EDITORIAL

Classifying drugs in pregnancy

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The thalidomide tragedy changed forever the way in which drug exposures during pregnancy were perceived by patients and their healthcare providers. As a result, in 1963 the Government established the Australian Drug Evaluation Committee to advise on the safety of new drugs being introduced into Australia and to monitor and evaluate potential adverse effects of drugs already in use. The Committee published an Australian categorisation of the risk of drugs in pregnancy (A, B1, B2, B3, C, D, X) (see Box)[1] and the first 'Medicines in pregnancy' booklet in 1989. Because the letter categorisation appears so simple and easy to find in prescribing guides, it is probably the most widely used first-line information about medicines in pregnancy.

Because most women use at least one drug during their pregnancy (average range 1.2–3.2), practitioners will be faced with questions about the safety or otherwise of drugs during pregnancy or breastfeeding.[2,3] It is important to remember that there is a background risk of 3–5% for all couples to have a baby with a major birth defect. Any risks associated with medicine exposures therefore need to be expressed in relation to this background risk – in other words, is the risk increased over the background risk.

To decide if a drug is safe during pregnancy, most doctors (and dispensing pharmacists) depend on the information found in sources such as the Australian Medicines Handbook and medical databases. This information essentially consists of the Australian Drug Evaluation Committee categorisation and the company product information, in which pregnancy and lactation are almost universally included as special precautions or contraindications.

The biggest problem is the alphabetical nature of the A–X categorisation. It implies (incorrectly) that there is a hierarchy of risk with category C being 'worse' than category B. Unfortunately the apparent simplicity of the categories means that clinicians tend to use it as a gold standard rather than as a guide. This can result in misinterpretation of risk.

The categories also cannot provide clinical context to the risks and do not differentiate between use of medicines for more or less significant conditions – for example, a woman who takes gabapentin (category B1) to treat 'restless legs' syndrome as opposed to someone taking gabapentin to treat a seizure disorder. The time pressures of busy practice coupled with the relative accessibility of the categories mean that practitioners may not consider the complexities involved in balancing the harms and benefits of using a particular drug for a specified indication at a certain stage in pregnancy.

It is reasonable to assume that drugs within the same category carry a similar risk, but this is not true. For example, valproate and paroxetine are both category D, but valproate is associated with a significantly increased risk of birth defects and neurodevelopmental sequelae, while the main concern about paroxetine is a slightly increased risk (in some studies) of heart defects.

The categories also do not consider the stage of pregnancy. For example, tetracyclines cause tooth discoloration only after 14 weeks of pregnancy so being categorised as D is misleading and will cause unnecessary worry for a first-trimester exposure.

Rarely do the categories take dose or route of administration into account. A good example of dose differences is fluconazole (category D). A single dose of 150 mg is not associated with an increased risk of defects, as compared with high-dose intravenous therapy for systemic fungal infections which is associated with an increased risk of craniofacial and skeletal malformations. Topical or inhaled exposures are generally less concerning than oral or parenteral ones. There is less systemic absorption and lower maternal serum concentrations so transplacental passage and risk to the embryo is negligible.

The categories are also not very useful for new drugs as they are assigned before market release and are

From the Editor

It is now 50 years since the Australian Drug Evaluation Committee was established following the discovery that thalidomide had caused birth defects. Thalidomide was used to manage morning sickness, so there is concern about treating nausea and vomiting in pregnancy. Tricia Taylor tells us about the current guidelines, and Debra Kennedy reviews how the harms of drugs in pregnancy are classified.

Antenatal assessments have advanced since 1963 and Jon Hyett discusses the developments in screening for Down syndrome.

Advances in genetics have led to a better understanding of drug metabolism. Ben Snyder explains why this is important for codeine in his article on the pharmacology of opioids.

While technological advances can result in better treatment, the benefits will be lost if the drugs are taken inappropriately. Rohan Elliott evaluates the evidence for using dose administration aids. This article will be the first subject for *Australian Prescriber's* new continuing professional development activities for pharmacists.

