Journal of Medicine, Physiology and Biophysics
ISSN 2422-8427 An International Peer-reviewed Journal
Vol.23, 2016

Adverse Drug Reactions: An Overview

Tilaye Shibbiru[1*] Fanos Tadesse[2]
1.School of Veterinary Medicine, Wolaita Sodo University
2.College of Veterinary Medicine and Agriculture, Addis Ababa University

Abstract
Drug is single active chemical entity present in a medicine that is used for diagnosis, prevention and treatment of diseases. Adverse drug reaction is unexpected effect of drug on animal and human being and considered as one of causes of morbidity and mortality of hospitalized patients. Although many drug reactions are preventable such as those associated with prescription errors while others are not preventable. The adverse drug reactions are often not discovered until after the drug has been marketed. The occurrence of ADR can be explain on basis of the drug's pharmacology and show apparent dose-response relationship in susceptible animal and human being. Adverse drug reactions caused by immune and non-immune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5% to 15% of therapeutic drug courses. Adverse drug reactions can be divided schematically into two major categories: type A and type B. Type A reactions are common, predictable and may occur in any individual. Type B ADRs are uncommon and unpredictable and only occur in susceptible individuals. A critical factor in the drug response such as in ADRs could be the inter-patient differences in plasma concentrations arising from the same drug regimen. Pharmacogenomics is likely to be particularly useful for drugs that have variable kinetics and dynamics, and narrow therapeutic index. Management strategies employed for the ADRs is categorized as drug withdrawal, dose reduction, additional treatment for ADR, and no change in regimen with no additional treatment. Managing these cases should be done immediately after their appearance and those individuals or animals with the problem should be carefully handled with the appropriate medical expertise. Better approaches must be devised for reporting and assessing ADR. In addition, pharmaceutical companies should strive to reduce the adverse effect of a drug.
Keywords: adverse drug reaction, causalities, drug kinetics, genetic polymorphism, toxicities.

INTRODUCTION

Drug is single active chemical entity present in a medicine that is use for diagnosis, prevention and treatment of diseases. (Mererjone, 2003). The person-to-person variability of drug response is a major problem in clinical practice and drug development (Meyer, 2000). It can lead to therapeutic failure or adverse effects of drugs (ADRs) in individuals or subpopulations of patients. Adverse drug reaction is unexpected effect of drug on animal and human being and considered as one of causes of morbidity and mortality of hospitalized patients (Ditto, 2004).

A productive hospital-based reporting program can be instrumental in providing valuable information regarding potential problems of drug usage in an institution. Through these efforts, problems are identified and resolved, which results in continuous improvement inpatient Care (Murphy and Frigo, 1993). Spontaneous reporting program, a common method of drug surveillance is capable of recognizing ADRs in the daily medical practice even though under reporting and absence of information on number of people actually exposed to the drug are its disadvantages (Alvarez-Requejo *et al*., 1998).

Although many drug reactions are preventable such as those associated with prescription errors while others are not preventable. The adverse drug reactions are often not discovered until after the drug has been marketed. Pharmaceutical companies strive to work out the adverse effect profile of a drug before it is marketed, but because the complete range of adverse effects is not known, therefore, most severe drug induced reactions cannot be elucidated before licensing, therefore efficient post marketing surveillance is needed. However, even if improved surveillance is carried out the problem will not be resolved. As more drugs are marketed and as more individuals take multiple drugs, the occurrence of adverse drug reactions will probably continue to increase. Adverse drug reaction are still considered as problem of drug therapy in association with considerable morbidity, mortality, decrease compliance and therapeutic success as well as high direct and indirect medical cost (Tripathis,2003). There for the objectives of this seminar paper are: to high light the causality, clinical manifestation and management of ADR, and to recommend further study in the area of ADR.

DEFINITION AND EPIDEMOLOGY

Definition

Adverse drug reaction can be defined as any noxious unintended and undesired effects of a drug that occur at doses used for prevention, diagnosis or treatment or it is an unwanted or harmful reaction following the administration of a medication or combination of medications which is suspected to be related to the medication.

