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A REVIEW IN PHARMACOVIGILANCE SYSTEM AND SAFE DRUG TREATMENT; VALPROIC ACID

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ABSTRACT

Pharmacovigilance is the best way to reduce reaction the adverse drug reaction of drug and safe guide drug taken safe drug treatment during disease Condition. pharmacovigilance system run by main Component of pharmacovigilance i. e. adverse event management safety case management and individual case report.These review artice focus on aim component of pharmacovigillance and pharmacovigilance programme of India & studyof Valproic acid there adverse reactions and toxicology study.

The valporic acid is antiepileptic class drug use in partial and generalised seizures. Main machanism of valporic acid is inhibition of GABA transaminase ultimately GABA metabolism decrease. The article report side effect, adverse drug reactions of valporic acid and safe use of valporic acid.

Keywords: Valporic Acid, Safety, Adverse Drug Reaction, Reporting,

I. INTRODUCTION

Pharmacovigilance is also known as drug safety. Pharmacovigilance is the branch of Pharmacy which deals with the study of activities relating to the detection assessment understanding and prevention of adverse effect or any other possible drug related problems.

Pharmacovigilance is a healthcare proffesion it plays important role in insuring that doctors together with patients have appropriated information. To take a dicision to choose a drug for a disease treatment. In Some countries ADR rank among the top 10 leading course of mortality. In machanism for evaluting monitoring safety of the medicine in the clinical use.

History

order to reduce or to prevent harmful effect to patient and thus improve public health. The In 1950 the west german pharmaceutical Company provide medicine of Thalodamide drug use as sedatives and Hepnotics.The drug use in treatment of seditive and Hepnotic condition in Australia. In the Europian country, drug use as treatment of nausea in pregnant women. But, in new born baby the malfunctioning develop after some days the ADR detected by European Country the development of malfunctioning due to Thalidomide administration.

Afted delection of ADR of Thalidomide ,the drug banned in 1961 this tragedy consideter as black day in Europe. After this tragedy the WHO decide & Create the Intrnational Drug Monitoring Program (IDMP)in 1968 ensure the evidence about harm to patients was collected from as many sources as the possible. In 1997 India became the member of WHO program for International Drug Monitoring Center which is managed by Upsala Monitoring Center.

In 2005 the PVPI program by MOHFW Govt. Of India and with rules and regulations started in 2010 .At the AIIMS new Delhi as National co- ordition center (NCC).

Objectives -:

- To improve patient care & safety in the treatment for use of medicine. The main objective of pharmacovigilance involves to exhibiting the efficacy of drug by monitoring the adverse effect. Profile collected many years from lab.to pharmacy. Tracking any drastic effects of drug improving public health & safety in choosing medicine.
- In addition providing information to consumers regulators and practitioners for effective use of drug.

components of pharmacovigilance

1.Adverse event Case management 2.Aggregate report managemens intramar 3.Safety signal management/ megal 4.Risk management 5.Individuay case reporting,

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Adverse event Case management- The ADE System is health data system, safety management & Survilence method. Reporting system use for administrative data as the sole data, those focusing only on non-medication related adverse effect which is related to Complementary and alternative medications food suppliments & over the counter medication. We take a data Form in the Microsoft Excel 2010. Two study authors (CBCH) independantly extracted data on field characteristics & prop. Including wheather fields were mandatory or optional data type & data quality Checks & alerts. Were embedded.

Reporting Elements → patient information →ADE description→ suspect & concomitant drugs

→ Reporter information → Discusion → conclusion.

Aggregate report management:- In the aggregate report management the reporting is the process of review the cumulative safety information from a wide range of sources on a periodic basis and also submit the finding to regulator world wide.

The reports focus not so much on individual cases but on the overview assessment of safety profile and risk benefit ratio of the adverse drug reaction and the serious adverse event and also pregnancy reports.

