House have had to be withdrawn so the College will now stay at 50 Hallam Street for the time being , additional office space on a different site will needed.

Finally I would like to thank everyone who attended the Joint Meeting with the Irish Paediatric Association in Cork. We should be particularly impressed by the junior doctors who were very supportive. The quality of the presentations from the Society was of an extremely high standard. We really need to be proud of the young Paediatricians in Wales, and even though we see difficulties and challenges for the NHS we must be confident about the standards and quality of care for children in Wales in the future.

RESEARCH IN FOCUS **YMCHWIL MEWN FFOCWS**

DRUG RELATED IATROGENIC DISEASE: THE SPECIAL VULNERABILITY OF CHILDREN

Shalini Sri Ranganathan, (Research Fellow in Paediatric Clinical Pharmacology), Department of Pharmacology, Therapeutics and Toxicology, University of Wales College of Medicine, Cardiff

SUMMARY

- Only about 2500 people will have been exposed to a drug before it is marketed and the chance of finding an adverse reaction with an incidence of less than 1 /1000 prior to marketing is therefore small.
- Drugs may not be extensively tested in children so that many medicines given to children are not licensed for a particular indication, age of the child, or presented in a suitable formulation or route of administration
- The use of 'off label' or unlicensed drugs to treat children is widespread throughout Europe so that continued monitoring is essential to detect the adverse drug reactions in children.
- The Yellow Card Scheme is an important mechanism for doctors and pharmacists to report their suspicions about a possible adverse drug reaction and allow early detection of an adverse effect.
- Early detection and reporting of suspected adverse drug reactions by doctors caring for children will prevent other children experiencing adverse drug reactions.
- Regrettably Paediatricians and other doctors caring for children seem to have a poor record for completing Yellow Cards although there is no hard evidence for this. To improve our knowledge and understanding of drug safety in children, we must have comprehensive reporting.
- A recent circulated self assessment bulletin on which the article is based to paediatricians in Wales is an intervention to improve reporting of adverse side effects of drugs given to children.

Key words:
Iatrogenic disease; drugs; children; Yellow Card Scheme

Introduction

Iatrogenic disease results from the treatment of another disease. This includes adverse and unwanted effects of drug treatment. In 1976 Vere first described the propensity of iatrogenic disease to masquerade as natural illness and proposed five main reasons why so many adverse drug reactions escape unnoticed.(1)

- The reaction may be so odd or bizarre that an often used and apparently innocent drug escapes suspicion.
- The drug-induced disorder can closely mimic a common natural disease.
- There is a long delay in the appearance of the adverse effect.
- The drug evokes a relapse of natural disease or may evoke a disorder in a naturally susceptible subject.
- The clinical situation may be so complex that its drug- related components pass unnoticed

Twenty years further on iatrogenic diseases are still regularly unrecognised. Vere concluded that although many new discoveries are made by national and

international adverse reaction monitoring agencies, many of the important new observations continue to be made by individual doctors. Fibrosing colonopathy in association with some pancreatic enzyme supplements is an example of drug related iatrogenic disease that was more easily identified as being drug induced because there was no similar condition with which to confuse it. However the situation is often not so clear.

Case study

John, a four year old boy with cystic fibrosis, was admitted as an emergency with severe abdominal pain and vomiting. An emergency barium enema showed a large bowel stricture confirming the diagnosis of intestinal obstruction. He had been receiving a large dose of one of the high strength pancreatic supplements. In 1994 it became clear that these agents could cause a hitherto unknown condition, FIBROSING COLONOPATHY which always required surgical excision. The condition is commonest in males, usually between 2 and 8 years old with severe disease receiving more than 15,000 units of lipase /kg body weight per day(2). Prior to the introduction of high- strength pancreatic enzyme preparations, fibrosing colonopathy had not been reported. It is therefore an iatrogenic disease in the purest sense since it has a characteristic histological pattern and is induced by drug therapy alone.

A subsequent case control study using a national data registry showed that affected patients were taking almost twice as many capsules. This problem was highlighted by the Yellow Card Scheme, which alerted regulatory authorities throughout the world.(5)

Iatrogenic disease in children: is it a problem?

