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Regulatory Decisions in a Globalised World

The Domino Effect of Phenylpropanolamine Withdrawal in Latin America

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Abstract

Rapid drug regulatory decisions regarding phenylpropanolamine (PPA)-containing common cold remedies and diet pills were taken in some Latin American countries following a Food and Drug Administration (FDA) decision in the US. This situation is described as one that illustrates the important changes that regulatory decisions are experiencing as a consequence of globalisation.

The evidence for the efficacy of PPA as a nasal decongestant and as an appetite-suppressant is very limited, at least by modern standards. Its potential to increase blood pressure and induce haemorrhagic stroke was described soon after its marketing. Although this poor benefit/risk ratio had been known for more than 20 years, regulatory action was taken in Latin America only after the US FDA withdrew the drug in the US on the basis of the results of a case-control study which added limited new evidence to the already known risk of stroke, but which, on the other hand, had attracted much attention from the media.

Drug regulatory decisions regarding marketing authorisations for new chemical entities and drug withdrawals because of adverse effects are experiencing important changes as a consequence of globalisation. Four processes have contributed to shape the new situation in the field of pharmaceuticals: mergers of pharmaceutical firms; the so-called harmonisation of regulatory procedures; the World Trade Organisation Trade-Related Aspects of Intellectual Property Rights Agreements (TRIPs); and health sector reform and privatisation.[1]

Recently, several drugs (e.g. grepafloxacin and trovafloxacin,[2] tolcapone[3]) have been withdrawn soon after their launch because of severe type B adverse effects (i.e. hypersensitivity-based reactions following the classification of Rawlins and Thompson[4]). The case of phenylpropanolamine (PPA) withdrawal and other restrictive regulatory decisions in several countries is different from these, because the drug had been marketed for more than 30 years, the adverse effect leading to withdrawal was of type A (i.e. due to augmented effects[4]) and had been well known since the 1970s,

and its patterns of use (in terms of dose, indications, route of administration, and associated drugs) varied widely from one country to another.

1. Phenylpropanolamine (PPA) Withdrawal Timetable: Speeding Up Market Regulation

On October 14, 2000, a short message was posted in the discussion list *e-drug*[5] by a member of the US Public Citizen's Health Research Group (PCHRG). It showed a short title in the subject line: 'Phenylpropanolamine', and it asked for information on the availability of the drug in non-US countries. On October 19, the same message was translated and posted in the discussion list *e-farmacos*, a Spanish and Portuguese discussion list with the same aims as *e-drug*.[6] Several messages answering the request were posted in the following days; all of them reported on availability and prescription or over-the-counter (OTC) status of PPA in Canada, Iceland, Italy, India, Norway, Pakistan, Thailand, South Africa, and Spain.

On October 17 and 19, a reader of *e-drug* and the PCHRG informed that the latter had testified about the safety of PPA before the US Food and Drug Administration's (FDA's) Non Prescription Drugs Advisory Committee, and had petitioned the FDA to immediately remove this drug from OTC status in the US because of an increased risk of haemorrhagic stroke. The author was a correspondent in the discussion, who urged colleagues in other countries to use the material prepared by PCHRG, and petition their regulatory authorities to have the drug removed from all OTC products.

On October 20, a CNN report was circulated through *e-drug*, and translated to Spanish and circulated through *e-farmacos*. The conclusions of the FDA Advisory Committee regarding PPA were included, and the findings of an as then not yet published Yale University study, the Hemorrhagic Stroke Project, were given. This was a case-control study where a risk of haemorrhagic stroke associated with PPA use was found in women who had taken the drug as an appetite suppressant (see section 2). This message also stated that reports linking PPA to haemorrhagic stroke had begun to surface more than 20 years before,[7,8] that PPA was an active ingredient both in OTC diet products and cold remedies, and that the results of this study had been subject to early release through the *New England Journal of Medicine* website, and that they would be published in the printed edition two months later (on December 21[9]). Comments on this study and on the FDA decision were also briefly reported on October 28 in the News section of another widely circulated journal, the *British Medical Journal*.[10]

On November 6, the FDA decision to ban all PPA-containing products was made public; details were given through the FDA website (*http://www.fda.gov)*. From that moment on, the regulatory authorities of several non-US countries started to react to growing pressure from the media. As a response to a request from the Health Ministry of Peru posted in *e-farmacos* on November 20, several subscribers from Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, Mexico, Nicaragua, Peru and Uruguay commented on the regulatory decisions in their respective countries. Various restrictive decisions were taken during the first days of November 2000 (see table I). In some European countries the status of at least some products containing PPA was also reviewed. In the UK, PPA had only been marketed as an ingredient of OTC cold remedies, generally at a lower maximum daily dose (100mg) than similar products in the US,[11] and the regulatory measure consisted in simply strengthening patient information by more prominently warning on contraindications.

