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Pharmacovigilance: review

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ABSTRACT

Pharmacovigilance outlined by the globe Health Organization (WHO) because the science and series of activities about the detection, evaluation, understanding rejection of adverse impact or Associate in Nursing different drug connected problem' and a clinical test could be an analysis study in human volunteers to answer specific health queries. Fastidiously conducted clinical trials square measure quickest and safest thanks to realizing treatment that employment in individuals and thanks to improving health. Play a crucial role in guaranteeing that patient to be provided the safe drug. The Pharmacovigilance has been recognizing to play a crucial role in the rational use of the drug by providing data concerning the adverse impact possess by drug normally population. The information of drug Adverse Drug Reaction (ADRs) are often increased by numerous suggests that such information studies, intensive observation, spontaneous reportage and different new method at dictatorial and scientific level square measure being developed with the intention of step-up Pharmacovigilance. As a result of assessment strategies are not entirely void of individual judgments, integrator reliableness is often low. In conclusions, there's still no methodology universally accepted for casualty assessment of ADRs.

Keywords: Need of Pharmacovigilance, History of Pharmacovigilance Adverse Drug Reaction, Clinical test, Methods utilized in Pharmacovigilance, Treatment.

INTRODUCTION

According to the world Health Organization, "Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effect or any other possible drug-related drawback, particular, long term and short term adverse effects of medicines" .

The history routes of the word "Pharmacovigilance" are: Pharmakon (Greek word of 'drug') and vigilare (Latin word for 'to keep watch'). These adverse drug reaction (ADRs) not only increase the suffering of patients but also increase morbidity and mortality in conjunction with a financial burden on society. The overall incidence of ADRs in hospitalized patients is estimated to be 6.7% (0.1-0.85%) 5. Data indicates

that in patients World Health Organization experience ADRs death rates area unit 19.18% higher and the length of hospital stay is 8.25% higher. The Total medical cost for patient with ADRs unit increased by average of 19.86%.

Pharmacovigilance is not new to Asian nation and has infect been going on from 1998 3. When Asian nations decided to join the Uppsala centre for adverse event monitoring. Spontaneous reporting of adverse drug reaction and adverse events is an important tool for gathering the safety data for early detection. it is widely accepted that a drug has to go through various phases of trial to establish its safety and efficacy before it is marketed commercially. However, the clinical trials offer various limitations, like; strict criteria of inclusion and exclusion make it to be used in a very selective group of patients; special population groups like kids, pregnant lady, and maturity population are not studied during the trials; and other factor causing drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trials.

NEED OF PHARMACOVIGILANCE

Improvement of patient care and safety in respect to use of medicines with medical and paramedical interventions remains to be a crucial parameter. The main objectives of Pharmacovigilance involve exhibiting the effectuality of medicine by observation their adverse impact profile for several years from the research lab to the pharmacy; trailing any forceful impact of drug rising public health and safety respect to the utilization of medicines; encouraging the safe, rational and efficient use of drugs; promoting understanding, educations and clinical coaching in Pharmacovigilance; and effective communications to the generic public

HISTORY OF PHARMACOVIGILANCE IN ASIAN NATION

Pharmacovigilance in Asian nation started from 1986. A proper Adverse Drug Reaction (ADR) watching system was initiated with twelve regional centers, every covering a population of fifty million. However, no noteworthy growth was created. Later in 1997, Bharat joined the globe Health Organization (WHO) and Adverse Drug Reaction (ADR) scrutinized program primarily based at 2 urban centers, Kingdom of Sweden however got fail. Hence when 2005 UN agency supported and World Bank fund National Pharmacovigilance Programme (NPPV) of Bharat was created.

Table 1: Chronology of Pharmacovigilance developments with special reference to India

Year	Developments
1747	Very first known clinical trials by James Lind, proving the usefulness of lemon juice in preventing scurvy.
1937	Death of more than 100 children due to toxicity of sulfanilamide.
1950	Apalstic anemia reported due to Chloramphenicol toxicity.
1961	Worldwide tragedy due to thalidomide toxicity

1963	16th World Health congregation recognize significant to rapid action on Adverse Drug Reactions (ADRs).
1968	WHO research project for international drug monitoring on pilot scale.
1996	Global standards level clinical trials initiated in India.
1997	India attached with WHO Adverse Drug Reaction Monitoring Program.
1998	Initiation of Pharmacovigilance in India.
2002	67th National Pharmacovigilance Center established in India.
2004-05	India launched National Pharmacovigilance Program.
2005	Accomplishment of structured clinical trials in India.
2009-10	Pharmacovigilance Program (Pv. PI) started.