The newborn, infants and children are a very heterogeneous population because they represent the developmental period of human life. Adverse drug reactions can have profound immediate, delayed and long-term implications for their neurological and somatic development. The intrauterine, neonatal and infancy periods of developments are the only stages in life where there is potential harm by exposure to drugs that are administered to another person, the mother. The fragile nature of the newborn (especially those born prematurely) and the complexity of their illnesses make this group particularly vulnerable. Adverse drug reactions can be difficult to identify with differences in the morphology, spectrum of disease and administered treatments, infants and children experience a different range of adverse drug reactions, which are not necessarily predictable from the adult experiences with the same drugs(3). Specific age dependent differences include:-(4)

- Pharmacokinetic differences in the rate of absorption, body water distribution, protein binding, metabolic pathways and renal excretion.
- Altered pharmacodynamic responses :probably due to differences in receptor and homeostatic function
- The process of normal growth and development physical and neuro developmental, that can be adversely influenced by medicinal products (e.g. retarded growth with corticosteroids)
- Specific pathology that may require children to be given medicinal products for diseases that differ from adults either because of increased frequency (e.g. otitis media, invasive bacterial infections), increased severity (e.g.diarrhoea), a different natural history (e.g. acute leukaemia, nephrotic syndrome) or specific pathology (e.g. neonatal apnoea, surfactant deficiency, patent ductus arteriosus, vitamin K deficiency bleeding, inborn errors of metabolism, growth hormone deficiency, paediatric tumours).

The overall incidence of adverse drug reactions in paediatric in-patients ranges from 5.6 -16.8% and it is especially high in newborn(5). This very wide range of estimates reflects the different methodologies used in detecting and reporting ADRs.

They test drugs, don't they?

About twenty new chemical substances are introduced into the UK market each year. The current price to develop such a product to marketing is around £ 200 million. Much of this relates to the extensive testing that has to be performed at each stage of the drug development process and which may take as long as ten years. This testing can be considered as a pre clinical and clinical process. A marketing authorisation is granted only after careful consideration of pre-clinical and clinical data on safety and efficacy as well as the quality of the product from a pharmaceutical viewpoint. On average only two to three thousand individuals will have been exposed to the drug prior to marketing: only common adverse events (> 1 in 1000) are likely to be detected at this stage.

Do they test drugs in children?

In the UK, most medicines given to adults have been granted a licence for a particular indication, formulation and route of administration but ***many medicines given to children have not*** because (i) licence application has not been sought by a pharmaceutical company, (ii) no suitable paediatric preparation has been developed, (iii) insufficient information is available to satisfy the requirements of the Licensing Authority.

The main reason for their difficulty in conducting clinical trials in children due to: (i) the inability to recruit sufficient numbers in the different age ranges, (ii) safety in the effect of a particular medicine on developing and growing tissues and which may take time to emerge, (iii) technical challenges because of the size of the young person, (iv) lack of co-operation, (v) the very difficult issue of consent to participate in a clinical trial.

Infants and children have therefore become 'therapeutic or pharmaceutical orphans' because many drugs released since 1962 carry an 'orphaning' clause, for example, ' Not to be used in children;...is not recommended for use in infants and young children...etc..' What this often means in reality is that a particular medicine has not been tested in children.

DEFINITIONS: (7)
Unlicensed: Medicine is only administered to children, which has no license at all for human administration
Off label: Medicine is a licensed medicine used outside the conditions of the license (7). (Tables 1 and 2)

Many drugs given to children in the UK are unlicensed or prescribed 'off label'. Yet without these prescriptions possible effective treatment will be denied to children.(6) This is the continuing dilemma in drug prescribing for children. A recent study of children in hospital in five European countries reported that over two thirds (67%) were receiving an unlicensed or 'off label' drug preparation.(6)

Table 1: Examples of unlicensed medicines given to children (7,8)

Category	Examples
Medicines used without any license	* Captopril 2 mg tablets * Nifedipine drops * Fluoxetine
Imported medicines (licensed elsewhere)	* Chlorothiazide suspension * Iron dextran injection * Multivitamin injections paediatric
Medicines which are licensed but the particular formulation is a 'special'	* Digoxin paediatric injection * Frusemide 10 mg/ml mixture * Amiloride suspension
Novel medicines available as specials	* Caffeine injection * Nitric oxide gas * Sodium benzoate injection * Tolazoline injection

Table 2. Examples of medicines used off label

Category	Example
Limited formulation	* Acetylcysteine (nebulised) * Calcium gluconate (used orally for babies) * Lorazepam injection (used rectally)
In neonates	* Amiloride * Cimetidine injection * Theophylline syrup * Trimethoprim suspension
Used outside the age ranges	* Amiloride * Salbutamol syrup (licensed > 2 years) * Omeprazole (licensed in children > 2 years)

What has been done to improve the situation?