Types of aggregate report management:-

a) Pre marketing reports

1) Investigation new drug annual report
2) Clinical study report
3) Development safety update reports
4) Annual safety reports

b) post marketing reports

1) Periodic benefit is evolution report
2) Periodic advanced drug experience report
3) NDA and ANDA annual reports
4) Addendum to clinical overviews.

Safety signal management :-

The process of the safety signal management is based on examination of the individual case report aggregate data from active survival system.

Following are the steps of the safety signal management

Signal detection:-Signal detection and management in pharmacovigilance involves the ongoing monitoring of individual case safety reports (ICSR) to identify case reports or case report series of adverse events (AE) for further exploration and requires safety actions such as a safety signal investigation.

Signal validation:-Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association.

Signal confirmation:- The signal confirmation is the process of determination of signal if the validity signals have a further analysis and prioritisations by the PRAC then the safety signal is confirmedn. If a validated safety signal could be non conform for a several reasons for example if safety signal was previously reviewed, Limited evidence submitted.

Signal analysis and priorization:- The signal analysis is necessary to separate safety signals that have big impact on a patient or the public health care or also can significantly affect the risk benefit ratio of the medical product. The safety signal analysis and prioritizsation process will determine the need for further analysis under time frames of it.

Signal assessment and recommendation for action:- The last stepof the safety signal management is signal assessment and recommendation for the action this process will take into the account of all available evidence and determine or the determination if there are changed risk or new.The PRAC recommendations for the taking action can be more or less severe.

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Depending on the type of signal

4) Risk Management -: The medicinal product authorized On the basis of specified indications (s), at the time of authorisation the risk Benefit is judged positive for the Population.

Diff.steps of Risk Management -:

a) Risk detection of Assesment

1. Identify the risk -:

The identification" of risk by the following

Sources -:

Preclinical studies

Harm & identified in clinical trials & meta-analyses.

-formal mortality & morbidity studies 2.Understand the risk:-

Following are ways to understand the risk

-Rigorous Case defination

- Case series analysis.

- Clear description in label

iii) Monitor the risk -: The data collected. Firstly identification of risk & then understanding of risk. The monitoring of risk by

following -:

•Postmarketing Survillence

•Database analyses.

•prospective cohort disease & registries (to study potentially meme but important risks Where risk identificat | Product attribut" is difficult.

b) Risk minimisation & Communication -:

1. Communicate misk – Advice in liable (not enough to communicate specific misk mimimi Gation activities / change behaviours.

• Partneeship with regulators

• Education of Physician Patients & company staff

2. Act to reduce the risk -:

Following are the important steps to reduce the risk.

- Limited distribution .
- Limited prescribing rights.
- Contraindicate for certain groups indication route of administration.
- Advice for high risk group. Function -:

1) Identification and analysis of new adverse reaction signal from case report
2) provision of WHO database as refference source for signal strengthning
3) Information exchange between WHO & National centres by email information exchange system.
4) Running training courses in Pv.
5) Publication of periodical news letter in Pharmacovigilance

Preclinical Studies -:

In India regulatery guidelines schedule Y are conducted for the preclinical studies of drug In schdule Y there are some regulations and guidelines for preclinical or clinical that is permission for development manufacturing of newer drug and selling and marketing in India. These guideline last mention in jan, 2005.

The data are generated or submitted along with IND application to conduct the above mentioned studies which includes mainly.

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1) Introduction (Brief description of drug and therapeutic class)
2) chemical and Pharmaceutical information
3) Animal Pharmacology and toxicology
4) Clinical trials

- Determination of pharmacological action -: The determination of pharmacological action of chemical substance (potential drug) these are screened on series of biological system example. isolated organ
- General pharmacological action-:

Essential safety Pharmacology study need to be conducted or investigated underable pharmacodynamic effect of drug on pharmacological function.

In this story study of pharmacudaynamic properties which are safe to human adverse recodynamic. The aim of essential safety Pharmacology is study of effect of functiot taste drug on vital function

Specific Pharmacology Action -:

Demonstrate therapeutic potential for humans. These design individual properties and uses of investigational drug.

