Rev Psiquiatr Salud Ment (Barc.). 2015;8(3):167–188

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental

SPECIAL ARTICLE

The effects of antiepileptic inducers in neuropsychopharmacology, a neglected issue. Part II: Pharmacological issues and further understanding☆

Jose de Leon[a,b,c]

[a] *University of Kentucky Mental Health Research Center at Eastern State Hospital, Lexington, KY, United States*
[b] *Grupo de Investigación en Neurociencias (CTS-549), Instituto de Neurociencias, Universidad de Granada, Granada, Spain*
[c] *Centro de Investigación Biomédica en Red en Salud Mental (CIBERSAM), Hospital Santiago Apóstol, Universidad del País Vasco, Vitoria, Spain*

Received 5 September 2014; accepted 23 October 2014
Available online 20 July 2015

KEYWORDS
Anticonvulsants;
Aryl hydrocarbon receptor;
Constitutive androstane receptor;
Estrogen receptors;
Glucocorticoid receptor;
Pregnane X receptor

Abstract The literature on inducers in epilepsy and bipolar disorder is seriously contaminated by false negative findings. Part II of this comprehensive review on antiepileptic drug (AED) inducers provides clinicians with further educational material about the complexity of interpreting AED drug–drug interactions.

The basic pharmacology of induction is reviewed including the cytochrome P450 (CYP) isoenzymes, the Uridine Diphosphate Glucuronosyltransferases (UGTs), and P-glycoprotein (P-gp). CYP2B6 and CYP3A4 are very sensitive to induction. CYP1A2 is moderately sensitive while CYP2C9 and CYP2C19 are only mildly sensitive. CYP2D6 cannot be induced by medications. Induction of UGT and P-gp are poorly understood. The induction of metabolic enzymes such as CYPs and UGTs, and transporters such as P-gp, implies that the amount of these proteins increases when they are induced; this is almost always explained by increasing synthesis mediated by the so-called nuclear receptors (constitutive androstane, estrogen, glucocorticoid receptors and pregnane X receptors). Although part I provides correction factors for AEDs, extrapolation from an average to an individual patient may be influenced by administration route, absence of metabolic enzyme for genetic reasons, and presence of inhibitors or other inducers. AED pharmacodynamic DDIs may also be important. Six patients with extreme sensitivity to AED inductive effects are described.

☆ Please cite this article as: de Leon J. Efectos de los inductores antiepilépticos en la neuropsicofarmacología: una cuestión ignorada. Parte II: cuestiones farmacológicas y comprensión adicional. Rev Psiquiatr Salud Ment (Barc.). 2015;8:167–188.

E-mail address: jdeleon@uky.edu

PALABRAS CLAVE
Anticonvulsivos;
Receptor de aril hidrocarburos;
Receptor constitutivo de androstano;
Receptores de los estrógenos;
Receptor de los glucocorticoides;
Receptor de pregnano X

Efectos de los inductores antiepilépticos en la neuropsicofarmacología: una cuestión ignorada. Parte II: cuestiones farmacológicas y comprensión adicional

Resumen La literatura sobre los inductores en los casos de epilepsia y trastorno bipolar está contaminada por falsos negativos. Esta segunda parte de una amplia revisión sobre los fármacos antiepilépticos (FAE) aporta más material educativo a los clínicos acerca de la complejidad de interpretar las interacciones farmacológicas.

Se revisa la farmacología básica de la inducción incluyendo los citocromos P450 (CYP), las enzimas de glucuronización (UGT) y la glucoproteína P (P-gp). CYP2B6 y CYP3A4 son muy sensibles a la inducción. CYP1A2 es moderadamente sensible. CYP2C9 y CYP2C19 son solo levemente sensibles. CYP2D6 no puede ser inducida por los fármacos. La inducción de las enzimas metabólicas, CYP o UGT, y los transportadores como la P-gp, se debe a un incremento de la síntesis de estas proteínas mediado por los denominados receptores nucleares (receptores constitutivo de androstano, de los estrógenos, de los glucocorticoides y de pregnano X). Aunque la primera parte de este trabajo describe los factores de corrección para los antiepilépticos inductores, la extrapolación de estos valores para un paciente promedio a un individuo concreto está influenciada por la ruta de administración, la carencia de la enzima metabólica debida a razones genéticas, y la presencia de inhibidores, u otros inductores. También pueden ser importantes las interacciones farmacológicas de los fármacos antiepilépticos al nivel de los mecanismos farmacodinámicos. Se describen 6 pacientes con una sensibilidad extrema a los inductores antiepilépticos.

Introduction

The neuropsychopharmacology literature on drug–drug interactions (DDIs) with drug metabolic inducers is seriously contaminated by false negative findings. Inducers' effects are systematically denied or at least undervalued, and the published literature on antiepileptic drugs (AEDs)[1] and on bipolar disorder[2] systematically de-emphasizes their clinical relevance. This two-part article provides information for clinicians to compensate for this oversight in the literature on AED inducers. Part I introduced the subject of potent (Table 1) and mild inducers (Table 2) and provided clinical recommendations on correcting the effect of inducers through dose modifications of the induced substrates by using correction factors (Table 3).[a] As the available literature for calculating these correction factors is seriously limited, the author acknowledges that it is likely that in 5 years this review article may be obsolete and that the correction factors provided may need to be extensively modified.

Unfortunately, it is a major simplification to think that correction factors can completely resolve clinicians' problems when trying to deal with the complex issue of induction in neuropsychopharmacology. Many of the drug combinations that neurologists and/or psychiatrists find in daily clinical practice are not addressed in Table 3. Part I provides a conservative attempt to reflect the complexity of the issue by describing mild inducers that can also behave as inhibitors (Table 4). Part II is an effort to further educate clinicians about the complex nature of interpreting AED DDIs through the provision of basic pharmacological knowledge to help to improve their ability to interpret complex DDIs.

Although this second part has much more theoretical information than the first part, the author has selected the information according to his experience with the deficiencies of the literature for teaching clinicians how to navigate the turbulent waters of DDI with inducers in neuropsychopharmacology. Using this practical approach, the author presents seven sections that address three issues: basic pharmacology, the true pharmacological complexity of DDI, and the existence of individuals who are unusually sensitive to induction.

The basic pharmacology of induction reflects the increased production of the proteins involved in pharmacokinetic mechanisms. Inducers increase the metabolism of many neuropsychopharmacological drugs metabolized by the Cytochrome P450 (CYP) isoenzymes, the major oxidative enzymes. Inducers sometimes increase the activity of other less well understood metabolic enzymes, the Uridine Diphosphate Glucuronosyltransferases (UGTs), which are the most important conjugative enzymes. Only very recently has it become clear that, besides metabolizing enzymes, another major group of pharmacokinetic proteins called transporters, which usually work in tandem with metabolic enzymes to eliminate xenobiotics from the body, can also be induced. P-glycoprotein (P-gp) is the most important transporter and is briefly described. A new rapidly expanding area in the literature, describing nuclear receptors, is beginning to provide some understanding of how inducers increase the activity of CYPs, UGTs and P-gp.

In summary, basic pharmacology accounts for the first four sections: (1) CYPs, (2) UGTs, (3) P-gp, and (4) nuclear receptors. The fifth and six sections address the second

[a] Tables 1–4 were developed for part I of this article but are included here to facilitate the lecture.