ADVERSE DRUG REACTION (ADRS)

An adverse drug (ADRs) is outline as AN fortuitous and harmful to a health product that causes at the doses sometimes or tested for the diagnosing, hindrance or treatment of a malady or the alteration of AN organic function 25,26,27 Though, it's tough to acknowledge the actuating agent connected with the adverse drug reaction (ADRs) encountered contain quite ingredients 28. The magnitude f risk must be thought-about together with magnitude of expected medical specialty advantages decide whether or to use a specific drug in an exceedingly given patient 29. Adverse drug (ADRs) are classified in two ways:

- Foreseeable (Type-A) Reaction
- Unpredictable (Type-B) Reaction

Predictable (Type-A) Reaction

These square measure supported pharmacologic properties of the medicine like increased however quantitatively response to the drug that embody aspect effects, Gyanogenic effects and consequences of drug withdrawal 28,31.

Unpredictable (Type-B) Reaction

These square measure supported peculiarities of patient and not on drug's acknowledged actions; embody allergic reaction and specialty. These are less common, usually non dose connected, typically a lot of serious and need withdrawal of drug. An inventory of some suspected and acknowledged medicine related to adverse effect 28,30,31. The known Drug and its adverse effect shown in below table no. 2.

Table 2: known Drug and its adverse effect.

Drug	Adverse Drug Reactions (ADRs)
Thalidomide	Phocomelia,
Methotraxate	Multiple defects, Foetal death
Androgen	Virilization, limb, esophageal, cardiac defects
Progestins	Virilization of female foetus
Stilboestrol	Vaginal carcinoma in teenage female offspring
Tetracyclines	Discolored or deformed teeth, retarded bone growth
Warfarin	nose, eye and hand defects, growth retardation

CLINICAL TRIAL

A clinical trial could be an analysis study that tests a replacement medical treatment or a replacement manner of mistreatment Associate in nursing existing treatment to ascertain if it'll be higher thanks to stop and screen for diagnose or treat disease 34. Wide selection of dose of the study drug is given to Associate in Nursingimals subjects or to an in-vitro substrate so as to get preliminary effectuality, toxicity and pharmacokinetic information 35. Before pharmaceutical firms begin clinical test on a drug they conduct in depth pre-clinical studies

Pre-Clinical Studies

Pre-clinical studies involve in vitro (i.e. tube or laboratory) studies and trial or animal population. Wide travel dose of the study in drug area unit given so as to get preliminary effectualness, toxicity and pharmacokinetic data and to help pharmaceutical firms decide whether or not it's worthy to travel ahead with more testing.

Clinical Studies

Phase-0

Phase zero may be a recent designation for exploratory, first-in-human trial conducted in accordance with U.S. food and Drug administration (FDA) 2006 steerage on exploratory. Distinctive options of part zero trials embrace the administration of single sub-therapeutics doses of the study drug to a little range of subjects (10-15) to collect preliminary information on the agent's pharmacological medicine (how to body processes the drug) and Pharmacodynamics (how the drug add the body).

Phase-I

Phase I path area unit 1st stage of testing in human subject. Ordinarily a little (20-80) cluster of healthy volunteers are going to be elite. This part includes trails designed to assess the security (Pharmacovigilance) tolerability, pharmacological medicine and Pharmacodynamics of a drug. There are unit totally different styles of clinical trial trials.

SAD

Single Ascending Dose studies area unit those within which tiny cluster of subjects' area unit given one dose of the drug whereas they're ascertained and tested for a amount of your time.

MAD

Multiple Ascending Dose studies area unit conducted to raise perceive the pharmacological medicine of multiple dose of drug.

Phase-II

Once the initial safety of the study drug has been confirmed in clinical trial trials, clinical trial trials area unit performed on giant cluster (20-300) and area unit designed to assess however well the drug work in addition on continue clinical trial safety assessment in a very larger cluster of volunteers and patients. clinical trial studies area unit generally divided into clinical trial A and clinical trial B. clinical trial A is specifically style to access dosing necessities (what proportion drug ought to be given), wherever as clinical trial B is specifically designed to check effectualness (however well the drug work the prescribed dose (s)). Some trials mix clinical trial and clinical trial, and take a look at each effectualness and toxicity.