The reaction may be a known side effect of the drug or it may be a new previously unrecognized ADR. (Jill *et al*., 2008).

Epidemiology

Adverse drug reactions caused by immune and no immune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5% to 15% of therapeutic drug courses. In the United States, more than 100,000 deaths are attributed annually to serious adverse drug reactions. Three percent to six percent of all hospital admissions are because of adverse drug reactions and 6% to 15 % of hospitalized patients (2.2 million persons in the United States in 1994) experience a serious adverse drug reaction .Epidemiologic data support the existence of specific factors that increase the risk of general adverse drug reactions, such as female, gender, or infection with human immunodeficiency virus (HIV), or herpes(Alvarez-Requejo *et al*.,1998) Factors associated with an increased risk for hypersensitivity drug reactions include asthma, systemic lupus erythematosus, or use of beta blockers although atopic patients do not have a higher rate of sensitization to drugs, they are at increased risk for serious allergic reactions .Incidence and severity of ADRs vary by patient characteristics (e.g., age, sex, coexisting disorders, genetic or geographic factors) and by drug factors (e.g., type of drug, administration route, treatment duration, dosage, bioavailability). Incidence is probably higher and is more severe among the elderly. The contribution of prescribing and adherence errors to the incidence of ADR is unclear (Lazarou *et al*., 1998)

In animal recent UK study following vaccination of dog revealed a similarly incidence of sign of health in recently vaccinated and unvaccinated dog s which account 19% and 25% into week period (Jill *et al*.,2008).

CAUSALITIES OF ADVERSE DRUG REACTION

In assessing the likelihood of ADR, a causality rating is assigned to each drug using the validate Kramer's algorithm using the parameter like: previous experience of ADR, no other factor related to underlying disease, as well as no other drug-unrelated etiology may explain the presence of the clinical manifestation in the patient and time elapsed between drug administration and its manifestation; its onset also immediately follows drug administration (Kramer *et al*., 1979). ADR attenuates after drug reduction or disappears after drug interruption. Its reappearance after drug re-administration; not done in any of the patients are analyzed (Hutchinson *et al*., 1979). The diagnostic criteria in Kramer's algorithm are divided into six axes, with a scoring system incorporated into each axis. The cumulative score corresponds to the probability that the clinical manifestation represents an ADR and compared to the score obtained for a suspected ADR caused by a drug interaction with the scores obtained for the clinical manifestation caused by the single drugs (table 1 below). When a candidate single drug had a higher score, that drug rather than the interaction is held responsible for the ADR. The four distinct defined classes with regard to ADRs causality are:

- **Certain**: temporal or spatial correlation confirmed by de challenge and re challenge and/or laboratory test
- **Probable**: temporal or spatial correlation confirmed by de challenge and not induced by disease, and/or recovery on withdrawal of the drug if no other drug was withdrawn and no therapy given;
- **Possible**: a possible alternative explanation exists when a strict temporal relationship is not clear, and/or a recovery occurs after therapy prescription in addition to drug withdrawal, and/or more than one drug is suspected
- ❖ **Unclear causality**: the clinical event could be consistently attributed to either the underlying disease or to drug –related cause.

Table .1: Six axis and total score in Kramer's algorithm of ADR

Axis	Scoring of evidence of reaction		
	Favors	Uncertain	Against
History	+1	0	-1
No alternative illness	+2	0	-1
Timing event	+1	0	-2
Drug level	+1	0	-1
Dechallege	+1	0	-1
Rechallege	+1	0	-1
Total score	+7	0	-7

Source: (Hutchinson, *et al*. 1979**)**

CLASSIFICATION OF ADVERSE DRUG REACTION

Immunologic and Non-immunologic Drug Reactions

Drug reactions can be classified into immunologic and non immunologic etiology (table.2). The majority (75% to 80%) of adverse drug reactions are caused by predictable, no immunologic effects. The remaining 20% to 25 % of adverse drug events are caused by unpredictable effects that may or may not be immune mediated. Immune-mediated reactions account for 5% to 10% of all drug reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category (Marc *et al*., 2003).

