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PHARMACOVIGILANCE: AN OVERVIEW ON TRAMADOL

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ABSTRACT

Pharmacovigilance, defined by the World Health Organization as 'the science and series ofactivities relating to the detection, evaluation, understanding and avoidance of adverse effectsor any other drug-related problem' plays an important role in ensuring that patients be givensafe drugs. India is now a preferred clinical trials port of call for drug entities to be launched.By viewing the increasing incidences, dug related mortality rate, proper identification of ADR's, reporting, evaluation and under standing of adverse drugreaction lead stothe development of pharmacovigilance. In India, the Central Drug Standard Control Organization (CDSCO) whose headquarter is located at New Delhi regulate the PV activity. For smoothand effective working of PV a Pharmacovigilance Program of India (PvPI) was proposed andimplemented by government of India in 2010.Ithelps to detect previously unknown effectsof a drug and provides information from real-life clinical practice, throughout the life of thedrug.

KEYWORDS: Pharmacovigilance, Adverse Drug Reactions, CDSCO, health care professionals, National Pharmacovigilance Programme (NPPV), ADRreporting, Tramadol Dependence.

INTRODUCTION

Pharmacovigilanceisdefinedasthepharmacologicalscience relatingtothedetection,assessment,understanding,andprev entionofadverseeffects,particularly long-termandshort-term side effects, of medicines. While not well understood by those outside of the drugsafety world, pharmacovigilance plays a pivotal role in helping to ensure patient safety forbothnewlyreleasedd rugsandthosethatarewell-establishedinthemarket.[1]

Pharmacovigilance involves consumers, health care professionals (HCPs), pharmaceuticalcompanies, and global regulatory agencies, each of whom plays a unique and critical role inthisprocess.[2]

Importance of PV

It is the science which deals with the complex processof the understanding and explainingthe nature of ADR occurred in a patient taking either oral or parenteral or intravenous (I.V.)drugs for an ailment. The drugs being marketed worldwide underwent a whole array of testsand also underwent clinical trials in animals and human subjects to assess the safety of thedrug for a particular disease and to know the exact side effects associated with it. Still there isa major part of it goes undetected and some of the ADR are detected in post marketingsurveillance. It is estimated that there is significant amount of ADRs which decreases thequalityoflife,increasehospitalizationstayandincreasest hemortality. Alandmarkstudyby

Lazarou in 1998 described, ADRs to be the fourth to sixth leading cause of death in the USandADRs areestimatedto cause3-7%of all hospital.[1,3,7]

Aim of Pharmacovigilance Programme of India

1. Improve patientcareandsafetyinrelationtothe use ofmedicinesandallmedicalandparamedicalinterventio ns.
2. Improvepublichealth andsafetyin relation totheuseof medicines.
3. Contributetotheassessmentofbenefit,harm,effectiven essandriskofmedicines,encouragingtheirsafe,rational and moreeffective (includingcosteffective)use.
4. Promoteunderstanding,educationandclinicaltrainingi nPVanditseffectivecommunicationto thepublic.[6,11]

History of Pharmacovigilancein India

History of Pharmacovigilance in India Pharmacovigilance in India started from 1986.[8] Aformal Adverse Drug Reactions (ADR) monitoring system was initiated with 12 regionalcentres, each covering a population of 50 million.[9] However, no noteworthy growth wasmade. Afterward in 1997, India joined the

World Health Organization (WHO) and AdverseDrug Reaction (ADR) scrutinizing program based at Uppsala, Sweden but got fail. Hence, after 2005 WHO supportedand World Bank–funded National Pharmacovigilance Programme (NPPV) of India was made operational.[11,13]

Developmentin Pharmacovigilance[1,5,27]

Table 1: The sequential pharmacovigilance developments with special reference toIndia.

Year	Developments
1747	Veryfirst knownclinicaltrialsbyJamesLind,provingtheusefulnessoflemonjuicein preventingscurvy.
1937	Deathofmorethan100childrenduetotoxicityofsulfanilamide.
1950	Apalsticanemiareportedduetochloramphenicoltoxicity.
1961	Worldwidetragedyduetothalidomidetoxicity.
1963	16thWorldHealthcongregationrecognizesignificanttorapidactiononAdverseDrug Reactions(ADRs).
1968	WHOresearchprojectforinternational drugmonitoringonpilot scale.
1996	Globalstandardslevelclinicaltrialsinitiatedin India.
1997	IndiaattachedwithWHOAdverseDrugReactionMonitoringProgram.
1998	InitiationofpharmacovigilanceinIndia.
2002	67thNationalPharmacovigilanceCenterestablishedinIndia.
2004	IndialaunchedNationalPharmacovigilanceProgram.
2005	Accomplishmentofstructuredclinicaltrialsin India.
2009-10	PharmacovigilanceProgram(PvPI)started.