- Pharmacokinetic studies -:

Pharmacokinetic testing is done to provide data on how drug is absorbed, distributed, metabolised and excreted by body.

- screening test -:

1) Indicate presence or absence of particular form pharmacokinetic or pharmacodynamic activity.
2) Teste on isolated organs -: To detect specific activity.
3) Teste on animal models of human disease -: example. experiment TB on Mouse
4) pharmacoKinetic -: study of absorption distribution metabolism and excretion.

- clinical trials-:

Trials in man is identify by animal studies which are approaches by FND. In which encompasses the design conduct termination, audit,analysis ,report and documention of studies involving human subjects.

- phases of drug development --:

These alarmed in FDA and cost cutting approaches in drug development many drug fail in clinical trials due to substance optimal pharmacoKinetics on healthy volunteers.

Phase 1-: Human pharmacology safety

The first human administered of drug carried out by qualified clinical pharmacologiest mostly Healthy volunteers and patients are used.

The emphasis even safety lerability and to detect dangerous effect on vital function Phase 2-: Theraputi explanation of dose ranging

Involve 100 to 500 patient.

Efficacy and pharmacokinetic are studies. Phase 3 -: Therapeutic confirmation

500 to 3000 patients used.

Safety and tolarity study by FDA and NDA convined marketing permission

1) Trial conducted after efficacy of the medicine is demonstrated, but prior toregulatory submission of a NDA.
2) clinical trials conducted after regulatory submission of an NDA may directed towards phase 4 evolution.

Phase 4 -: PMS

Phase 4 trials includes additional drug drug interaction dose response and safety

Phase 4 studies are required to follow the some scientific and ethical standards as per marketing studies.

Function of NDA -:

New Drug (approved) Application.

The NDA application is is the vehicle through which drug sponsor fromally purpose that the FDA approve a new pharmaceutical for sale and marketing.

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The data gathered during in the animal studies and human clinical trials of an investigation drug becomes.

Function of IND -: Investigation new drug Exploratory IND -: conducted early in Phase 1.

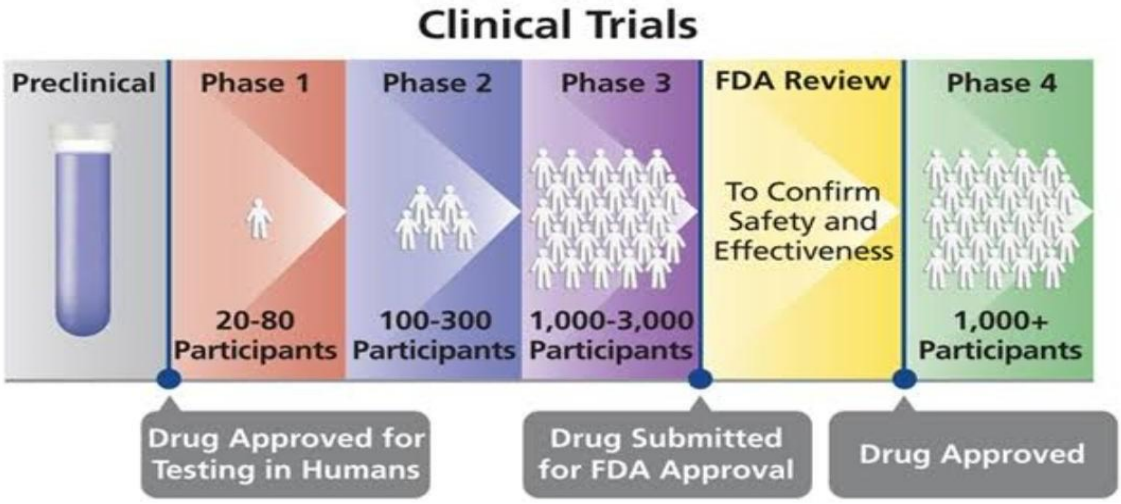
Allow the experiment drug in emergency situation. Investigation IND-:

Submitted by physician to purpose studying.

