dtbn

DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN

25 1993-2018 TWENTY FIVE YEARS OF INDEPENDENT INFORMATION

YEAR 2018
VOL 26, No 1
www.dtb.navarra.es
@DTB_Navarre.es

VALPROIC ACID AND PREGNANCY
A PROBLEM FOR REFLECTION

This bulletin was prepared jointly with the Basque Country Pharmacotherapeutic Information Bulletin (INFAC) using the Butlletí Groc 2018; 31[1] as a basis. We would like to thank the Fundació Institut Català de Farmacologia and especially its Director, Joan-Ramon Laporte, for their generosity in sharing with us the bibliographic search carried out to publish this bulletin, as well as their own content, which have been offered unselfishly and used as script for this article.

index

Introduction

Valproic acid (Depakine®) was first marketed in Spain in 1970 for the treatment of epilepsy. In 1987, Depakine Crono® was approved for the treatment of bipolar disorder.[1]

In October 2014, following the guidelines of the Pharmacovigilance Risk Assessment Committee (PRAC), the Spanish Medicines and Health Devices Agency (AEMPS) published a safety warning by which the use of valproic acid was restricted in girls, adolescents and women of childbearing age. This warning was issued in response to the growing published evidence that valproic acid increased the incidence of physical developmental and neurodevelopmental disorders (up to 40% of cases) and congenital malformations (up to 10% of cases) in children born to women who were administered valproic acid during pregnancy.[2]

In 2017, in response to pressure from the Association of Parents of Children with the Syndrome Anticonvulsant (www.apesac.org/), PRAC reviewed the use of valproate in pregnancy.[3] This review revealed that the measures adopted in 2014 had not been effective. As a result, PRAC recommended that terms of approval were modified to include new contraindications. Additionally, PRAC recommended that a pregnancy prevention plan was developed. These two recommendations were included in the new safety warning issued in February 2018.[4]

It is estimated that tens of thousands of children and their families have been affected by the teratogenic effects of valproic acid. This situation could have been avoided, as there was evidence published on the risk of its use in pregnancy. Once again, information was not translated into knowledge and appropriate action. This tragedy reminds us of thalidomide, which affected thousands of persons for years due to the late manifestation of some of its adverse effects. All this happened despite pharmacovigilance programs.

The mental health network of Bizkaia (Red de Salud Mental de Bizkaia) warned about the negative effects of valproic acid in pregnancy in its journal of psychopharmacology (Boletín de Psicofarmacología,[5] The Butlletí Groc[1] also devoted a whole issue to this problem.

The purpose of this article is to investigate the factors that led to this situation and identify potential solutions.

When were the risks associated with taking valproic acid during pregnancy known? What is the magnitude of its effects?

For three decades, research has consistently shown that valproic acid is the epilepsy drug with the strongest tetarogenic effect. Its use is associated with a high risk for congenital malformations and cognitive and motor developmental disorders.[1,5]

Numerous studies have been published on the use of valproic acid during pregnancy since the 80s. An official report of the French Medicines Agency documented that, by 2015, a total of 934 papers had been published on this subject in Medline.[1]

In 1979, ten studies had already been published reporting a higher risk for congenital malformations in children exposed to valproic acid during gestation, as compared to other epilepsy drugs. Two systematic reviews published later[6,7] revealed that valproic acid is the epilepsy drug with the highest risk for congenital malformations.

In a review of 59 studies[6] published between 1970 and 2006 that reported congenital malformations in children born to women with epilepsy (65,533 women), the incidence of malformations associated with the use of valproic acid as monotherapy was 10.73% (95%CI: 8.16-13.29). Valproic acid is the epilepsy drug with the highest associated incidence of malformations. The incidence of congenital malformations in the general female population is 2-3%, and 4-5% in subjects exposed to carbamazepine.

Similar results were obtained in a Cochrane systematic review[7] that compared the prevalence of congenital malformations after intrauterine exposure to several epilepsy drugs taken as monotherapy. The same conclusion was drawn: valproic acid is the epilepsy drug entailing the highest risk for congenital malformations: 10.93% (95%CI: 8.91-13.13).

Data on the risk for congenital malformations associated with intrauterine exposure to eight epilepsy drugs in children born between 1999 and 2016 were published in the international EURAP Epilepsy Pregnancy Registry.