Phase-III

Phase III studies irregular controlled multi-center trials on giant patients cluster (300-3,000 or additional relying upon the disease/medical condition studied) and area unit geared toward being the definitive assessment of however effective the drug is compared with current 'gold standard' treatment.

Phase-IV

Phase IV trial is additionally called Post promoting police work Trial. Phase IV trials involves the security police work (Pharmacovigilance) and current technical support of a drug once it receive permission to sold.

Table 3: Phases of Clinical Trial

Phase	Group
0	10-15
1	22-80
1A	Single Ascending Dose (SAD).
1B	Multiple Ascending Dose (MAD)
2	20-300
3	300-3000
4	Post Marketing Surveillance Trial.

The security police work is intended to observe any rare or semi permanent adverse result over a far larger patient population and longer period than was potential throughout the harmful result discovered by phase IV trials might end in a drug being not sold, or restricted to bound uses. Recent example involves Baycol (branch names Bycol and lipobay) trogelitazone (Rezulin and Vioxx-vioxx) 35. The segment of phase IV was shown in figure no. 3.

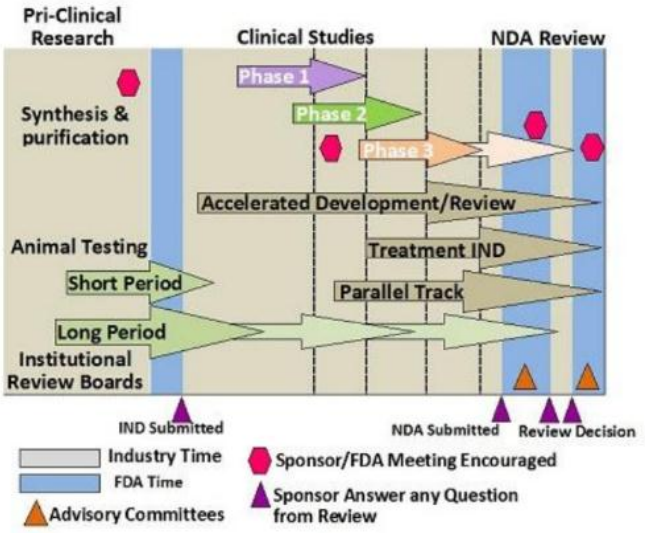

Figure 2: Phase of Clinical Trial

METHODS UTILIZED IN PHARMACO-VIGILANCE

The activities undertaken in the name of Pharmacovigilance can be roughly divided into three groups: regulatory, industry, and academia. Regulatory Pharmacovigilance is driven by the aim to provide drugs with a positive benefit- harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by a description of the methods used to detect new ADRs and a discussion of the pros and cons of each method

- Dangaumou's French method
- Kramer et al. method
- Naranjo et al. methodology (Naranjo scale)
- Balanced assessment method
- Ciba-Geigy method
- Loupi et al. method
- Roussel Uclaf casuality assessment method
- Australian method

Dangaumou's French method

This rule of thumb has been used by the French government agency since 1977. The way of doing thing separates an intrinsic imputability (possible case between abused substance and dispassionate event) from an extrinsic imputability (bibliographical data) by the agency of seven criteria (three connected and four semiological) in two different tables. The criteria are (i) drug challenge, (ii) dechallenge, and (iii) rechallenge by the overall score of four possible categories. The semiological criteria are (i) semiology (clinical signs) using per se (suggestive or other), (ii) favoring component, (iii) arbitrary non drugrelated (none or possible), and (iv) laboratory tests show with three possible outcomes (positive, negative or no test for the event-drug pair). Scores are grouped as possible and dubious.

Kramer et al. method

This method applies when the offending drug is administered and a single adverse drug event has taken place. Each adverse event is assessed independently and assessment is prepared. One of the advantages of this algorithm is its transparency. However, certain levels of experience, expertise, and time are required to use this method effectively.