An approved drug or product new indications or in new patient population.

Submission of experimental drug showing promise in clinical testing for serious or immediately life threatning condition

	Phase 1	Phase 2	Phase 3	Phase 4
Objectives	Determine the metabolic & P'codynamic effect in human	Establishment of therapeutic efficacy dose range	Safety , tolerability And possible drug interaction are assesed on wider scale	monitor safety in large population
Factor to be identified	Checking for safety	Checking for efficiency	Both efficacy and safety	Efficacy and safety within large population
Population	Healthy volunteers	Individuals within target disease	Individuals and target disease	Individuals with target
	sometimes patient		gastric patient and pregnant women	disease as well as age, groups ,gender
Sample	20 to 1000	100 to 300	100 to 1000	1000 to 3000



Good clinical Practice

ICH -: International Conference on Harmonization GCP -: Good clinical Practice

ICH =GCP

Quality data + ethics = GCP

- The good clinical a practice cover the step.

1. Design 2.Performance

3. Inonitoring 4.Auditing 5.Analysis

6. Reporting

objectives. -:

1) To provide on overviews of history of good clinical practice (ICH) .

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2) To emphasis importance of ICH CGP complaints when conducting clinical trials.
3) To recognise implication of non compliance .
4) To review positive and negative cause studies.
5) protect the patient
6) Avoid trials duplications for medicinal product containing new.

scope of GCP -:

Good clinical lab. show be used by an Laboratories where teste are done on biological specimen diagnosis, patient care, disease cannol.

- Microbiological and scleroology
- Hematologic and blood banking
- Molecules biology and Molecular Pathology
- Histopathology

Key change in 2019 new drug and clinical trials rules -:

In new rule 2019 search research has been defined to include studied on basic applied and operational research or clinical research designed primary to increase scientific knowledge about disease and condition(Physico-social behavioural) they are, detection and cause and involving strategic, health promotion, amiliaration disease erehabitation does not include CT study type include.

- Intire diagnosis (IVDS) performance testing for research.
- New surgical invention.
- Assisted reproductive technique
- Public Health surgery
- observation and non- inventional study of old drug.

These type studies should be approve ethics committees constitute under rule 16 registerd under rule 17 with CBSCO office as ethics committees for biomedical and health research.

Academic clinical trials -: New drug rule 2019 describe academic clinical trials as clinical of drug add ready approved for certain claim and initiated by investigator academic research institution for new indications or new route of Administration or new dose or new dosage form.

- some important points for academic clinical trials
- only for approved drugs.
- CT initiated investigator academic aur research authority(CLA) most response in indication,

new rate dose or new dosage.

•EC can sick clarity from Central licensing authority (CLA) respond in 30 days or(Deemed that no approval needed) medical management and compensation complicable as per ICMP guideline biomedical research on human partition or participant CTS required conduct accordance with CT protocol approval EC and ethical principle specified in the ICMP guideline for biomedical research human participant.

Ethics committees (ECS) -:

As a decinated in the 2019 CT rule and additional resources CA India has decentralized process for the ethical review of clinical trials application and required ethical Committer(EC) for each trial use.

In accordance with 2019 CT rules and addition resource(A) ethics committees (ECS) that review drug clinical trial use required to register with new drug controller general of India (DCHI) head of drum general standard control organisation (CDSCO) prior to Recivewing and approving clinical trials protocol.

In additional the 2019 T- rules established a separated registration and monitoring system for ECS that anarase biomedical and health.

Research studies -:

Per noticed 15th September 2019 and chapter 4 of the 2019 (T-rules any institution) or organisation that plans

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to conduct biomedical and health research involving human participant is now required to have CC to review and overcase conduct such research before study.

EC composition-:

- Pursuant the 2019CT rules and ICMR guideline iinstitutional or independent should be multidisciplinary, multisectorial representing mixed gender age composition.