The outcomes of 7,355 gestations a year after birth were analyzed. The prevalence of major congenital malformations associated with the use of valproic acid was 10.3%, (95%CI: 8.8-12.0), the highest among all epilepsy drugs included.

Malformations associated with valproic acid include spina bifida, facial dysmorphism, cleft lip and palate, craniosynostosis, cardiac defects, anorectal atresia, limb defects (including polydactyly and bilateral radial aplasia), and other urogenital anomalies (such as hypospadias)[1,2,6]

The first case reports of developmental disorders and autism in children exposed to valproic acid during gestation were published at the end of the 80s. The studies published since 2001 show a high incidence of cognitive and motor developmental disorders (30-40%)[1,2,9,10]

The use of valproic acid during gestation increases the risk for:

- A lower intellectual quotient.
- Impaired language abilities (speaking and understanding).
- Impaired memory.
- Child autism and other autism spectrum disorders.
- Speech and walking delay.
- Greater need for special education support.
- Higher risk for attention deficit disorder and hyperactivity (ADHD).

The stage of pregnancy at which the fetus is at most risk for experiencing tetarogenic effects is unknown. Indeed, the risk may exist through all stages of pregnancy.[2,11]

The risk for congenital malformations and developmental disorders is dose-dependent. However, a threshold dose below which the risk for malformations and disorders disappears has not yet been established.[2,11]

How many children could have suffered its effects?

Considering the incidence of somatic congenital malformations (10%) and motor and cognitive developmental disorders (30-40%), it is estimated that valproic acid may have affected tens of thousands of children.[1]

APESAC estimates that about 41,000 pregnant women used valproic acid in France between 1967 and 2014. Of the 28,800 neonates born alive, 11,500 showed malformations and/or neurological-cognitive development disorders. The UK Organisation for anti-convulsant syndrome (OACS www.oacscharity.org/) estimates that

Information alone does not generate knowledge

It is estimated that tens of thousands of people have been affected in Europe

77,000 children born to mothers who used valproic acid showed malformations or developmental disorders.[1]

In Spain, there is not a registry of children with anti-convulsant syndrome. The Spanish Asociación de Víctimas por el Síndrome del Ácido Valproico estimates that there may be 10,000 children affected in Spain. Children are referred to the Unit of Pediatric Environmental Health of Virgen de la Arrixaca University Hospital in Murcia for diagnosis, which is considered the national reference hospital.

In Navarre, the number of women of childbearing age (14-50 years) on treatment with valproic acid decreased from 492 in 2014 to 454 in 2017 [1].

What initiatives have been launched to minimize exposure of pregnant women to valproic acid?

The increased risk associated with intrauterine exposure to valproic acid as compared to other epilepsy drugs has been known since the 80s. Yet, the 2000 label of Depakine® states: The overall risk for malformation after the administration of valproate during the first trimester of pregnancy is not superior to that of other epilepsy drugs and "valproate seems to prevailingly induce neural tube closure defects: myelomeningocele, spina bifida, malformations in which antenatal diagnosis is possible. The frequency of this effect is 1%".[12]

It is worth noting that, in 2001, the manufacturer (Sanofi) and the European Medicines Agency (EMA) were aware of the risks associated with valproate. The EMA included it in its evaluation reports.[1] However, it was not until 2014 that –in response to pressure from associations of victims– these organizations issued the first safety warning about the use of valproate by women of childbearing age.

(*) Data from the Unit of Pharmaceutical Services of the Spanish Ministry of Health, Consumption and Social Well-Being.

BIPOLAR DISORDER

DÉPAKOTE® + GROSSESSE = INTERDIT

Ne pas utiliser chez les femmes en âge de procréer et sans contraception efficace, ou enceintes.

EPILEPSY

DÉPAKINE® + GROSSESSE = DANGER

Ne pas utiliser chez les filles, adolescentes, femmes en âge de procréer ou enceintes, sauf en cas d'échec des autres traitments.

