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Risk Management Strategies in the Physicians' Desk Reference Product Labels for Pregnancy Category X Drugs

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Abstract

Background: Drugs that carry a concern for teratogenicity are often classified as pregnancy category X in the drug label and contraindicated for use during pregnancy. Many drug labels can be found in the Physicians' Desk Reference (PDR), a widely used source of drug information by American clinicians and patients.

Objective: To review product labelling in the electronic PDR for the pregnancy category X products for pregnancy prevention risk management components in labelling.

Methods: The electronic version of the 2001 and 2002 PDR was searched for 'pregnancy category X' products using the full text search feature. All product labels identified were retrieved and reviewed for trade name, generic name, manufacturer and indication. Product labels were manually searched for any pregnancy prevention risk management strategies included in labelling. Those labels that had specific pregnancy prevention risk management strategies were further evaluated.

Results: One hundred and seventeen pregnancy category X products were obtained from 2249 products searched in the 2001 PDR database and 124 pregnancy category X products were obtained from the 2150 products in the 2002 PDR database. All pregnancy category X products identified were drug products. The label/package insert for each drug was reviewed to identify risk management strategies for pregnancy prevention. The majority of the labels include as the sole risk management strategy either a black box warning and/or a contraindication for use in women who are or may become pregnant. Only 13 drugs contained specific pregnancy prevention risk management strategies in the label directing the clinician and/or patient, e.g. frequency of pregnancy testing, number and type of contraception methods. Two drugs, bexarotene capsules and gel, were only included in the 2001 PDR. Three drugs, isotretinoin, acitretin, and thalidomide, have formal pregnancy prevention risk management programmes.

Conclusion: This study demonstrates the varied risk management approaches in labelling for pregnancy prevention for pregnancy category X drugs. There is a need for consistency in the classification of pregnancy category X products and the pregnancy prevention risk management strategies utilised in the labelling for them.

Background

The US Food and Drug Administration (FDA) implemented a classification system for drug use in pregnancy in 1980 whereby all pharmaceuticals were to be classified into one of five pregnancy categories: A, B, C, D, X. The labelling of prescription drugs had to include all available information about the teratogenic and non-teratogenic effects of a drug. The source of the risk ascertainment determines the pregnancy category designation (table I). The system was intended to indicate the potential for a drug to cause birth defects[1] and to provide information to physicians and patients regarding risk of teratogenic outcome following exposure during pregnancy. Drugs that carry a concern for teratogenicity are often classified as pregnancy category X and are contraindicated for use during pregnancy. Other classification systems for teratogenic risk exist, including the Swedish Catalogue of Approved Drugs (FASS) and the Australian Drug Evaluation Committee (ADEC). In addition, the large electronic searchable databases, REPROTOX System, TERIS, Shepard's, available via Micromedex provide useful teratogenic risk information.

In the US, there are 60 million women of reproductive age (15 to 44 years) and approximately 10% of women become pregnant annually. Over 9 million of these women have chronic medical conditions that require treatment with prescription medication. Most women and clinicians would want to avoid exposure to teratogenic drugs in those women who are intending to or inadvertently become pregnant.

Table I. US Food and Drug Administration pregnancy labelling categories

Pregnancy category	Category description
A	No adverse effects in humans
B	No effect in humans with adverse effects in animals OR no effects in animals without human data
C	Adverse effects in animals without human data OR no data available for animals or humans
D	Adverse effects demonstrated in humans OR adverse effects in animals with strong mechanistic expectation of effects in humans
X	Adverse effects in humans or animals without indication for use during pregnancy

During pregnancy in the US, the average number of medical products (excluding vitamins, iron, and folic acid) prescribed to a woman is three, increasing to five with increasing maternal age.[2] In a survey of the French Health Insurance Service of drug prescribing during pregnancy, 99% of women received a prescription for at least one drug during pregnancy, with a mean of 13.6 medications per woman, and 1.6% of women received one or more prescriptions for pregnancy category X drugs.[3] According to the Swedish pregnancy classification system, a high proportion (over 35%) of women were exposed to one or more drugs in high risk categories during pregnancy.[4]

The Physicians' Desk Reference (PDR) is a widely used source of drug information used by American clinicians and patients. The PDR is a collection of package inserts or labels and contains written and pictorial information that is provided and paid for by pharmaceutical manufacturers. The majority of US prescribers rely on the PDR as their source of drug information.[5,6] The PDR is well indexed, easy to use, free to a large number of users and is perceived as government-approved information about drugs. The PDR is a compilation of package inserts that have been evaluated by the FDA; however, pharmaceutical companies must pay a fee to have inserts published in the PDR. Therefore, not all approved products are included in the PDR. Other shortcomings of the PDR include inadequate dosage information and guidelines including dose adjustments for special populations, unfocused adverse effect information, and outdated information.[5]

