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ADR is a threat more to children and women than adult male

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Adverse drug reactions (ADR) are a major health problem to the individual as well as for society

The World Health Organisation's definition of an ADR is ''a response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function''[1]



Adverse drug reactions (ADRs) are occur as type A, dose-related, or type B, idiosyncratic (i.e. allergic) reactions.

ADRs are very important as up to 5% of all hospital admissions are the result of ADRs. Once in hospital, as many as 30% of patients will experience an ADR, and it may be the cause of death in 0.3% of hospitalized patients.



Amongst the known risk factors for adverse reactions are increasing age, polypharmacy, liver and renal disease as well as being female[2].

Female patients have a 1.5- to 1.7-fold greater risk of developing an ADR, including adverse skin reactions, compared with male patients. The reasons for this increased risk are not entirely clear but include gender-related differences in pharmacokinetic, immunological and hormonal factors as well as differences in the use of medications by women compared with men.



Women generally have a lower lean body mass, a reduced hepatic clearance, have differences in activity of cytochrome P450 (CYP) enzymes (40% increase in CYP3A4, varied decrease in CYP2D6, CYP2C19 and CYP1A2), and metabolize drugs at different rates compared with men. Other important factors include conjugation, absorption, protein binding and renal elimination, which may all have some gender-based differences.

There are pharmacodynamic differences between men and women, seen particularly with cardiac and psychotropic medications.



It is possible that gender difference in T cell activation and proliferation account for this as well as the increased prevalence of skin diseases such as systemic lupus erythematosus and photosensitivity.

Whatever the mechanism(s), it is important to be aware that gender is a significant factor in ADRs.



In an analysis of 48 community- based cohort studies from the UK, the overall incidence of suspected ADRs in males was 12.9 per 10 000 patient-months of exposure, and in females was 20.6 per 10 000 patient-months of exposure. The overall age-standardized odds ratio of an ADR in females compared with males was 1.6 [95% confidence interval (CI) 1.5 to 1.7]. This gender difference was significant in all age groups above 19 years of age, and was relatively consistent across all age groups.



In a report from the Spanish System of Pharmacovigilance, 60% of 1609 adverse reactions to nonsteroidal anti-inflammatory drugs were in women (i.e. odds : 1.67).

In a further Canadian study, 74.1% of ADRs were in women. Drug classes most frequently reported to elicit an adverse event were general anti-infectives (60.4%), nervous system agents (21.5%), and musculoskeletal agents (3.7%). Skin-related reactions accounted for 49.0% of all reported ADRs. More than 1 agent was reported to be responsible for the ADR(s) in 50% of the female patients, compared with only 33.1% of all male patients.



In a prospective study of 1920 hospitalized patients in Chile, the frequency of ADRs was significantly higher in females than in males ($p < 0.0005$).

In a large Italian study of ADRs in a population of over 20 million people, cutaneous ADRs made up 45% of all reports



There are several gender-based differences in both drug pharmacokinetics and pharmacodynamics. Differences in lean body mass are important for some drugs. Examples include diazepam, where women have a higher volume of distribution compared with men and, alcohol, where the reverse occurs.



A number of studies suggest that cytochrome P450 (CYP)3A4 activity is higher, by up to 40%, in women compared with men. CYP3A4 is probably the most important enzyme associated with drug metabolism accounting for, perhaps, 50% of metabolism of therapeutic drugs. Examples of increased CYP3A4 activity include erythromycin which is metabolized 25% more rapidly in women.



Gender difference in steroid hormones influencing CYP3A4 activity (e.g. estrogen and progesterone), which may act as competitive inhibitors. Most other enzyme systems involved in drug metabolism (e.g. CYP2D6, CYP2C19 and CYP1A2) appear to be more active in men than women, although results from studies are not consistent.



The effects of gender on pharmacodynamics are less clear. Women are at increased risk of QT prolongation with certain anti-arrhythmic drugs compared with men even at equivalent serum concentrations. There is no doubt that a number of psychotropic drugs, including chlorpromazine, fluspirilene and various antipsychotics appear more effective in women than men for the same dosage.

Idiosyncratic drug reactions, particularly cutaneous reactions, appear to have an immunological etiology.



The onset of drug hypersensitivity involves drug bioactivation, covalent binding to proteins, followed by uptake, antigen processing and T cell proliferation. Whilst drug metabolism plays a critical role (with the balance between metabolic bioactivation and detoxification being an important component), T cell activation and proliferation maybe as important.