As for 2019 (T-rules) ICMR guideline composition should include following

- chair person from outside the institute.
- 1-2 basic medical scientist (preferably one pharmacological)
- legal expert 20 reviewed judge
- one social scientist or representative none government voluntary agency.
- one philosophers or ernisist theologain
- one lay person from community
- Member secretory (authorities) members secreter optional
- one member independent institution is non scientific. Phase 4 and phase marketing studies (PMS) -:
- Previously there was amobiguity definition requirement Phase 4 and DMS.
- New rule to 2019 was differentiated requirement conducting phase 4 CT and post marketing surveillance for new drug.
- New rule 2019 phase 4 study.
- Drug-Drug interaction
- Dose response interaction
- Trials design to support use under approved indications.

PMS such new drug Studies are conducted with approved condition of its use with. Scientific objectives approved by CLA.

Orphane drug registration -:

New rules intended 2019 defines orphane drug as drug intended condition which affect not more than true learn (60000) in Person in indian .

Provision Status for Fast tract approval process special status orphan drug includ complete fee waiver (T Filling)

Provision expenduries review process in situation when evidance for clinical safety efficiency have been established.

Provision for 150 years level clinical study and phase 4 on satisfaction of CLA.

Post trial Access -:

New rule 2019 defines Post trials acies as moring new dru g investingational new drug available to Subject after completion of clinical trial throug which said drug has been subject during cylindrical trials.

These are still raised about issues needed to address CDSCO include new long post trial access medicines should provide to current and this is Special importantance there is chronic disease with long movement.

How Safety signal monitor for this period and would sponsal investigator ethics committee

-Should Species continued provide drug under. post-trial access marketing authorisation approval and drug availability in market.

Import and manufacture of unapproved new drug -:

under the rule 36 of Drug and cosmetics rule 1945 provision makes for Patient to apply for license to import unapproved new drug. The applicant is required to Degree using form no. 125 along Perscription aap registered medical Practioner (RMP).

Protocol and amendanntes compounds

- Assesmentof efficacy.