2. PPA: From Pharmacological Guess to Case-Control Evidence

PPA (d,l-norephedrine) is a sympathomimetic amine with α-adrenergic agonist activity. Other α-adrenergic agonists are phenylephrine, ephedrine and pseudoephedrine, and are common ingredients

Table I. Regulatory decisions regarding phenylpropanolamine (PPA) marketing taken in several Latin American countries[5]

Country	*e-farmacos* message date	Regulatory decision reported	Not to be sold after
Mexico	November 15 2000	Withdrawn	Unknown
Dominican Republic	November 20 2000	Withdrawn	December 5 2000
Costa Rica	November 20 2000	Withdrawn	December 1 2000
Nicaragua	November 21 2000	Withdrawn	December 15 2000
Argentina	November 21 2000	Expecting expert panel decision	
Brazil	November 22 2000	Withdrawn	December 8 2000
Colombia	November 22 2000	Withdrawn	April 6 2001
Uruguay	November 22 2000	Expecting expert panel decision	
Peru	November 22 2000	Excluded from OTC status. Diet pills containing PPA withdrawn. Prescription of dosages <100mg allowed	November 21 2000
Argentina	November 23 2000	Withdrawn	February 28 2001

OTC = over-the-counter.

of OTC cold remedies and nasal decongestants.[12] PPA has vasoconstrictor and anorectic effects, and it has hence been used as a nasal decongestant and, at higher doses, as an appetite-suppressant since the late 1970s. Its pharmacological similarity with amphetamine explains the amphetamine-like adverse effects of PPA, including hypertension. In fact, the first case reports describing young patients with raised blood pressure were published soon after its marketing.[13,14] Cerebrovascular adverse effects associated with its use were reported soon afterwards.[7,8] The series started with two cases of right-sided hemiparesis in two young men who had been taking PPA-containing diet pills.[7] In 1984, a study was published on the experience with PPA gathered in an automated database; no association was found between the use of PPA and cerebral haemorrhage,[15] but exposure and diagnostic biases inherent to the method (information on the use of OTC products in the database is unreliable), as well as lack of data from hospitalisation outside the study area are obvious methodological limitations which could explain why no association was found.[16] In 1990, a review series of 142 patients was published; it included 24 cases of intracranial haemorrhage, eight of seizures, and eight of death (most due to stroke) associated with the use of PPA.[17]

The study which prompted recent FDA regulatory action, the Hemorrhagic Stroke Project, was conducted in 43 US hospitals and included 702 patients aged 18 to 49 years enrolled between December 1994 and July 1999.[9] It had been conducted in response to the FDA's concern about the safety of PPA.[17] An association was found between the use of diet pills containing PPA and haemorrhagic stroke. However, the study had serious limitations. First, the association was found in women, but not in men (there were no men reporting the use of PPA as an appetite suppressant). Second, the confidence intervals of the relative risk were very wide (odds ratio = 16.6; 95% confidence intervals 1.5 to 182.2), based on only six exposed cases (1.6%) and one exposed control (0.1%). Third, no association was found with the use of oral anticoagulants (0.3% of cases and 0.4% of controls exposed). Fourth, similarly, no association was found with the use of other α-adrenergic agonists which, similarly to PPA, are common ingredients of cough and cold remedies (0.3% of cases and 8.4% of controls exposed). Fifth, unexpected and unexplained associations were found with exposure to caffeine-containing agents (7.0% of cases and 2.9% of controls, $p < 0.01$) and with exposure to nicotine-containing agents (1.3% of cases and 0.1% of controls, $p < 0.01$). This association could reflect bias (e.g. by smoking status).

3. Globalised Decisions – Who Stirs Up Trouble?

The sequence of events described with PPA reminds us of a sort of domino effect started by the announcement of the main results of the Hemorrhagic Stroke Project[9] and the subsequent decision taken by the FDA. In less than one month, drug regulatory authorities from the main Latin American countries (and markets) withdrew the drug or implemented similar restrictive actions with an unprecedented speed.

The PPA saga was the result of an unfortunate and long standing sequence of events and actions contravening basic principles of drug regulation (i.e. regular review of the benefit-risk ratio in each one of the approved indications, based on evidence on efficacy, safety, convenience and cost) and promotion of rational drug use.

With regard to efficacy, PPA is an old drug which was first marketed for parenteral maintenance of blood pressure, subsequently as a nasal decongestant, and lately as an anorectic agent.[17] However, the clinical evidence in support of its efficacy in some of these indications is limited[18] and would probably be considered as unacceptable by today's regulatory standards.

With regard to safety, the actions and adverse effects of α-adrenergic stimulants are compatible with pressor and amphetamine-like adverse effects. Reports on these 'theoretical' adverse events appeared as more or less isolated warnings more than 20 years before the present regulatory actions took place.[13,14,17] The case-control study did not add new evidence about these risks, mainly because of the uncertainty of the magnitude of the risk and lack of consistency in its results. On the other hand, estimating the risk of an adverse effect associated with a particular drug is useful for benefit/risk evaluation, but it has little or no relevance when the efficacy of the drug in question has not been demonstrated.

In the case of PPA, the decisions taken by drug regulatory authorities had additional implications, as they had been taken up by a number of countries apparently following a globalised pattern. It seems clear that when the safety of drugs with doubtful efficacy is questioned, a regulatory action should be taken. What is most interesting about the PPA story is that both premises were fulfilled, but the intervention of the regulatory authorities only took place: (i) when the results of a case-control study were highlighted by the media, even before its publication; and (ii) following some reactions from consumer associations and the media. An additional noteworthy fact is that, contrary to other drug withdrawals, the regulatory decisions did not follow a developed versus less developed countries pattern, as has happened with some drugs which although withdrawn from European and US markets because of well-known risk, continued to be sold in less-developed countries.

New communication technologies allow wide and rapid circulation of drug information. In addition, there is a growing trend to support regulatory decisions with so-called evidence- based information. However, common sense and clinical perspective must lie behind apparently evidence-based regulatory decisions.

It has been suggested that, in the US, PPA may have caused between 200 and 400 cases of haemorrhagic stroke per year.[19] The worst part of this story is that nobody knows how many people had been victims of an adverse effect that could had been easily prevented if rational drug regulatory principles had been applied.

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