This study reviewed product labelling in the electronic version of the PDR for pregnancy category X products and searched for pregnancy prevention risk management components in labelling for these products. The study was undertaken to understand what risk management tools are being utilised in product labelling to prevent or minimise

Table II. Pregnancy categories in Physicians' Desk Reference (PDR)[a]

Pregnancy category	2001 PDR (no. of products = 2249)	2002 PDR (no. of products = 2150)
A	5	7
B	291	296
C	821	802
D	99	81
X	117	124
None listed	916	840

a Electronic version.

pregnancy occurrence. The pregnancy category X drugs were selected for investigation because they are contraindicated for use during pregnancy and therefore may contain the most information regarding risk management tools to prevent pregnancy.

Methods

A search was performed on the electronic version of the 2001 and 2002 PDR[7] using the full text search feature. The search terms used were: 'pregnancy category A', 'pregnancy category B', 'pregnancy category C', 'pregnancy category D', and 'pregnancy category X'. All product labels identified with the pregnancy category X search were manually retrieved from the same database and reviewed for tradename, generic name, manufacturer, and indication. All products were initially grouped by indication and pharmaceutical class. Product labels were manually searched for any pregnancy prevention risk management strategies included in labelling. Those labels that had specific pregnancy prevention risk management strategies, were further evaluated. All components of the risk management strategies (i.e., frequency of pregnancy testing, number and type of contraception methods, restricted distribution, supply limitations, 'black box' warning, pregnancy registry information, medication guide, and informed consent) were identified and entered into an Excel® spreadsheet by the primary author for analysis and comparison by all authors.

Results

The results of searches of the electronic version of the 2001 and 2002 PDR performed on November 16, 2001 and July 2, 2002, respectively, are found in table II. Of those products with a pregnancy category designation, over 60% are pregnancy category C products; however, approximately 40% of products in the PDR have no pregnancy category designation. A search of the 2001 PDR revealed a total of 117 pregnancy category X products from the 2249 products listed, and a search of the 2002 PDR gave a total of 124 pregnancy category X products from the 2150 products listed. All identified pregnancy category X products were drug products. Approximately two-thirds of all pregnancy category X drugs are classified as such because they are not intended for use during pregnancy and have the following indications for use: drugs for male only indications, female contraception, postmenopausal hormone replacement therapy, infertility treatment, and other gynecologic indications (table III). The remaining

Table III. US Food and Drug Administration pregnancy category X drugs

	2001 PDR (n = 117)	2002 PDR (n = 124)
Labelled indications		
Male use only	11	14
Contraception	28	32
Postmenopausal hormone therapy	21	21
Fertility	9	10
Miscellaneous gynaecological	7	6
Total	**76 (67%)**	**83 (67%)**
Pharmaceutical class		
Androgens/hormonal	9	8
Antimetabolites	3	4
Antiviral	3	3
Benzodiazepines	2	2
Ergotamines	4	2
HMG-CoA reductase inhibitors	7	9
Retinoids	6	4
Other	7	9
Total	**41 (33%)**	**41 (33%)**

PDR = Physicians' Desk Reference.

Table IV. Labelling recommendations for pregnancy testing

Drug (tradename)	Before treatment	Continued testing	Sensitivity of test (at least 50 mIU/ml)
Isotretinoin (Accutane®)	✓(2 negative tests)	✓(monthly)	✓
Leflunomide (Arava®)	✓(before)		
Diclofenac + misoprostol (Arthrotec®)	✓(within 2 weeks)		
Misoprostol (Cytotec®)	✓(within 2 weeks)		
Interferon-α-2b (Intron A®)			
Ribavirin and interferon-α-2b (Rebetron Combination Therapy®)	✓(immediately prior)		
Acitretin (Soriatane®)	✓(within 1 week)	✓(on a regular basis)	✓
Bexarotene (Targretin Capsules®)	✓(within 1 week)	✓(monthly)	✓
Bexarotene (Targretin Gel®)	✓(within 1 week)	✓(monthly)	✓
Tazarotene (Tazorac Gel®)	✓(within 2 weeks)		✓
Thalidomide (Thalomid®)	✓(within 24 hours)	✓(weekly for the first month, then monthly)	✓
Ribavirin (Virazole®)			
Goserelin acetate implant (Zoladex®)	✓(prior to)		

✓= information present in the product label.

one-third of the pregnancy category X drugs have the potential for use during pregnancy and include the following pharmaceutical classes: androgens and other hormonal products, antimetabolites, antiviral products, benzodiazepines, ergots, HMG CoA reductase inhibitors (or statins), retinoids/psoralens, and others (table IV).