In 2011, the FDA issued the first safety warning on the potential risk for cognitive developmental disorders associated with intrauterine exposure to valproic acid. The observational study NEAD carried out in USA and UK revealed that 3 year-old children exposed to this acid during pregnancy had lower scores on cognitive tests (Differential Ability Scales, DAS), as compared to children exposed to other epilepsy drugs or non-exposed children. DAS has an average score of 100 (SD=15), and exposed children had a score of 92 (95%CI: 88-97). Safety warnings about these effects were included in the label of valproic-containing drugs for the interest of patients and health professionals.[13]

At the age of 6, children exposed to valproic acid included in the NEAD study had a lower IQ than children exposed to other epilepsy drugs (average DAS score 97 for children exposed to valproic acid as compared to 105-108 for other epilepsy drugs, respectively). Based on these results, the use of valproic acid in pregnant women for the prevention of migraine was included in the contraindications of the drug by the FDA. This led USA authorities to increase the teratogenic category of valproic acid from D to X in its indications for migraine.[14]

In Spain, the AEMPS issued a safety warning in October 2014.[2] In December 2014, following AEMPS requirement, Sanofi sent an information letter to health professionals, pharmacy services, pharmacies and some medical societies[15] warning about these risks. In May 2015, AEMPS modified the labels and package inserts of valproate to include information on "the risk for evolutionary disorders" and congenital anomalies, without providing any information on incidence rates. In June 2015, Sanofi distributed "material for risk minimization" among health professionals and scientific societies.[11] In June 2016, the manufacturer published a patient information sheet.[16] Although the impact of these preventive measures has not been reported, the AEMPS recognized that they were not effective.[1] This may be due to the fact that safety information notices do not reach all health professionals and are not written in a simple and clear language. In addition, information notices always have the same format, whether they report a risk of 30-40% for severe cognitive disorders in children born to women who used valproic acid during pregnancy or report the risk for a rare effect of a restricted-use drug.[1]

The Mental Health Network of the Basque Country, Spain, (Redes de Salud Mental de Osakidetza) persistently warned their professionals about this problem and included AEMPS recommendations in clinical protocols.

In France, pressure from APESAC led to the inclusion of a warning pictogram about the risk of using Depakote® (indicated for manic episodes in bipolar disorder when lithium is contraindicated or poorly tolerated) and Depakine® (indicated for generalized or partial epilepsy) during pregnancy.[17]

In UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) promoted programs to guarantee that all women on treatment with valproate were aware of its associated risks during pregnancy. Yet, in April 2017, the MHRA itself recognized that programs had not been effective. Thus, in a survey conducted in 2016, one out of five women on valproate was not aware of its associated risks.[18] Another survey performed in 2017 revealed that 28% of women had not been informed of the risks associated with valproate.[19] Although prescription rates have progressively decreased in the last years, the measures adopted did not have a significant impact.[18]

In light of the measures implemented in 2014, APESAC achieved in 2017 that PRAC held a public audit for the first time in its history on the safety problems associated with the use of valproate. After an analysis of the situation, PRAC imposed new tough restrictions to its use and launched a pregnancy prevention plan for patients of childbearing age who took valproate. The AEMPS safety warning of February 2018 describes the measures adopted:[4]

Valproic Acid SHOULD NOT be administered to girls and women of childbearing age, except when another therapeutic option is not available and a pregnancy prevention plan is accomplished. This plan includes:

- Performing a pregnancy test before the treatment starts and while the user is on treatment.
- Using effective contraceptive methods during treatment.
- Performing a treatment review at least once a year. During treatment review, women will be asked to sign the risk sheet every year to ensure that she is fully aware of the risks of the treatment.
- Visiting their doctor to consider other therapeutic options, in case the woman is planning to have a baby.
- In case of pregnancy, seeing their doctor immediately.

In pregnant women with bipolar disorder: DO NOT use valproic acid.

In pregnant women with epilepsy: It can ONLY be used when another therapeutic option is not available.

The EMA requested the laboratory to perform a retrospective observational study to determine the potential association between exposure to valproic acid in men and the risk for congenital malformations and developmental disorders –including autism– in their offspring.[20]

How can this have happened if information about valproate's negative effects has been available for a long time?