Table 2: Immunologic and Non-immunologic Drug Reactions

Type	Example
Immunologic • Type I reaction (IgE-mediated) • Type II reaction (cytotoxic) • Type III reaction (immune complex) • Type IV reaction (delayed, cell-mediated) Specific T-cell activation • Fas/Fas ligand-induced apoptosis • Other	✓ Anaphylaxis from β-lactam antibiotic Hemolytic anemia from penicillin ✓ Serum sickness from anti-thymocyte globulin Contact dermatitis from topical antihistamine ✓ Morbilliform rash from sulfonamides ✓ Stevens-Johnson syndrome ✓ Toxic epidermal necrolysis ✓ Drug-induced, lupus-like syndrome ✓ Anticonvulsant hypersensitivity syndrome
Non-immunologic ***Predictable*** • Pharmacologic side effect • Secondary pharmacologic side effect • Drug toxicity • Drug-drug interactions • Drug overdose ***Unpredictable*** • Pseudo allergic • Idiosyncratic • Intolerance	✓ Dry mouth from antihistamines ✓ Thrush while taking antibiotics ✓ Hepatotoxicity from methotrexate ✓ Seizure from theophylline while taking erythromycin Seizure from excessive Lidocaine (Xylocaine) ✓ Anaphylactic reaction after radio contrast media ✓ Hemolytic anemia in a patient with G6PD* deficiency after primaquine therapy ✓ Tinnitus after a single, small dose of aspirin

*G6PD = glucose-6-phosphate dehydrogenate
Source: (Marc *et al*., 2003)

Type A and B drug reaction

Adverse drug reactions can be divided schematically into two major categories: type A and type B. Type A reactions are common, predictable and may occur in any individual. Type B ADRs are uncommon and unpredictable and only occur in susceptible individuals (Pirmohamed *et al.,* 2001). Type A reactions are the most frequent and can be observed in as many as 25–45% of patients. These represent an exaggeration of the known primary and/or secondary pharmacological actions of the drug, they are dose related and could probably be avoided and/or foreseen (Carbonin *et al*., 1991). In contrast, type B reactions or idiosyncratic drug reactions cannot be explained on the basis of the drug's pharmacology and show no apparent dose–response relationship in susceptible individuals. They are often undiscovered until the drug has been marketed and are generally associated with high mortality. Genetically determined alterations in drug metabolizing enzymes can predispose to both pharmacological and idiosyncratic toxicity. Single gene defects account for only a minority of ADRs. For most adverse reactions, particularly of an idiosyncratic nature, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infections (Hallas *et al*., 1990).

Table 3 . Characteristics of Type A and Type B adverse drug reactions

Characteristics	**Type A**	**Type B**
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors might be important	Dependent on host factors
Frequency	Common	Uncommon
Severity	Variable but usually mild	Variable proportionately severe
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall proportion of adverse drug reactions	80%	20%
First detection	Phases I–III	Usually phase IV
Animal models	Usually reproducible in animals	No known animal models

Source: (Giovanni *et al.,* 2003)

GENETIC POLYMORPHISM AFFECTING ADVERSE DRUG REACTION

Genetic polymorphism and drug kinetics

CYP and ABC genes

Most work has focused on enzyme polymorphism in drug oxidation and conjugation as risk factors for drug toxicity but genes involved in cell repair mechanisms, elaboration of cytokines and immune responsiveness cannot be excluded to predict individual susceptibility to different forms of ADRs (Hutchinson *et al*., 1979). Genetic polymorphisms are a source of variation of drug response in the human body. In relation to ADRs, most in tersest has centered on the involvement of pharmacokinetic factors and, in particular, drug metabolism. However, there is now increasing realization that genetic variation in drug targets (pharmacodynamic factors) might also predispose to ADRs, although research into this area is in its infancy (Alvarado *et al.,*2002).