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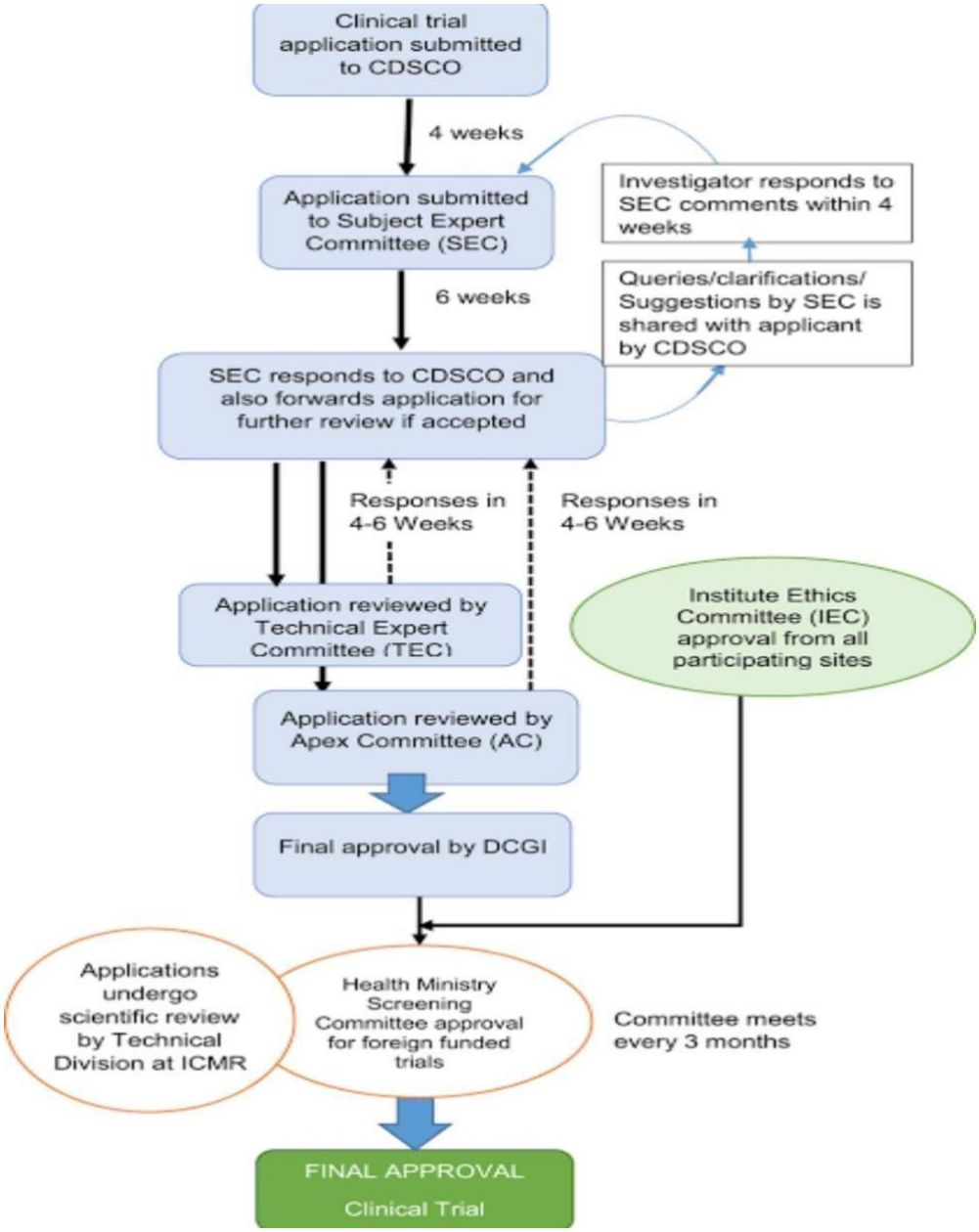
- Assesment of safety
- Statistics
- Data handing abd management
- Quality control and Quality assurance
- Finance and insurance
- Evalution
- Supplimeteries and Applendices

clinical trials application process (CTA) -:



Selection of Drug **Divalproate (valproic Acid)** Discovery -:

Valproic acidis an fatty acid derivative and anticonvulsant originally synthesizer in 1810 by Beverly S. Burton.

Tread Name -: Dapakene

Brand Name -: Dapakene, Depakote, Epival Generic Name -: valproic Acid

Chemical Formula -:

Molecular weight -: 144.2114 Structure -:

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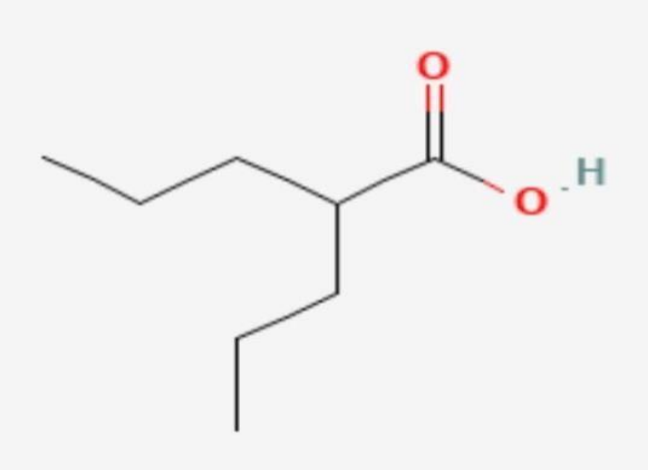

Uses -: Epilepsy, Migraine, Headache , bipolar Disorder Dosage Form -:

1) Oral- capsule (125mg)

Tablet -125mg , 250mg , 500mg

2) I. V Administration

Administer as rapid infusion over 5-10 min (1.5-3ng /kg/ min)

Pharmacokinetic -:

Divalproate Or valproic Acid have broad spectrum antiepileptic activity , which is use in generalize and partial seizures valproic Acid potentiates GABA effects on CNS.

