy baby boy was subsequently born. VPA was then reintroduced with sperm motility and concentration consistently remaining within normal reference ranges on a lower maintenance dose. However, sperm morphology again deteriorated following prolonged VPA therapy.

Sequential sperm analyses demonstrating recovery of sperm parameters following cessation of VPA treatment and progressive deterioration on recommencement of treatment

Conclusion

VPA is a broad-spectrum drug commonly used as monotherapy or as part of a multidrug treatment regime for epilepsy. The evidence outlined suggests VPA has a potentially deleterious effect on sperm morphology, motility and concentration. The exact mechanisms in which it results in these abnormalities has yet to be fully elucidated though suggested mechanisms include central effects on gonadotropins, direct effects on the gonads, oxidative stress and mitochondrial dysfunction. While VPA induced infertility has been previously reported [14,18–19], only one demonstrated a dose-dependent pattern in abnormal sperm parameters [14]. Our case supports this effect and introduces the prospect of

Table 4
Sperm analyses related to VPA therapy, dosage and duration of treatment [1].

	Lower Reference Limit	July 2017	September 2017	March 2018	March 2019	June 2020
Volume	1.5 ml	0.6	1.5	1.90	1	1.8
Concentration	15mill/ml	9.5	13	24	40.5	56
Motility	32%	32	27	30	42	50
Morphology	4%	1	1	3	4	2
ASD dose		VPA 500 mg a.m. + 1200 mg p.m. + Lamotrigine 150/200 mg	VPA 500 mg a.m. + 1200 mg p.m. + Lamotrigine 150/200 mg	3 months off VPA, On Lamotrigine 150 a.m. + 200 mg p.m. and clobazam	5 months on VPA 500 mg p.m. + Lamotrigine 150/200 mg	VPA 500 mg p.m. + Lamotrigine 150 a.m. + 200 mg p.m.

a relationship between duration of treatment and progressive deterioration of sperm parameters, namely morphology, in line with animal studies. This is an under-recognised and infrequently documented adverse effect of VPA therapy which warrants further emphasis. The choice to commence and establish young men on VPA treatment should be made in light of the above evidence and in light of the individual patient's wishes with regards to starting a family. It is important to counsel men on VPA about this potential chronic and progressive adverse effect of VPA, and to consider stopping or switching to an alternate ASM in couples where there is ongoing infertility, particularly if there is an abnormal sperm analysis while taking VPA. Successful pregnancies have been reported following the cessation of VPA therapy, as in our case report.

Ethical statement

This case report was written with the express permission of the patient and his family. There is no identifying information included. It was completed in line with Beaumont Hospital Group ethics requirements.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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