A critical factor in the drug response such as in ADRs could be the inter-patient differences in plasma concentrations arising from the same drug regimen. Many drugs are substrates for cytochrome P450 (CYP) enzyme is forms and of Adenosine Tri phosphate binding cassette (ABC) membrane transporter proteins. Several polymorphisms that effect CYP genes and ABC genes have been described to alter the protein product function influencing metabolism, absorption, distribution and excretion of many drugs and to contribute to many clinically relevant diseases (Evans *et al*. 1999).

CYP genes

There are more than 30 families of CYP genes in humans and all of them have genetic variants, many of which translate into functional changes in the proteins encoded (Nebert *et al.,*2002).

One member of this family, CYP2D6 gene, represents one of the most studied and best understood examples of pharmacogenetic variation in drug metabolism that is responsible for the metabolism of more than 100 drugs including many central nervous system and cardiovascular drugs (Hosking *et al*.,2002).More than 75 CYP2D6 alleles have now been described .Using so called “probe drugs” like de brisoquine or sparteine, CYP2D6 polymorphisms can be subdivided in poor, normal, rapid and ultra rapid metabolism activity forms. Thus, in multi-drug therapies drug–drug interactions can cause ADRs or less therapeutic efficacy (Evans *et al*., 2003).

ABC genes

The ABC genes represent the largest family of Tran’s membrane proteins described in human genome the principal function of ABC proteins is to translocate a variety of substrates across extra and intra-cellular membrane including several anticancer drugs, cardiac glycoside (digoxine), immunosuppressive agents, glucocorticoids and many other medications including some antiretroviral drugs. In the intestine ABC proteins limit drug entry into the body. Particular ABC proteins are also present in the apical membrane of many other epithelial barriers such as the blood brain, blood testis, and maternal-fetal barrier. A member ABC family is the ABCB1 gene. Synonymous single-nucleotide polymorphism (3435C→T) (single-nucleotide polymorphism that does not alter the amino acid encoded) in the axon 26 of the ABCB1 gene has been associated with variable expression of transporter protein in the duodenum. In patients with ABCB1 3435-TT genotype, duodenal expression of the gene was less than half respect to patients with the ABC1 3435-CC genotype. Dioxin shows higher bio availability in subjects with the ABCB1 3435-TT genotype. Interestingly, most substrate of transporter protein is also metabolized by the CYP3A4 enzyme. This is of particular importance because transporter protein and CYP3A4 enzyme are localized in tissue with major function for drug disposition, such as small intestine and liver (Schwab *et al*., 2003). Generally speaking there is not a clear relationship between

MDR1 3435C→T polymorphism, transporter protein expression and plasma concentrations of substrates. This could be due to the following confounding factors:

- The effect of the transporter protein expression polymorphism on protein tissue level expression is rather modest,
- Disposition of most transporter protein substrates is also determined by other factors, such as metabolism (e.g. CYP3A4) or active transport by other ABC proteins transporters,
- Modifications of drug disposition may occur by exogenous factors (e.g. diet, drugs), which could explain different results, even if the same drug is investigated,
- The presence of multiple SNPs in the transporter protein gene and pronounced inter-ethnic differences in frequencies of some of these polymorphisms,
- Not all pharmacokinetic parameters are likely to be determined to a major extent by modulation of intestinal transporter protein expression (Schwab, 2003).

Genetic polymorphism and drug toxicity

Pharmacogenomics is likely to be particularly useful for drugs that have variable kinetics and dynamics, and narrow therapeutic index. For example the three classes of anti-HIV drugs currently used, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), certainly fit in this category. Adverse effects caused by this class of drugs can be divided into several categories. Recently considerable interest has been focused on the hypersensitivity reactions caused by abacavir (at least 5% of patients treated) and on the predictive potential role of pharmacogenomics (Mallal *et al*.,2002) .The followings are some of adverse reaction of drugs ;

Dose related effects

There are marked inter-patient differences in plasma concentrations arising from the same drug regimen. For those adverse reactions where a clear dose–response relationship can be demonstrated, it can be hypothesized that patients who have low expression or deficiency of a particular metabolizing enzyme will be achieve high plasma drug concentrations and enhanced toxicity(Fellay *et al*., 2002).