However, well recognized that women have an increased incidence of a number of skin diseases thought to have an immunological basis. These include systemic lupus erythematosus, systemic sclerosis, photosensitivity, and lichen planus.



Women use a significantly different range of drugs than men, particularly drugs associated with oral contraception, the menopause and pregnancy

However, the observation that women consume significantly more over-the-counter medications, herbal remedies and vitamins, compared with men, suggests that access to healthcare is unlikely to explain the difference.



ADR in Children's

Adverse drug reactions in children are an important public health problem. We have undertaken a systematic review of observational studies in children.

Criteria for considering studies for this review

Included studies. Observational studies that estimate the incidence of ADRs including retrospective and prospective cohort studies of children.



Excluded studies. Studies which focus on ADRs in relation to a specific drug (e.g. antibiotics or carbamazepine), clinical condition (e.g. epilepsy, asthma) or specific clinical presentations of ADRs (anaphylaxis); case control studies; those carried out exclusively on a neonatal intensive care unit; studies reporting medication errors, therapeutic failures, non-compliance, accidental and intentional poisoning and drug abuse.

Participants.

Studies included three defined populations:

1) children admitted to hospital
2) children in hospital and
3) children within the community.



Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children (pooled estimate of 2.9% (2.6%, 3.1%)) and from 0.6% to 16.8% of all children exposed to a drug during hospital stay.

Anti-infectives and anti-epileptics were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital (17 studies; 12 studies respectively) and children in hospital (24 studies; 14 studies respectively), while antiinfectives and non-steroidal anti-inflammatory drugs (NSAIDs) were frequently reported as associated with ADRs in outpatient children (13 studies; 6 studies respectively).

Fourteen studies reported rates ranging from 7%–98% of ADRs being either definitely/possibly avoidable.



We have included 51 studies, where ADRs have been investigated in the hospital setting. The period under study varied widely and ranged from 1 day to ten years.

The majority of studies where described as being performed in a general paediatric unit or ward (n =24) [13] two of which included intensive care also .

Six studies were performed solely in the intensive care setting , one of which included general medicine . Three studies included children on an isolation ward . One study was performed using an integrated primary care information database and one in an isolation ward . The remaining thirteen studies covered a combination of clinical settings.



In agreement with previous studies, including those specific to adults [3], this review found that ADR incidence rates were generally higher in hospitalised children than ADR rates causing hospital admission or in an outpatient setting.



In September 2013, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a safety review on exfoliative dermatitis associated with ustekinumab.[4] This signal was identified through routine pharmacovigilance surveillance in the United Kingdom, where 12 cases of exfoliative dermatitis and 15 cases of erythrodermic psoriasis associated with ustekinumab treatment were received.