Box **The Australian categories for prescribing medicines in pregnancy** [1]

Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

based only on animal reproductive studies, not human data, due to ethical constraints. Categories are rarely changed despite new, often reassuring, evidence because of a reluctance to advocate the safety of drugs in pregnancy.

Some women may self-medicate with complementary products during pregnancy because they are perceived as natural and therefore safer. There are usually even less safety and efficacy data for these products and the pregnancy categories do not cover them. The pregnancy classifications categorisation also does not apply to breastfeeding, although this is often misunderstood.

Generally, advice given to women by healthcare providers about medicines in pregnancy is cautious and non-evidence-based. This is often compounded by incorrect and potentially frightening information from the internet and other lay sources. Some women even consider terminating otherwise wanted pregnancies because of perceived safety concerns.

Unfortunately, misleading advice based on the Australian Drug Evaluation Committee categorisations can cause significant consequences for both mother and baby. Some women stop the drugs they need because of safety concerns, for example regular asthma medications.[4] They put themselves and their baby at risk of untreated illness which is often higher than the potential risks of the drug.

Other women are switched from a drug which has been beneficial, to a drug which has unknown efficacy (in that particular woman) because of misunderstood grounds of fetal safety. An example of this is switching treatment for depression from citalopram, which is category C, to moclobemide, which is category B3.[5]

Having a discussion with a pregnant woman about the harms versus the benefits of a particular treatment is important. For example, nicotine replacement therapy is classified as pregnancy category D. Nevertheless, it is probably safer than continuing to smoke and may

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be helpful in women who find it hard to stop smoking during pregnancy.

The US Food and Drug Administration has been considering removing the letter categorisations and radically revising the product information in pregnancy.[6] This has proven to be extremely time consuming and has not yet been implemented despite years of discussion and planning.

In Australia, thought should be given to improving product information. More narrative style information of fetal risks in the context of background risk could be included, as well as what data the risks are based on, such as animal or human studies. Information about drugs in breastfeeding along the lines of LactMed[7] monographs could also be included in the product information and would help to inform healthcare providers and women about exposures during pregnancy and breastfeeding.

Sound evidence-based advice regarding pregnancy exposures is currently available to both healthcare professionals and consumers through obstetric drug information services located in most Australian states accessed via the Therapeutics Goods Administration* and through databases like REPROTOX† and The Teratogen Information System‡.

Conflict of interest: none declared

* www.tga.gov.au/hp/medicines-pregnancy-odis.htm (see also the table on page 44)

† http://reprotox.org

‡ http://depts.washington.edu/terisweb/teris

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Letters to the Editor

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Topical corticosteroids

Editor, – I enjoyed the article 'Rational use of topical corticosteroids' (Aust Prescr 2013;36:158-61). I did, however, find the sentence 'Topical treatment in children should be used with extreme caution' surprising. In general, topical corticosteroid treatment in children is remarkably safe – so safe that some products are available without any prescription. Possibly the authors were referring to more potent corticosteroids such as mometasone or methylprednisolone. Even then, 'extreme' caution is unnecessary given their excellent safety record, even when substantially misused. The article was otherwise excellent and appreciated.

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Pablo Férnandez-Peñas, one of the authors of the article, comments:

Thank you for your letter. The use of topical corticosteroids may induce atrophy and other adverse effects. If we consider that kids have a thinner skin, with higher absorption, the use of topical corticosteroids in this population should be more cautious. However, we are not saying that topical corticosteroids should be avoided. As we say in the article, 'Topical corticosteroids are safe and effective drugs. Always establish a clinical diagnosis before prescribing an appropriate topical corticosteroid according to the affected area, patient's age, clinical presentation and predicted responsiveness to treatment'.

One big problem with the 'perceived' effect of topical corticosteroids is adherence to treatment. Patients (and relatives) tend to largely exaggerate their use of topical products. This gives some doctors a false sense of security, and it is probably behind the concept of 'tachyphylaxis'. This is when patients say they are using the topical product when they are not, and suggests the disease is 'resistant' to treatment.

Controlled studies have found that atrophy changes appear after seven days of use with moderate potency topical corticosteroids. We should always