In market the valproic acid is available in the dosage form convention enteric coated tablet, oral solution, sustain released tablet capsule and intra- venous solution.

When the drug is administired completely and rapidly absorbed but variation in rate of absorption and bioavailability as per formulation, this all data are documented. As per this data the I. V. Solution of VPA having bioavailability 1.0 for oral route (capsule and other dosage form) approximately 0.8-0.9 for rate of absorption.

Tmax (Time of maximum concentration)

1. Oral solution -: 1 to 2 hr.
2. Enteric coated -: 3 to 6 hr.
3. Sustain released Tab. -: 10 to 12 hr.

The valproic Acid is the acidic drug therefore 90 to 95% drug bind to the albumin The volume of distribution range is 0.5 to 0.1 L. Kg-1.

The metabolism of VPA in liver there are three way to metabolise the drug which are, Glucuronide conjugation , β -oxidation in mitochondria, CYP4500

Half life is -: 10 to 12 hr.

Eliminated by the standard haemodialysis.

Due to narrow therapeutic window the Therapeutic Drug Monitoring (TDM) is important in drug therapy in the epilepsy the Therapeutic range of drug is 50- 100 mg l-1

In the bipolar disorder the Therapeutic range is 50-125 mg l-1 Side effects -:

1. Nausea
2. Vomiting
3. diarrhoea
4. Tremor

The exact mechanisms by which valproate exerts it's effects on epilepsy, migraine headaches, and b. Thrombocytopenia

Machanism of action -:

Valproate is known to inhibit succinic semialdehyde dehydrogenase. This inhibition results in an increase in

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succinic semialdehyde which acts as an inhibitor of GABA transaminase ultimately reducing GABA metabolism and increasing GABAergic neurotransmission. As GABA is an inhibitory neurotransmitter, this increase results in increased inhibitory activity. A possible secondary contributor to cortical inhibition is a direct suppression of voltage gated sodium channel activity and indirect suppression through effects on GABA.

It has also been suggested that valproate impacts the extracellular signal-related kinase pathway (ERK).1 These effects appear to be dependent on mitogen-activated protein kinase (MEK) and result in the phosphorylation of ERK1/2. This activation increases expression of several downstream targets including ELK-1 with subsequent increases in c-fos, growth cone- associated protein-43 which contributes to neural plasticity, B-cell lymphoma/leukaemia-2 which is an anti-apoptotic protein, and brain-derived neurotrophic factor (BDNF) which is also involved in neural plasticity and growth. Increased neurogenesis and neurite growth due to valproate are attributed to the effects of this pathway. An additional downstream effect of increased BDNF expression appears to be an increase in GABAA receptors which contribute further to increased GABAergic activity.

Valproate also appears to impact fatty acid metabolism. Less incorporation of fatty acid substrates in sterols and glycerolipids is thought to impact membrane fluidity and result in increased action potential threshold potentially contributing to valproate's antiepileptic action. Valproate has been found to be a non-competitive direct inhibitor of brain microsomal long-chain fatty acyl-CoA synthetase. Inhibition of this enzyme decreases available arichidonyl- CoA, a substrate in the production of inflammatory prostaglandins. It is thought that this may be a mechanism behind valproate's efficacy in migraine prophylaxis as migraines are routinely treated with non-steroidal anti-inflammatory drugs which also inhibit prostaglandin production. Finally, valproate acts as a direct histone deactylase (HDAC) inhibitor.

Hyperacetylation of lysine residues on histones promoted DNA relaxation and allows for increased gene transcription. The scope of valproate's genomic effects is wide with 461 genes being up or down-regulated. The relation of these genomic effects to therapeutic value is not fully characterized however H3 and H4 hyperacetylation correlates with improvement of symptoms in bipolar patients.