In the UK a joint working party of the British Paediatric Association, now the Royal College of Paediatrics and Child Health, and the Association of British Pharmaceutical Industry prepared a report on ' Licensing Medicines for Children' now approved by the Committee on Safety of Medicine (CSM). It made recommendations on age ranges, clinical trials, CPMP licensing guidelines, interpretation of clinical studies, surveillance of unlicensed and 'off label' usage and provision of suitable information. The latter includes statements on 'orphan drugs', expanded data sheets

and the preparation of a national formulary for children 8

There is an expert Paediatric Sub-group of the CSM which aims to improve the availability of licensed medicines for children and to stimulate adverse drug reaction reporting.

Currently there is an International Guideline adopted by the International Conference on Harmonisation in January 2001. This gives guidance on types of studies to be conducted in children, ethical issues including consent and gives guidance on age ranges.

Unlicensed and 'off label' medications: do they cause more adverse drug reactions?

Many drugs used in children have not been tested in formal clinical trials. The dosage used in children is therefore often empirically calculated from trial data in adults. Drugs used within the conditions of the product license may therefore be less likely to cause ADRs than drugs that are either unlicensed for use in children or are prescribed outside the terms of the product license. A study in paediatric wards covering a variety of sub specialities showed that the ADRs occurred in association with 3.9 % of the licensed drug prescriptions and 6 % of the unlicensed or off-label drug prescriptions.5

Adverse events and adverse drug reactions (ADR)

An adverse event is a harmful event that occurs in a patient in the context of drug treatment. A causative role of the drug is therefore not proven and indeed many adverse events are coincidental to the drug therapy .An adverse drug reaction is an event, which is related to the drug therapy and that occurs at drug doses associated with normal treatment (excluding overdose). An adverse drug reaction does not include failure of the drug to produce its wanted effect.

Several factors such as concomitant treatment can cloud the identification of ADR and there are few confirmatory specific laboratory or clinical methods. In clinical practice it is thus often difficult to separate adverse events from adverse reactions. In children, especially in newborns, it is even more difficult. However, studies are now being published where an effective ADR surveillance is carried out in a paediatric and Neonatal ICU. (9)

Suspecting adverse drug reactions

ADRs can occur in two forms:- Type A or 'dose related' adverse reactions, are an 'Accentuation' of an appropriate drug effect: they constitute 75% of all adverse drug reactions, but are proportionately less likely to cause morbidity and mortality than Type B reactions. They can often be managed by reduction in the dose or temporary discontinuation of the drug. Type B reactions are less common than those of type A and are 'Bizarre' in that they cannot be predicted by a drug's known pharmacology. These include allergic reactions and because of their often-dramatic onset, they are associated with a proportionately higher mortality than Type A reactions. The drug has invariably to be discontinued and not be re-administered in the future.

Since the body has a limited number of responses to noxious stimuli, it may be difficult to distinguish an ADR from disease caused by other mechanisms particularly if the disease has a high incidence in the community. A useful criterion to determine whether a reaction is drug induced is the timing of onset and offset of symptoms relative to the therapy. (Box 2)

Box 2 Criteria for identifying Adverse drug Reactions

* Timing of event relative to drug administration (and possible withdrawal)
* Previous evidence in literature implicating drug
* Absence of alternative explanations for event
* Effects of re-challenge

Type A reactions **usually** (but not always) occur when a drug has accumulated; thus five half-lives of a drug will be needed to reach maximum intensity. Because they are often immunological, Type B reactions, sometimes require a latent period up to 5 days before they are seen and most though not all occur within twelve weeks of initiation of drug therapy. This time course however may be 'clouded' by several factors. Drug induced agranulocytosis for example may take two or more weeks to occur and may therefore present after the drug has been discontinued. The same is true of drug induced jaundice, particularly when it occurs after the drug is used for short course therapy (e.g. co-amoxiclav).

The time course after stopping the drug (dechallenge) may also be of help in assessing causality.

Some ADRs may take a considerable time to disappear after drug discontinuation, particularly if the drug has a long half-life of elimination (e.g. amiodarone) and others may be associated with irreversible effects. (e.g. pulmonary fibrosis).

Doctors have been shown to rely to large extent on whether previous reports of adverse events in association with drug therapy have been published. The serendipity of individual reports may therefore be a major factor in identifying previously unrecorded drug reactions. Drug re-challenge may provide confirmatory evidence of the drug's involvement in an adverse event. With rare exceptions (for example when no other possible drug therapy is available for a particular condition) this approach is unethical and may be potentially life threatening. If such re-challenges could be performed routinely in an in vitro environment, assessment of causality would be much easier. At the present time however there are few sensitive and specific in-vitro tests for drug allergy.