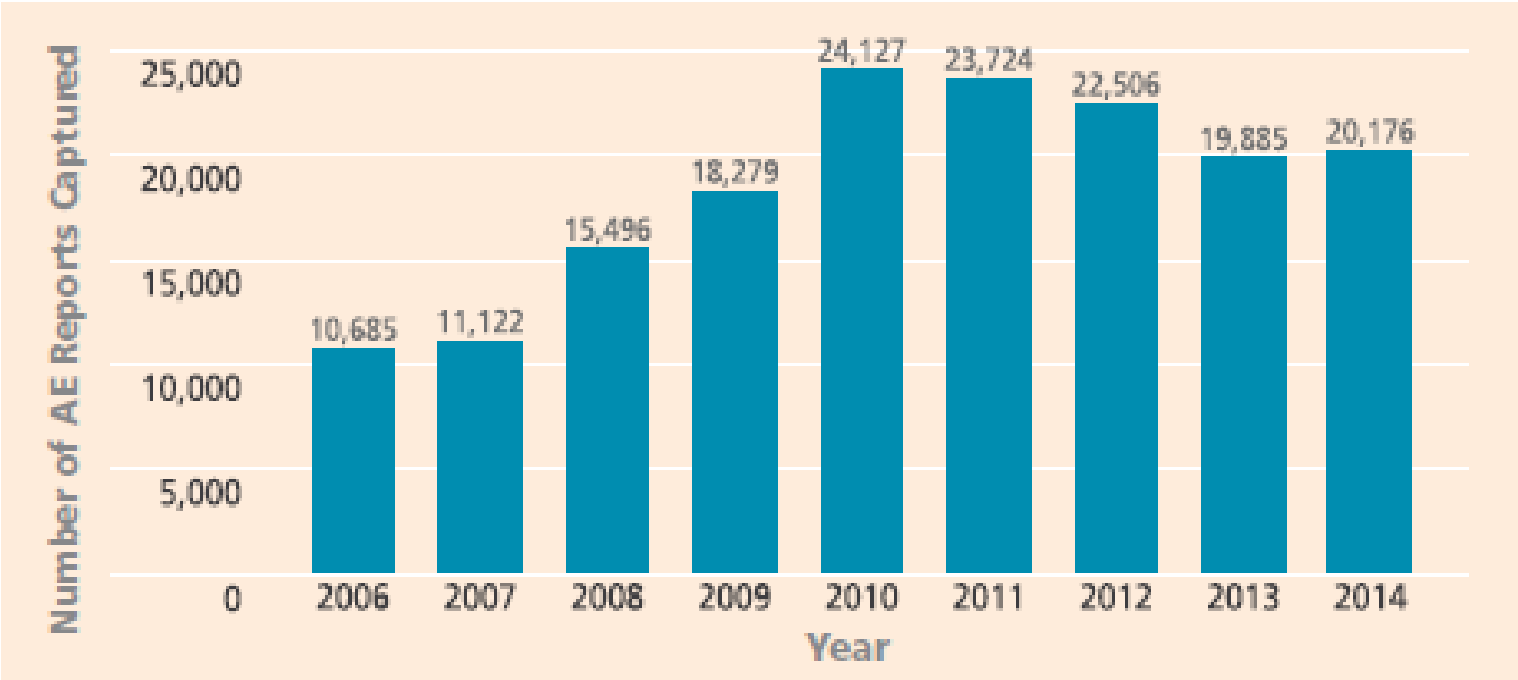
In November 2014, Health Canada issued a safety review summary highlighting the possible link between exfoliative dermatitis and erythrodermic psoriasis and ustekinumab treatment. In the safety review, Health Canada reported that it had received five reports of skin exfoliation (two serious and three non-serious) and one non-serious report of exfoliative dermatitis associated with the use of ustekinumab.

In 2014, the Vigilance and Compliance Branch of HSA captured a total of 20,176 valid[a] local adverse event (AE) reports suspected to be related to health products.



The breakdown of the number of valid reports captured in the national AE database from 2006 to 2014 based on the date of receipt is illustrated in Figure 1.

Figure 1. Number of AE reports captured into AE database from Year 2006 to 2014 based on date of receipt





There were more AE reports received for females (54%) than males (43%), and 3% of reports did not indicate the gender of the patients.

In 2014, HSA received a total of 249 AE reports suspected to be associated with vaccines, of which 209 reports (84%) involved children aged 12 years and below, which corresponds to the age group of vaccinees under the National Childhood Immunisation Schedule.

Of these, 84% of the reports (n=176) were captured by KK Women's and Children's Hospital (KKH) active surveillance sentinel site.



A total of 102 studies (117 citations), were included in the review. Eighty (80/102) studies described the clinical event as an ADR.

Some studies included multiple settings; 42 studies investigated ADRs as the cause of admission to hospital, 51 studies investigated ADRs in the hospital setting, and 36 studies investigated ADRs in the community setting. Studies included in our review were conducted in 31 different countries, mostly Europe (40/102) and America (32/102).



ADR detection methods were employed in 58/102 studies; these consisted of a combination of case record review, drug chart review, laboratory data, computerised ADR reporting system, attendance at ward rounds, and interviewing patients/parents or clinicians.

In thirty-one studies case record review alone was undertaken. The remaining eleven studies used; parental interviews/ questionnaires (5 studies), clinical assessments (3 studies), clinician questionnaires (1 study), ward round (1 study) and a nationwide computer database (1 study). The remaining study report did not refer to the methods used.



CONCLUSIONS:

Women certainly appear to have a significantly higher risk of developing adverse drug reactions than men. This appears to be because of a number of gender-based physiological differences as well as differences in the use of medications between men and women. This study have shown ADRs to be an significant problem in children and has highlighted therapeutic classes of drugs most commonly associated with them. Therefore avoidability of ADRs is needed and further work on how such ADRs may be prevented should be carried out in recent years.



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