This happened for numerous reasons:

Although the manufacturer of valproic acid and regulatory agencies have known its effects for decades, they did not inform the public about its associated risks. Also, it has only been recently that they have modified drug labels and package inserts (when evidence on its risks was overwhelming); and they did not warn about the use of valproic acid in pregnancy until as late as 2014. It is striking that, despite public data being available on its associated risks, the EMA has relegated the performance of retrospective observational studies on valproic acid to its manufacturer. This decision is explained by the outsourcing policy adopted by the EMA since 2009, by which it is the manufacturer itself who performs observational studies on their own products. Unfortunately, manufacturers are more interested in protecting their market share than in providing information on the risks associated with their products.[21] On the other hand, through safety notices, responsibility is delegated to health professionals, but they do not have a preventive effect. Safety information cannot be only provided in information notices, as they do not guarantee that recommendations are followed. Surveys should be conducted to assess the level of implementation of official recommendations.

The measures adopted so far have not been effective

The responsibility is of all the involved agents

Pharmacovigilance systems have not incorporated the information provided in intrauterine exposure databases and publications. Also pharmacovigilance systems have not been proactive or warned about the magnitude of the problem.[22]

Health systems have not launched effective information programs for health professionals. These programs should be aimed at informing professionals on the effects of valproic acid so that they limit its use in women of childbearing age to very specific cases where effective contraceptive methods are used. Patients using valproic acid have not been informed on the risks associated with its use; as a result they have not been given the opportunity to make informed decisions.

The lack of coordination between health professionals has resulted in poor follow-up of therapies and dilution of responsibility.

Pharmacovigilance systems –as the editors of BIT– have not considered the relevance of its effects or issued timely safety warnings.

Therefore, the whole system has failed health professionals and patients who use valproic acid, who trusted the system.

In the era of Big Data, we failed to address such a serious problem (for the severity of its effects and the number of persons affected) detected by pharmacoepidemiologic studies. It is evident that this is a flawed system. Effective preventive measures should have been adopted, such as the classification of valproic acid as a medication of special medical control, for example. These measures would have minimized exposure of pregnant women to valproic acid.

What can we do to prevent more children being exposed to valproic acid?

When a safety problem is detected, it is essential that health professionals are informed. This way, they will be aware of the safety problems related to the drugs they prescribe, deliver or administer.[23]

At a national level, AEMPS should be required to include a warning pictogram in the package insert of valproate and incorporate this drug in the classification of drugs subject to special medical control.

In our region, some measures could be adopted, namely:

Basque Health System and Department of Health

Alerting health professionals of their women of child-bearing age who are currently using valproic acid to be booked for a treatment review –especially in patients with bipolar disorder and ensure they use contraceptive methods.

Inserting a safety warning in the prescription system program so that it pops up when a doctor prescribes, modifies or renews a prescription. This warning should inform on restrictions of use of valproic acid in pregnant and childbearing-age women. A prescription support system should be implemented to ensure the fulfillment of the pregnancy prevention plan.

Promoting multidisciplinary coordination by including neurologists, psychiatrists, GPs and primary care nurses, gynecologists, and pediatricians

Professionals

Following AEMPS recommendations of limiting the prescription or renewal of prescriptions of valproic acid to women of childbearing age.

Providing detailed information to patients to ensure they are aware of the risks associated with the use of valproic acid during pregnancy.

Guaranteeing that patients on treatment with valproic acid use effective contraception.

Reviewing the suitability of maintaining treatment with valproic acid, especially in patients with bipolar disorder.

Acknowledgements

We would like to thank Dr. José J. Uriarte, head of the Unit of Clinical Management of the Network of Mental Health of Bizkaia and Montserrat García and Carmelo Aguirre, heads of the Unit of Pharmacovigilance of the Basque Country, for reviewing the manuscript and for their constructive comments and suggestions.

We are also grateful to James M Wright of the University of British Columbia, Vancouver (Canada) for reviewing the text

Diagnosed coded in Primary Care and Mental Health of the 421 women of childbearing age (14-50 years) on treatment with valproic acid in the Basque Health Service.

Epilepsy (ICPC N88): 189
Bipolar disorder or mania (ICPC P73 or ICD10 F30, F31): 92. Of which four also have epilepsy.
Migraine (ICPC N89) without any of the disorders above: 12. Is a non-approved use of valproic acid in Spain, although it is approved in USA.
None of the 132 remaining patients had any of the diagnoses above.

Data from the Population-Based Database of the Navarre Health Service as per 21st May 2018.