Approximately 80% of the labels for pregnancy category X drugs included a contraindication for use in women in general (i.e. indicated for use in males only) or in women who are or may become pregnant included as the sole risk management strategy. A black box warning, the highest level of product warning found at the top of labelling, was found in the remaining 20% of product labels. All labels with a black box warning also contained a contraindication for women who are or may become pregnant. Only 13 drug labels (11% of total pregnancy category X products) contained pregnancy prevention risk management strategies in product labelling beyond black box warnings. Specific pregnancy prevention risk management strategies identified include: pregnancy testing, contraception, restricted distribution, dispensing a limited drug supply, black box warning, company-sponsored pregnancy registry, medication guide, and an informed consent document.

Pregnancy testing is recommended before initiating therapy for 11 pregnancy category X drugs (table V). The recommendations range from a negative pregnancy test within 2 weeks of starting therapy to within 24 hours of starting therapy. Four drug labels (isotretinoin, [Accutane®],[1] bexarotene [Targretin® Capsules and Gel], and thalidomide [Thalomid®]) recommend the frequency of continued pregnancy testing and the label for acitretin (Soriatane®) recommends that pregnancy testing be repeated on a regular basis. Labels for six drugs provide information regarding the sensitivity of pregnancy testing that should be performed, e.g. sensitivity of at least 50 mIU/ml. Five recommend starting therapy on the second or third day of menses, while tazarotene (Tazorac®) is recommended to begin therapy during a normal menstrual period.

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

Some form of contraceptive therapy information is provided for approximately half of the pregnancy category X drugs with risk management programs (table VI). Five drug labels provide instructions on when to start contraceptive therapy in relation to starting the pregnancy category X drug, e.g. effective contraception must be used for at least 1 month before beginning therapy. Seven drug labels provide information for the length of time that a woman should continue contraception after stopping the pregnancy category X drug, as determined by the half-life of the drug or metabolites. In addition, six drugs recommend that two forms of contraception be used; however, only the labelling for bexarotene capsules recommends that one of the two reliable forms of contraception should be non-hormonal because the drug is metabolised via cytochrome 450 (CYP) 3A4. Information on the other risk management strategies can be found in table V.

Three drugs, isotretinoin, acitretin, and thalidomide have formal pregnancy prevention risk management programmes. The 'System to Manage Accutane-Related Teratogenicity' (SMART™) was implemented in January 2002 for isotretinoin. The 'Pregnancy Prevention Program for Soriatane®' and 'System for Thalidomide Education and Prescribing Safety' (STEP™) programmes were instituted at the time of drug approval in the US. Programmes that provide for restricted distribution of drug products are those through which drug is provided only to registered care providers, pharmacies, or patients. Of the drugs that carry labelling as pregnancy category X, only isotretinoin and thalidomide are subject to a restricted distribution programme. The programmes for these two products are somewhat different but in both cases the teratogenicity of the product is the reason for the programme. The new SMART™ programme for isotretinoin restricts prescription writing to those physicians who have voluntarily enrolled in the SMART™ programme and who use the requisite prescription materials. Thalidomide is available to patients only through enrolment in the STEPS™ programme. In order to receive thalidomide, the prescriber, pharmacy and patient must all be enrolled in the STEPS™ programme. A 1-month supply of drug is recommended for four products, isotretinoin, bexarotene capsules and gel, and thalidomide. A limited supply is also recommended for acitretin capsules; however, the amount is not specified. A black box warning in the label was found in nine of the pregnancy category X drugs, all located at the top of the product

Table V. Labelling recommendations for contraception

	When to start contraception (1 month before)	How long to continue contraception after stopping drug	Two forms of contraception required?
Isotretinoin (Accutane®)	✓	✓(1 month)	✓
Leflunomide (Arava®)			
Diclofenac + misoprostol (Arthrotec®)			
Misoprostol (Cytotec®)			
Interferon-α-2b (Intron A®)			
Ribavirin and interferon-α-2b (Rebetron Combination Therapy®)		✓(6 months)	✓
Acitretin (Soriatane®)	✓	✓(3 years)	✓
Bexarotene (Targretin Capsules®)	✓	✓(1month)	✓
Bexarotene (Targretin Gel®)	✓	✓(1 month)	✓
Tazarotene (Tazorac Gel®)			
Thalidomide (Thalomid®)	✓	✓(1 month)	✓
Ribavirin (Virazole®)			
Goserelin acetate implant (Zoladex®)		✓(12 weeks)	

✓= information present in the product label.