Table 2: Activitiescurrentlyincludedin thescopeofpharmacovigilance.

Category	SpecificActivities/Functions	Phase(s)*
Supportingpatientsafetyduringtheconductof clinicaltrials	Informed consent, institutional reviewboard,datamonitoringcommittee	1-4
Selecting the first safe dose; first-in-human	Preclinicaldata,especiallyPK/PDparameters	1
Establishingthesafetyprofile	Assessing all phases of development,focusing on dose-limiting toxicity,maximumtolerateddose, AEsofspecial interest,on-targetandoff-targettoxicities	1-4
Communicating information tostakeholders	Maintainingstandardformats:Investigator'sBrochure,CompanyCoreDataSheet,packageinsert, patient package insert,ClinicalTrials.gov	1-4
Attendingtosurveillance activities	Determiningrelationshipsbetweendrugsandadverseeventsthroughpassiveandactivemethods	1-4
Monitoring safety-related issues thatinvolvethequalityof themanufactured product	Conductinghealthhazardassessmentsformanufacturingdeviations, complaints	1-4
Managingrisk:REMS,RMP	Understandingbenefiteriskacrosspatientpopulationsand uses	1-4
Maintaininginspectionreadiness	Preparationforscheduledandunscheduledinspectionsofdepartmentactivities	1-4
Training	Clinicalinvestigators;internalcustomersthroughoutthecompany;vendors	1-4
Advertisingandpromotionreview	Assuring consistency with importantsafetyinformation	4
Providingmedicalinformationtohealthcareprofessionals	Supportforprofessionalqueriesregardingproductcomplaints,AEreports,productuse	4
Conductingduediligence	Understandingcriticalsafetyinformationaboutproductsbeingconsideredformerger,acquisition,orlicensing activities	1-4

Adverse Drug Reactions (ADRs)

Process of Adrreporting

According toWHO'S definition an Adverse Drug Reaction (ADR) isaresponse toa drugthatis noxious and unintended, andoccursat doses normally used in human fortheprophylaxis, diagnosis, and treatmentofdisease, or formodification of physiological function.[8]

Estimated that ADRs were the fourth to sixth largest cause of death in the United States.There are few recent reports on epidemiology of ADRs. In United Kingdom most of thestudies were performed in the previous two decades and were restricted to specific areas suchasmonitoring of ADR singeriatricpatients.[11] Thelargest UK studywasbasedonretrospective review ofcasereports andgavepoordocumentation.[19]

ADR reporting

To increase interest of consumer and Health Care Professionals (HCPs) a feedback letter orform facility

was started. All the universities incorporated PV as curricular subject and someprivateinstitution havestarted providingprofessional courses and trainingon PV.[14]

Indiaisamulti-linguisticnation, forthebetterunderstanding ofconsumer,reporting formsarepreparedinverna cularlanguages whichareavailable 24×7onofficialwebsite (pvpi.compat@gmail.com). In India it is mandatory for the Marketing Authorization Holders(MAH) to submit PSUR (Periodic safety update reports) to CDSCO twice ayear for 2consecutive years; this attempt helps to collect safety data of on-going marketed productregularly.[10]

Most of these reporting systems are voluntary, primarily relying on the vigilance of healthcare professionals. Voluntary reporting involves consumers in the US, and to a minor extent in Australia.However, in most countries, physicians are the main contributors to ADR databases, except in the Netherlands and Canada, where community pharmacists play the major role in ADR reporting.[28]

Table 2:-Some Known ADR.[4]

Drug	AdverseDrugReactions(ADRs)
Thalidomide	Phocomelia,Multipledefects
Methotraxate	Multipledefects,Foetal death
Androgen	Virilization,limb,esophageal,cardiacdefects
Progestins	Virilizationoffemalefoetus
Stilboestrol	Vaginalcarcinomainteenagefemaleoffspring
Tetracyclines	Discoloredordeformedteeth,retardedbone growth
Warfarin	nose,eyeandhanddefects,growthretardation
Phenytoin	Variousmalformations
Lithium	Foetalgoiter,cardiacand otherabnormalities
Aspirin/Indomethacin	Prematurecloserofductusarteriosus