This has been clearly shown with non-HIV drugs and with HIV antiretroviral drugs. For example, drug crystallization in urine and formation of renal stones is a well-known adverse effect associated with high plasma concentrations. Although environmental factors such as hot climate are also important the role of CYP polymorphism seems to be dramatic. A good relationship has also been shown between ritonavir and neurological and gastro-intestinal ADRs. Ritonavir is the most potent inhibitor of the CYP3A4 enzyme system and the combination of ritonavir and indinavir causes inhibition of the CYP3A4 increasing drug plasma concentrations (Lemberg *et al*., 2002). Both drugs are also targeted by the transporter protein that may be important in determining plasma concentrations. A similar situation exists in the case of efavirenz, the newest NNRTi which is poorly absorbed into CFS, where high plasma levels predict CNS side effects (Pirmohamed, *et al*., 2001). Efavirenz is metabolized by CYP3A4 to inactive hydrolyte metabolites which undergo glucuronide conjugation and are subsequently eliminated by the kidneys (Dean *et al.,* 2001).

Mitochondrial toxicity

Nucleoside analogues that inhibit the HIV reverse transcriptase can also inhibit the human DNA polymerase. Depletion in mitochondrial DNA and consequent mitochondrial toxicity is at least partially responsible for ADRs such as lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, and possibly the Lipodystrophy syndrome (LD) (Carr and Cooper, 2000). The gold standard for the diagnosis of nucleoside-related mitochondrial toxic effects is muscle or liver biopsy. However, biopsy is not practical for routine screening and monitoring. Random measurements of venous lactate have been used to monitor for mitochondrial damage, but the clinical usefulness of this method remains unclear. Lack of specificity is a problem, as is technical and physiological variability. In a recent study changes in mitochondrial DNA relative to nuclear DNA (cytochrome-c oxidase subunit-I gene, CCOI and polymerase accessory subunit gene, ASPOLG, respectively) in the peripheral blood cells is quantified by real-time polymerase chain reaction. (Coté *et al*., 2002).

Lipodystrophy syndrome

Lipodystrophy constitute a group of rare disorders characterized by highly variable or absence of adipose tissue. They may be inherited or acquired and are accompanied by insulin resistance, diabetes and hyperlipidaemia, and associated vascular disease. (Shevitz *et al*., 2001) The syndrome is reported to occur after the use of Ortiz and PIs. One hypothesis suggests it may be due to the inhibition of lipid and adipocyte regulatory proteins that have partial homology to the catalytic site of HIV-1 protease. Some features of this syndrome have been suggested to represent the mitochondrial toxicity of NRTIs. Thus, dissection of genetic predisposition is going to be difficult

and indeed is probably the result of a complex interaction between the disease, drugs, as well as host (Hogan et *al.,* 2001).

The genetic factor TNF can be considered to involved in the predisposition to lipodystrophy syndrome, but the same locus and more in general the MHC are suspected to play an important role in several immune mediated ADRs. A possible candidate gene in predisposing LD is the Tumor Necrosis Factor-gene (TNF). The TNF- locus is located within the MHC in the class III region. The TNF- is a candidate gene because it is thought to play a role in the insulin-resistance adipose tissue metabolism and viability and glucose homeostasis (Pirmohamed *et al*., 2001). Association between lipodystrophy and Tumor Necrosis Factor- gene has recently been investigated using a case-control design. Individuals are genotyped for the −238 and −308 G→A transition functionally active polymorphisms in the promoter region of TNF and the results suggests the frequency of the allele 238A was significantly more represented in the HIV-positive patients with lipodystrophy than HIV-negative controls without lipodystrophy. Thus the TNF 238A allele can be considered as a susceptibility factor which is neither sufficient for nor absolutely necessary to the induction of Lipodystrophy (Maher *et al*., 2002).