Naranjo *et al.* method (Naranjo scale)

It is utilized to verify causality in a variety of clinical situations utilizing the categories and definitions of definite, probable, possible, and doubtful. It consists of ten questions which are answered as yes, no and unknown. The event is assigned to a probability category predicated on the total score after totaling. A total score of ≥9 is definite, probable is 5-8, possible is 1-4 and doubtful ≥0. This scale is more powerful when the adverse event is associated with only one drug, but when multiple drugs are involved or there is any interactions between drugs, this scale fails to identify the offending agent.

Balanced assessment method [15]

This method evaluates a case report on various visual analog scale (VAS) models that each criterion is fulfilled individually. It has an added advantage that it considers an alternative causative factor as a possibility and not just as a separate factor. Each case is assessed independently by different assessors and the evaluation depends on the assessor's skills knowledge.

Ciba-Geigy method

Expert consensus meetings have resulted in Ciba-Geigy method. Experts used their clinical judgment to assess adverse drug events and assign causality on a VAS. This method uses a checklist which is composed of 23 questions, which is split into three sections: (i) History of present adverse reaction, (ii) patient's past adverse-reaction history, and (iii) monitoring-physician's experience. This updated method was found to have a high degree of agreement (62%) when compared with evaluator's assessments.

Loupi *et al.* method

This method developed to assess the teratogenic potential of drug. The first sections of the algorithm sanction for the drug to be omitted if not implicated in the inception of the abnormality. The second section weighs the bibliographical data. The three questions consider alternative etiological candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.

Roussel UCLAF causality assessment method

This method is used in disease states such as liver and dermatological problems. A retrospect assessment of the reproducibility of this method among four experts had showed a 37-99% agreement rate.

Australian method [18]

Australian method involves the evidence which helps in to draw the conclusion, such as timing, and laboratory information from case reports presented and the antecedent cognizance

SIGNAL DETECTION AND EVALUATION STEPS

The evaluation steps for safety and prevention of ADR are shows in figure (Reproduced with permission from the Report of CIOMS Working Group VIII

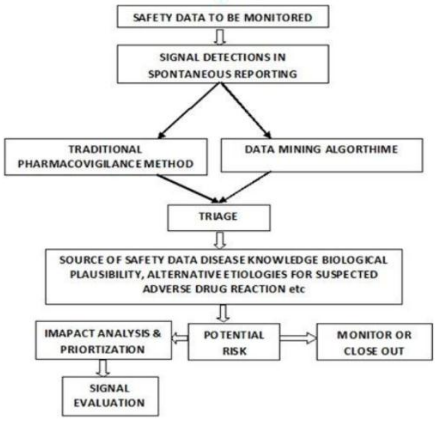

Figure no.2 Signal detection and evaluation steps (reproduced with permission from the Report of CIOMS Working

REFERENCES

[1]. Australian Wound Management Association (AWMA) Australia, 30/4/13, 2010. www.awma.com.au/

[2]. Australian Wound Management Association (AWMA). *Position Document of the Australian Wound Management Association: Bacterial impact on wound healing – from contamination to infection.* AWMA 2011.

[3]. Baranoski S. choosing a wound dressing, *nursing*, 38(1), 2008, 10–12.

[4]. Beele H et al. "Expert consensus on a new enzyme alginogel", *Wounds UK*, 8, 2012, 64–73.

[5]. Carville K.. *Wound Care Manual*, 5th ed. 2007 Osbourne Park: Silver Chain Foundation.

[6]. Flanagan M. *Wound Management*, 1997 New York: Churchill Livingstone.

[7]. Fletcher J. Dressings: cutting and application guide. Accessed 15/1/09 from www.worldwidewounds.com/2007/ may/Fletcher/Fletcher-Dressings-Cutting-Guide.html

[8]. Hess C. *Clinical Guide: Wound Care*, 3rd ed. Springhouse, Pennsylvania: Springhouse Corporation. Probst A et al. *Cutimed Sorbact Made Easy*, Wounds International, 3(2), 2012.

[9]. Selim P... The use of Antiseptics in Wound Management: A Community Nursing Focus. *Primary Intention*, 2000, 63–66.

[10]. Sussman C, Bates-Jensen B... *Wound Care: A Collaborative Practice Manual for Physical Therapists & Nurses*, Maryland: Aspen Publishers, 2000, 201-213.

[11]. Thomas S. A structured approach to the selection of dressings. *J Wound Care*, 6, 2000, 1-15.