How can drug safety be monitored in children?

Qualitative and quantitative information on adverse drug reactions in children can be found by spontaneous reporting systems, registries, studies focused on specific drugs or reactions and epidemiological surveillance programs. An effective active ADR monitoring system is feasible in children. A study in Italy showed that active monitoring of ADRs in children was associated with an incidence of 15.1 ADRs per 1000 children compared to 4 ADRs per 100,000 children reported spontaneously the year before. (10)

Spontaneous Reporting Schemes (SRS)

Schemes for spontaneous reporting suspected ADRs by health care professionals (SRS) have been an important part of pharmacovigilance for over 30 years in the UK and other countries. Because (at least in theory) the entire population of individuals receiving the drug is surveyed they can be effective in identifying uncommon reactions not identified during drug development. They have provided early warning of adverse reactions on numerous occasions (e.g. cisapride and arrhythmias, high strength pancreatic preparations and fibrosing colonopathy) and have given us information on factors predisposing to adverse reactions.

SRS also have their limitations. Substantial under-reporting means that the potential sensitivity to identify rare adverse reactions is not fully exploited. Less than 10% of even serious suspected adverse reactions are thought to be reported to regulatory bodies. Under reporting also allows bias to appear so that when adverse publicity in the media (e.g. MMR vaccine) may result in selective reporting and distortion of the adverse effect profile of a particular agent and cause in false signals. They are also poor at identifying associations between drugs and toxicity that mimic events commonly occurring in the untreated population. SRS are also insensitive in identifying adverse effects with a long latency period, particularly if the drug has been previously discontinued. The lack of placebo control group makes it more difficult to confirm new adverse reactions. Also the incidence cannot be measured due to lack of a denominator. (e.g. accurate usage data). Finally for most new drugs reporting rates peak relatively soon after marketing and begin to fall progressively from around two years onwards. Comparisons between drugs need to take account of this period- effect and prescribing rate.

Despite these weaknesses, spontaneous reporting schemes are valuable tools, although they are better at generating signals or hypotheses than testing them. In the latter event, cohort or case-control studies are of greater value and record linkage (where adverse events are automatically linked with drug exposure) may also be a powerful approach.

The Yellow Card Scheme

In 1964 in the wake of the thalidomide disaster the Committee on Safety of Drugs, now the Committee on Safety of Medicines (CSM), was established. All doctors were asked to report suspected ADRs on a yellow reply-paid card, which is now generally called the 'Yellow Card'. Around 100 reports were received in 1964 peaks to almost 20,000 in 1989. Currently around 17-18, 000 reports are received annually. There are now around 380,000 reports of suspected ADRs which are stored in the ADROIT (Adverse Drug Reactions Online Information Tracking) database. Reports are classified by organ class (e.g. cardiovascular disorders) with sub-classification into groups of disorder (e.g. ventricular arrhythmias) and further sub-classification into specific disorder.

The Yellow Card System and reporting ADRs in Children

The Yellow Card System reporting ADRs in children seems to result in a much lower yield compared to adults is an ironic finding, remembering it was the adverse effect of drugs in children that was the catalyst for the ADR scheme in the first place. (e.g. the thalidomide disaster and chloramphenicol-induced grey baby syndrome). Spontaneous Reporting Schemes and the Yellow Card System are easy and inexpensive means of monitoring drug safety in children. It needs only a vigilant Paediatrician and a yellow card to make it work.

Conclusion:- You can make the difference!

Doctors, dentists and pharmacists submit nearly 1000 Yellow Cards each year in Wales. However in 1998 only 68 suspected ADRs in children were reported. The Yellow Card Scheme is potentially a very effective method allowing doctors and pharmacists to highlight serious and rare drug reactions. The contribution of the Paediatrician is **essential** to the success of the system: serving at a primary point, general practitioners are also key participants in childcare. A positive attitude to submitting Yellow Cards can bring about the early detection of an ADR and prevent other children experiencing ADRs. Thus the Yellow Card Scheme is the professions' major tool to detect and avoid further adverse drug reactions.

This article and the Self Assessment Bulletin (allowing CME points) that has already been sent to paediatricians in Wales seeks to improve paediatricians understanding of drug safety in children. It is also intended as an intervention to affect the reporting rates of ADRs in children allowing comparison with the previous year. The long term aim must be the safer use of medicines in children to help prevent avoidable morbidity and mortality.

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