References

Date of literature search: May 2018

1. Depakine, el escándalo. No podía callarme. Butlletí Groc. 2018;31(1):1-8. [Accedido el 22/5/2018].

2. Nota Informativa MUH (FV), 16/2014. Ácido valproico: nuevas recomendaciones de uso en niñas y mujeres con capacidad de gestación. AEMPS. [Accedido el 22/5/2018].

3. EMA/144306/2017. New review of valproate use in pregnancy and women of childbearing age. EMA to consider if risks of these medicines require further restrictions of use. [Accedido el 22/5/2018].

4. Nota Informativa MUH (FV), 10/2018. Valproato (Depakine/Depakine crono): programa de prevención de embarazos. AEMP. [Accedido el 10/08/2018].

Continuación de: Nota Informativa MUH (FV), 3/2018. Ácido valproico: nuevas medidas para evitar la exposición durante el embarazo. AEMPS.

5. Boletín de Psicofarmacología. RSMB. 2017, nº26. [Accedido el 22/5/2018].

6. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81:1-13. [Accedido el 22/5/2018].

7. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224. [Accedido el 22/5/2018].

8. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E et al, for the EURAP Study Group. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018. [Accedido el 22/5/2018].

9. Meador K, Baker G, Browning N, Clayton-Smith J, Combs-Cantrell D, Cohen M et al, for the NEAD Study Group. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. N Engl J Med. 2009;360:1597-1605. [Accedido el 22/5/2018].

10. Meador K, Baker G, Browning N, Cohen M, Bromley R, Clayton-Smith J et al, for the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12:244-52. [Accedido el 22/5/2018].

11. Uso de valproato (Depakine®)/valpromida (Depamide®) en mujeres. Información sobre prevención de riesgos autorizada por la Agencia Española de Medicamentos y Productos sanitarios para profesionales (AEMPS). Febrero 2015. [Accedido el 22/5/2018].

12. Ficha técnica de Depakine de septiembre de 2000. (Accedido el 20/4/2018).

13. US FDA Drug Safety Communication: Children born to mothers who took Valproate products while pregnant may have impaired cognitive development. Posted 6/30/2011 [Accedido el 22/5/2018].

14. US FDA Drug Safety Communication: Valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children. Posted 5/6/2013. [Accedido el 22/5/2018].

15. Medicamentos relacionados con valproato (Depakine®, Depakine Crono®, Depamide® y Ácido Valproico GES y Ácido Valproico Genfarma EFG): riesgo de desenlace anormal del embarazo. Comunicación dirigida a profesionales sanitarios. Diciembre 2014. [Accedido el 22/5/2018].

16. Información sobre prevención de riesgos autorizada por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Tarjeta de información al paciente. Mayo 2016. [Accedido el 22/5/2018].

17. ANSM. Renforcement des conditions de prescription et de délivrance des spécialités à base de valproate et dérivés du fait des risques liés à leur utilisation pendant la grossesse. [Accedido el 22/5/2018].

18. Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures. Drug Safety Update. MHRA 2017;10(9). [Accedido el 22/5/2018].

19. Valproate and fetal anti-convulsant syndrome. House of Commons Library 2017. CDP 2017/0186. [Accedido el 22/5/2018].

20. EMA/145600/2018. New measures to avoid valproate exposure in pregnancy. [Accedido el 22/5/2018].

21. Spelsberg A, Prugger C, Doshi P, Ostrowski K, Witte T, Hüsgen D, Keil U. Contribution of industry funded post-marketing studies to drug safety: survey of notifications submitted to regulatory agencies. BMJ 2017;356:j337. [Accedido el 22/5/2018].

22. Laporte JR. Fifty years of pharmacovigilance. Medicines safety and public health. Pharmacoepidemiol Drug Saf. 2016;25:725-732. [Accedido el 22/5/2018].

23. Farmacovigilancia, ¿Quo vadis? Boletín de Farmacovigilancia del País Vasco. 2018;45. [Accedido el 22/5/2018].

Dirección útil: Unidad de Salud Medioambiental Pediátrica del Hospital Universitario Virgen de la Arrixaca en Murcia.

Servicio Navarro de Salud
Osasunbidea

ISSN
1138-1043

COPYRIGHT
NA-1263/1997

INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es