Tramadol

Tramadolasacentrallyactinganalgesicisextensivelyusedint hemanagementofmoderateto severe pain. It slightly affects opioid receptors and inhibits the reuptake of norepinephrinand serotonin in the CNS. There are reports about toxicity and abuse of tramadol. Tramadoloverdosehasbeenoneofthemostfrequentcausesof drugpoisoningintheworldintherecent years, especially in femalewith history of substance abuse and mental disorders. Nausea, vomiting, Central Nervous System(CNS) depression, tachycardia, and seizurearethe mostcommonfindingsinthiskindofpoisoning.Cardiopulmo naryarrestwasfoundasthecauseofdeathincaseswhohadinge stedmorethan5000mgtramadol.[25-27]

Table 3: Workontramadol indifferentgeographicalarea.

S. No.	Year	Title	Place	Reference
1	2017	Serious adverse drugreactions with tramadolreported to the Frenchpharmacovigilancedatabase between 2011and2015	French NationalPharmaco VigilanceDatabase	Moulis, Florence, et$_{al.}$[20]
2	2014	Acutetramadol poisoning and its clinical andlaboratory findings	LoghmanHakimhospital, Iran	Rahimi,HamidReza,et al.[22]
3	2013	Adverse drug reactionmonitoring: support forpharmacovigilance at atertiarycarehospital in NorthernBrazil	Hospital Geral de Palmas(HGP)inTocantins,Brazil	de Araújo Lobo, et$_{al.}$[16]
4	2013	Serious adverse drugreactions with tramadol: a2010-2011 pharmacovigilancesurveyinFrance	French PharmacoVigilanceCentres (CRPV) and pharmaceutical companies	Abadie, Delphine, et$_{al.}$[19]
5	2011	TramadolDependence: ACaseReport	AFMCPune, India	Prakash,J.,etal.[21]
6	2011	pattern of use and AdverseDrug Reaction of Tramadol; AReview of 336, 610,664 Insured Prescriptions During5Years.	International Journal ofPharmacology,Tehran,Iran	Soleymani,F., etal.[25]
7	2010	Tramadol overdose as acause ofserotonin syndrome:acaseseries		Tashakori, Ahmad, et$_{al.}$[14]
8	2009	Tramadol Induced Seizure:Reportof 106 Patients	Comparative Medicine Research Center, Shiraz	Pedramfar,P., etal.[13]
			University of Medical Sciences, Shiraz,Iran	

9	2008	Tramadol intoxication: areview of 114cases	Beheshti University of Medical Sciences, Tehran,Iran	Shadnia, Shahin, et$_{al.}$[24]
10	2007	New guideline for tramadolusage following adversedrug reactions reported totheIranian PharmacovigilanceCenter	Iranian PharmacovigilanceCenter	Gholami, K.,etal.[17]
11	2006	Pattern of adverse drugreactions notified byspontaneous reporting in anIndiantertiarycareteaching hospital	Kasturba Hospital, Manipal inSouthIndia	Jose,Jimmy,etal.[15]
12	2006	Tramadol-inducedhypoglycemia.2cases	PresseMedicale,Paris,France	Grandvuillemin,Aurélie,etal.[23]
13	2005	Side effects of tramadol: 12years ofexperienceinthe Netherlands	Netherlandssince1992 -2005	Kabel,J. S., etal.[18]

CONCLUSION

PV remains a dynamic part of the clinicians and the general population. After the appearanceof these adverse drugs effects, it is very essential that these are reported timely and analyzed.Not only the doctors should be aware of the PV programme but thepatients themselvesshould be made aware of this so self-reporting is increased and the burden on the clinicians isalso reduced. India is still in the growing. Phase of PV and more reporting is necessary toreach the world's standard of reporting these adverse events to provide effective drug use inchildren's and pregnant women which is one of the most vulnerable populations of all. ThePV programme must be able to identify these adverse events timely in the coming years withthe help of clinicians, patients, and the pharmaceutical industry to help shape the safety ofpatientsthemselves.

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