Hypersensitivity

True hypersensitivity adverse drug reactions are great imitators of disease and may present with involvement of any organ system with or without fever, and may also involve one or more internal organs. Drug reactions commonly manifest with dermatologic symptoms caused by the metabolic and immunologic morbidly form rashes activity of the skin. The most common dermatologic manifestation of drug reaction is typically, an erythematous, maculopapular rash appears within one to three weeks after drug exposure, originates on the trunk, and eventually spreads to the limbs. Urticaria is typically a manifestation of a truly allergic, Type I reaction, but it may appear with Type III or pseudo allergic reactions as well. Severe non allergic, hypersensitivity cutaneous reactions (i.e., erythema multiform, Stevens-Johnson syndrome, and toxic epidermal necrolysis) represent bulbous skin diseases that require prompt recognition because of their association with significant morbidity and mortality. Eczematous rashes are most commonly associated with topical medications and usually represent contact dermatitis, which is classified as Type IV reaction to a drug exposure (Pirmohamed *et al*., 2002).

Drug hypersensitivity is about 100 times more common in HIV-1 patients than in general population and it complicates 3–20% of all pharmaceutical prescriptions. Nevirapine, delaviridine and efavirenz (NNRTIs), acacavir (NRTI) and amprenavir (PI) are the common antiretroviral drugs that may cause hypersensitivity. Particular interest has been focused on the hypersensitivity to abacavir. Despite the fact that this event occurs at an incidence of <5%, its severity and lethality (2–4 per 100,000 patients treated), even following an aggressive treatment, warrant careful evaluation of the patient for whom abacavir has to be prescribed (Clay, 2002). Several observations support the possibility that genetic susceptibility factors for this syndrome involve genetic loci situated within the MHC region. The susceptibility locus or loci marked by the presence of different loci, could easily participate directly in recognition of the abacavir-specific antigen by the immune system.

The gene loci of TNF are approximately 200KB apart, not in strict linkage disequilibrium, but certainly close enough to exhibit considerable overlapping in the same set of abacavir hypersensitive patients. Available data suggest that the detection of the specific region involved in abacavir hypersensitivity does not need to be based solely on strictly defined blocks of linkage disequilibrium (Rose, 2002) Of course; the existence of different mechanisms or many genetic factors is commensurate with the predicted heterogeneity of complex traits and pharmacogenetic mechanism and should not come as a surprise. Although the arbitrary candidate-gene-variation panel described cannot be used for definitive conclusion in terms of applicability for screening test for hypersensitivity reaction to abacavir, it is possible that additional genetic markers with sufficient predictive values involving racially diverse populations provide a plausible basis for the development of sufficient predictive test as well as for an increased understanding of the pathogenesis of this potentially life-threatening ADRs (Lindpainter, 2002).

MANAGEMENT OF ADVERSE DRUG REACTION

Management strategies employed for the ADRs is categorized as drug withdrawal, dose reduction, additional treatment for ADR, and no change in regimen with no additional treatment. Further, categorization of the outcome of ADRs is done for response after de challenge and re challenge as well as the final outcome of the event (Jimmy *et al.,* 2006).

For dose-related ADRs, modifying the dose or eliminating or reducing precipitating factors may suffice. Increasing the rate of drug elimination is rarely necessary. For allergic and idiosyncratic ADRs, the drug usually should be withdrawn and not tried again. Switching to a different drug class is often required for allergic ADRs and sometimes required for dose-related ADRs. The most important and effective therapeutic measure in managing drug hypersensitivity reactions is the discontinuation of the offending medication, if possible. Alternative medications with unrelated chemical structures should be substituted when available (Busto *et al.,* 1982).