[12]. Thomas S. Soft silicone dressings: frequently asked questions. Accessed 14/01/09 from www.worldwidewounds.com/2003/october/Thomas/Soft- Silicone-FAQ.html

[13]. Ulcer and Wound Management Expert Group *Therapeutic Guidelines: Ulcer and Wound Management*, version 1, 2012 Melbourne: Therapeutic Guidelines Limited.

[14]. World Union of Wound Healing Societies *Principles of Best Practice: minimising pain at wound dressing-related procedures. A consensus document*. 2004 London: MEP Ltd.

[15]. World Union of Wound Healing Societies *Principles of Best Practice: Wound exudate and the role of dressings. A consensus document*.2007 London: MEP Ltd.

[16]. Wound Healing and Management Node Group Evidence *summary: wound infection: silver products and biofilms*. 2012 Joanna Briggs Institute.

[17]. Wound Healing and Management Node Group Evidence *summary: wound management: dressings – alginate*. 2012 Joanna Briggs Institute.
[18]. http://www.fortunejournals.com/abstract/a-thoroughgoing-detail-of-surgical-dressings-406.html
[19]. Pipasha B, Biswas AK. Setting standards for proactive pharmacovigilance in India: The way forward. Indian J Pharmacol 39(3), 2007, 124-8.
[20]. WHO. Pharmacovigilance: Ensuring the Safe Use of Medicines. Geneva: WHO; 2004.
[21]. Skalli S, Soulaymani Bencheikh R. Safety monitoring of herb-drug interactions: A component of pharmacovigilance. Drug Saf 35(10), 2012, 785-91.
[22]. Arnott J, Hesselgreaves H, Nunn AJ, Peak M, Pirmohamed M, Smyth RL, *et al.* What can we learn from parents about enhancing participation in pharmacovigilance? Br J Clin Pharmacol 75(4), 2013, 1109-17.
[23]. Gerritsen R, Faddegon H, Dijkers F, van Grootheest K, van Puijenbroek E. Effectiveness of pharmacovigilance training of general practitioners: A retrospective cohort study in the Netherlands comparing two methods. Drug Saf 34(9), 2011, 755-62.
[24]. Kshirsagar N, Ferner R, Figueroa BA, Ghalib H, Lazdin J. Pharmacovigilance methods in public health programmes: The example of miltefosine and visceral leishmaniasis. Trans R Soc Trop Med Hyg 105(2), 2011, 61-7.
[25]. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 279(15), 1998, 1200-5.
[26]. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. J Clin Epidemiol 46(11), 1993, 1323-30.
[27]. Agbabiaka TB, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: A systematic review. Drug Saf 31(1), 2008, 21-37.
[28]. Macedo AF, Marques FB, Ribeiro CF, Texeira F. Causality assessment of adverse drug reactions: Comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel. Pharmacoepidemiol Drug Saf 14(12), 2005, 885-90.
[29]. Dangoumau J, Evreux JC, Jouglard J. Mehtod for determination of undesirable effects of drugs. Therapie 33(3), 1978, 373-81.
[30]. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. JAMA 242(7), 1979, 623-32.
[31]. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30(2), 1981, 239-45.
[32]. Lagier G, Vincens M, Castot A. Imputability in drug monitoring. Principles of the balanced drug reaction assessment method and principal errors to avoid. Therapie 38(3), 1983, 303-18.
[33]. Venulet J, Ciucci A, Berneker GC. Standardized assessment of drug-adverse reaction associations – Rationale and experience. Int J Clin Pharmacol Ther Toxicol 18(9), 1980, 381-8.
[34]. Loupi E, Ponchon AC, Ventre JJ, Evreux JC. Imputability of a teratogenic effect. Therapie 41(3), 1986, 207-10.
[35]. Mashford ML. The Australian method of drug-event assessment. Special workshop – regulatory. Drug Inf J 18(3-4), 1984, 271-3.
[36]. Hutchinson TA. Computerized Bayesian ADE assessment. Drug Inf J 25, 1991, 235-41.
[37]. Hutchinson TA, Dawid AP, Spiegelhalter DJ, Cowell RG, Roden S. Computerized aids for probabilistic assessment of drug safety: I. A spreadsheet program. Drug Inf J 25, 1991, 29-39.
[38]. World Health Organization (WHO), Uppsala Monitoring Centre. The use of the WHO-UMC System for Standardized Case Causality Assessment. Available from: http://www.who-umc.org/graphics/4409.pdf.