Table VI. Other risk management labelling recommendations

	Restricted distribution	Limited supply	Black box warning	Pregnancy registry	Medication guide	Informed consent
Isotretinoin (Accutane®)	✓(voluntary)	✓(1 month)	✓	✓	✓	✓
Leflunomide (Arava®)			✓	✓		
Diclofenac + misoprostol (Arthrotec®)			✓			
Misoprostol (Cytotec®)			✓			
Interferon-α-2b (Intron A®)						
Ribavirin and interferon-α-2b (Rebetron Combination Therapy®)			✓	✓	✓	
Acitretin (Soriatane®)		✓(not specified)	✓			✓
Bexarotene (Targretin Capsules®)		✓(1 month)	✓			
Bexarotene (Targretin Gel®)		✓(1 month)				
Tazarotene (Tazorac Gel®)						
Thalidomide (Thalomid®)	✓	✓(1 month)	✓	✓		✓
Ribavirin (Virazole®)			✓			
Goserelin acetate implant (Zoladex®)						

✓= information present in the product label.

label (table V). In addition to a black box warning at the top of the label, acitretin has a black box in the warnings section of the product label. A company-sponsored pregnancy registry with a toll free telephone number to report pregnancy exposures was provided for four products (isotretinoin, leflunomide [Arava®], ribavirin/interferon-α-2b [Rebetron Combination Therapy®], and thalidomide). A medication guide is required with dispensing only isotretinoin and ribavirin/interferon-α-2b. Informed consent documents are enclosed in the label for only three drugs (isotretinoin, acitretin and thalidomide).

Discussion

Drugs given during pregnancy can potentially adversely affect the development of the fetus. The overall incidence of major malformations in the general population has been estimated at 1 to 5%.[8] The aetiology of most congenital malformations remains uncertain, although most authors agree that approximately 20% are caused by genetic factors and chromosomal abnormalities, and estimate that 10% are caused by environmental factors such as maternal conditions and infections, chemicals and drugs. During the first trimester (specifically the second and third months of gestation), typically designated as the period of organogenesis, exposure to various substances can produce congenital malformations or teratogenicity. Exposure during the second and third trimesters, although not usually associated with major malformations, can affect the growth and functional development of the fetus.[9] In most cases, the percentage of infants born with a malformation is usually quite low even when the mother has received the medication during the sensitive period of organogenesis. However, the perception of teratogenic risk related to medications used in pregnancy is much higher than the true risk.[10,11]

In this study we examined the product labels for the pregnancy category X products to identify the risk management strategies utilised to minimise pregnancy occurrence with the use of these products. The range of risk management strategies for the pregnancy category X products is quite broad, without consistency or uniformity. Although not applying the exact language of the pregnancy category X classification, over half the products currently labelled as pregnancy category X are so simply because they are not intended for use during pregnancy, e.g. treatment for male only indications, female contraception, postmenopausal hormone replacement, and infertility. The class label

used for the contraceptive products, for example, clearly states that 'extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy'. Approximately 40% of product labels had no pregnancy category, which is misleading since some generic and over-the-counter drug products contain little more than the drug name and product description in the label. Older products that were approved prior to the implementation of the pregnancy category classification system also have no pregnancy category designation.

At the FDA, risk management is a responsibility that is taken very seriously. The FDA has published proposed regulations that would change the format of prescription drug and biologic labelling to make it more useful for prescribers and healthcare practitioners.[12] It is hoped that these changes will make the product label a more useful resource for prescribers and patients. In addition, an extensive effort has been undertaken by the FDA's Pregnancy Labeling Task Force to revise the current pregnancy category system.[13] The goal is to develop a more clinically useful tool that will assist practitioners and patients in making informed decisions regarding the use of pharmaceutical products in pregnancy. The new labelling proposal anticipates using human data from retrospective and prospective epidemiological studies and has been referred to as a philosophical departure for the FDA.[14] Although the generally accepted gold standard for labelling, controlled clinical trials with pregnant women are scarce, waiting until these data are available would make prescribing for pregnant women even more challenging.

Conclusion

Drugs that carry a concern for teratogenicity are often classified as pregnancy category X and contraindicated for use during pregnancy. This study demonstrates varied pregnancy prevention risk management approaches in labelling for pregnancy category X drugs. The implementation of risk management strategies should have well defined programmatic goals with which to monitor the success or failure of such strategies. Since the purpose of this study was not to evaluate the effectiveness of the various pregnancy prevention risk management strategies no specific recommendations can be made regarding appropriate strategies. This type of epidemiological study, however, would be useful to assist with the development of future risk management programmes. There is a need for consistency in the classification of pregnancy category X drugs and it is hoped that the revision of the current FDA pregnancy category system will address this.

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