The clinical consequences of medication cessation or substitution should be closely monitored. In the majority of patients, symptoms will resolve within two weeks if the diagnosis of drug hypersensitivity is correct. Additional therapy for drug hypersensitivity reactions is largely supportive and symptomatic. Systemic corticosteroids may speed recovery in severe cases of drug hypersensitivity. Topical corticosteroids and oral antihistamines may improve dermatologic symptoms. The severe drug reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis require additional intensive therapy. Thus the following points are considered to prevent ADR (Tripathi, 2003);

- Avoid all inappropriate use of drug in context of patient's clinical condition.
- Use of appropriate dose, route and frequency of administration on base of patients, specific variable.
- Elicit and take into consideration previous history of drug reaction.
- Elicit history allergic disease exercise caution
- Rule out possibility drug interaction when more than one drug is prescribed.
- Adopt correct drug administration technique
- Carry out appropriate laboratory monitoring.

CONCLUSION AND RECOMMENDATIONS

Adverse drug reaction is one of causes of morbidity and mortality on animal as well as human being. Sex, gender and immune suppression increases the risk of ADR. The occurrence of ADR can be explain on basis of the drug's pharmacology and show apparent dose-response relationship in susceptible animal and human being. Pharmaceutical companies strive to work out the adverse effect profile of a drug before it is marketed, because the complete range of adverse effects is not known, therefore efficient post marketing surveillance is needed. Although, improved surveillance is carried out the problem will not be resolved. Managing this cases should be done immediately after their appearance and those individuals or animals with the problem should be carefully handled with the appropriate medical expertise.

In line with the above conclusive statements the followings are some of the recommendations:

- ✓ Better approaches must be devised for reporting and assessing ADR.
- ✓ Medical and veterinary professionals should be trained in diagnosing and managing ADR.
- ✓ Pharmaceutical companies should strive to reduce the adverse effect of a drug.
- ✓ Further research should be conducted in the area of ADR.

REFERENCES

Alvarado, I., Wong, M.L., Licinio, J. (2002): Advances in the pharmacogenomics of adverse reactions. *Pharmacogenom J*. 2:273

Alvarez-Requejo, A., Carvajal, A., Begaud, B., Moride, Y., Vega, T., Martin, Arias, L.H. (1998): Under reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. *Eur .J. Clin Pharmacol* .54:483–488.

Busto, U., Naranjo ,C.A., Sellers. E.M.(1982):Comparison of two recently published algorithms for assessing the probability of adverse drug reactions. *Brit. J.Clin.Pharmacol*.13:223–227.

Carbonin, P.,Pahor, M., Bernabei, R., Sgadari ,A.(1991): Is age an independent risk factor of adverse drug reactions in hospitalized medical patients *Am. Geriatr .Soc.* 39: 1093–1099.

Carr, A and Cooper, D.A. (2000): Adverse effects of anti-retroviral therapy. *Lancet*.356:1423 1430.

Clay, P.G. (2002): The abacavir hypersensitivity reaction: a review. *Clin. Ther*.24:1502–1514.

Coté, C.F.H., Brumme .Z.L., Craib, K.J.P., Alexander, C.S., Wynhoven B., Ting, L., (2002): Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *New Engl J Med.*346:811–20.

Dean, M., Rzhetsky, A., Allikmets, R. (2001): The human ATP-binding cassette ABC transporter super family. *Genome Res*. 11:1156–1166.

Ditto, A.M. (2004): Drug allergy: In: (Grammer, L.C and Greenberger, P.A.) Eds.Patterson's allergic diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins. p. 295.

Evans, W.E., Relling, M.V. (1999): Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 286:487–491.

Evans, W.E., McLeod, H.L. (2003): Pharmacogenomics-Drug disposition. *New Engl. J .Med*. 348:538–48.

Fellay, J., Marzolini .C., Meaden, E.R., Back, D.J., Buclin ,T., Chave., J.P. (2002):Response to antiretroviral treatment in HIV-1 infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet*. 359:30–36.

Giovanni, Severino, Maria, Del Zompo. (2003): Adverse drug reactions and role of pharmacogenomics. *Pharmacological Research .49:363-373*

Hallas, J., Harvald, B., Gram, L.F., Grodum, E., Brosen, K., Haghfelt, T.,Damsbo, N. (1990): Drug related

hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J .Intern. Med.* 228: 83–90.

Hogan, C.M and Hammer, S.M.(2001):Host determinants in HIV infection and Disease. *Ann. Intern .Med.* 134:978–996.

Hosking, L.K., Boyd .P.R., Xu, C.F., Nissum, M., Cantone, K., Purvis, I.J. (2002): Linkage disequilibrium mapping identifies a 390 kb region associated with CYP2D6 poor drug metabolizing activity. *Pharmacogenom .J.2*:165–175.

Hutchinson, T.A., Leventhal, J.M., Kramer, M.S., Karch, F.E., Lipman, A.G,Feinstein, A.R. (1979): An algorithm for the operational assessment of adverse Drug reactions. II.

Demonstration of reproducibility and validity. *JAMA.* 242: 633–638.

Jill, Madison, Stephen, W. page. David, B. Church. (2008): Small animal veterinary medicine clinical pharmacology .2nd ed. ELBS Bailler, Scotland.Pp.44-45.

Jimmy, Jose, Padma, G.M., Rao. (2006): Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacological Research.* 54: 226–233.

K.D, Tripathis. (2003): Essential of medical pharmacology .5th ed. Butlera Tanners Ltd .London, Uk .Pp.60-67.

Kramer, M.S., Leventhal ,J.M., Hutchinson ,T.A.,Feinstein, A.R.(1979): An algorithm for the operational assessment of adverse drug reactions. Background, description, and instructions for use. *JAMA.* 242:623–32.

Lazarou, J., Pomeranz, B.H., Corey, P.N. (1998): Incidence of adverse drug reactions in hospitalized patients (in reply). J*AMA* .280:1743.

Lemberg, D.A., Palasanthiran, P., Goode, M., Ziegler, J.B. (2002): Tolerabilities and antiretrovirals in paediatric HIV infection. *Drug Safety.*25:973–991.

Lindpaintner, K. (2002): The importance of being modest-reflections on the pharmacogenetics of abacavir. *Pharmacogenomics.* 3:835–838.

Meyer Jone, (2003): Veterinary pharmacology and therapeutics .4th ed. The Lows a state university press. USA.P.7.

Mallal, S., Nolan, D., Witt, C., Mase, G., Martin, M., Moore, C. (2002): Association between presence of HLA-B5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* .359:727–732.

Maher, B., Alfirevic, A., Vilar, F.J. (2002): Promoter region gene polymorphisms in HIV- positive Patients with lipodystrophy.(Wilkins ,E.G.L, Park, B.K, Pirmohamed,M.)Eds. *AIDS.* 16:2013–2018.

Marc, A., Riedl, M.D., Adrian M., Casilla, M.D. (2003): Immunologic and non immunologic drug reaction.*Journal of allergy*.56:34-45.

Meyer, U.A. (2000): Pharmacokinetics and adverse drug reactions. *Lancet.*356:1667–1671.

Murphy, B.M and Frigo, L.C. (1993): Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. *Hosp Pharm.* 28 (12):1199–1204.

Nebert ,D.W., Russell ,D.W.(2002): Clinical importance of the cytochromes P450. *Lancet*. 360: 1155–1162.

Pirmohamed, M., Lin, K., Chadwick, D., Park, B.K. (2002): TNF- promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology*. 56:890–896.

Roses, A.D. (2002): SNPs-Where's the beef? *Pharmacogenom .J.* 2:277–283.

Pirmohamed, M and Park, B.K. (2001): Genetic susceptibility to adverse drug reactions. *Trends. Pharmacol. Sci.* 22:298–305.

Roses, A.D. (2002): SNPs-Where's the beef? *Pharmacogenom .J.* 2:277–283.

Schwab, M., Eichelbaum, M., Fromm, M.F. (2003): Genetic polymorphisms of the human MDR1 drug transporter. *Annu. Rev. Pharmacol Toxicol*. 43:285–307.

Shevitz, A., Wanke, C.A., Falutz, J., Kotler, D.P. (2001): Clinical perspectives on HIV- associated lipodystrophy syndrome: an update. *AIDS.* 15:1917–1930.