Finally, valproate acts as a direct histone deactylase (HDAC) inhibitor. Hyperacetylation of lysine residues on histones promoted DNA relaxation and allows for increased gene transcription. The scope of valproate's genomic effects is wide with 461 genes being up or down-regulated. The relation of these genomic effects to therapeutic value is not fully characterized however H3 and H4 hyperacetylation correlates with improvement of symptoms in bipolar patients.

Histone hyperacetylation at the BDNF gene, increasing BDNF expression, post-seizure is known to occur and is thought to be a neuroprotective mechanism which valproate may strengthen or prolong. H3 hyperacetylation is associated with a reduction in glyceraldehyde-3-phosphate dehydrogenase, a pro-apoptotic enzyme, contributing further to valproate's neuroprotective effects.

Toxicology -:

1. Drug Diaease intereaction -:

VPA contraindicated in the person who have urea cycle disorder (USD)

2. Drug -Drug intereation -:

VPA is not given with -:

•Benzodizipine.

•Abacavir .

- Aceclofenac .
- Acamprosat .
- Acemetacin.

3. Drug -Food Intereation-:

- Not give with Alcohol
- Not give with milk and dairy product
- Give with food

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Reproductive Toxicity-:

When VPA is given in pregnancy increase the chances of neural tube difect and other abnormalities.

The malformation range is 9-11%

This malformation contain the defect like neural tube defect , cardiovascular malformation craniofacial defect hypospaidas, limb malformation.

Other Toxicity -:

If VPA given in pediatrics under 24 age that increase risk fetal hepatotoxicity. Contraindication-:

Contraindicated in patient with hepatic disorder and in pregnant lady.

Clinical Trials -:

PHASE 1-:

Sponsor -: Dr. Hasan Alam

Information provided by(responsible party) Dr. Hasan Alam, university of Michigan.

In phase first study of determine the safety and tolerability of VPA. Determination of safety and tolerability of asending dosage of VPA which is administer iv infusion in healthy volunteers range vary from 15mg/kg to 250mg/kg.

After that study which determine the safety and tolerability of VPA by single asending dose. The study is single center study intended to assess the safety and tolerability of VPA dose is 15mg/kg ,30mg/kg , 60mg/kg , 90mg/kg , 120mg/kg, 150mg/kg , 180mg/kg, 210mg/kg , 250mg/kg for 72 healthy volunteers group of 8. In each group 9 volunteers. Volunteers give a single dose of VPA by iv infusion in ratio 3:1 for 60 min.

PHASE 2 -:

Volunteers and investigators where aware of treatment allocation. The volunteers are 12 years or older the initial dose of VPA is 500mg twice in a day . The children 5 to 12 year initial dose is 25mg/kg the dose administired orally.

PHASE 3-:

In Phase 3 the determination of safety and efficacy.

On day one the exprimental group recive loading dose of VPA for one hr. Within 24 hrs of injury. After that patients divided in two groups . From day two through one month the one group recive VPA tablet 4 times in a day.

Second group of patient recive VPA iv 4 times daily and this continue for 6 month. If the patients recover from seizure between 8 to 6 month . The no. Of tablets of VPA tapered over one week each patient the patients get full neuropsychological and Psychosocial examination at 6 to 12 month after injury. The untreated symptoms of the patient continues 2 year after injury

PHASE 4 -:

520participents are recruited between 30 April 2013 and 2 Aug 2016 follow up to 2 year.

Randomly 260 participants recive VPA the ITT analysis includes all the participants PP analysis contains randomly 255 participants ,Median age of participants is 13.9 year, in that 65% male , 35% female

The generalised epileptic participants are 397 and 123 unclassical epilepsy the PP analysis shows 1 year remission was superior with VPA and 2 deaths.

The ADR reported 37% that is 96 participants

Cost effectiveness was base on difference between treatment group in cost and quality adjusted life year.

- Identification of most widely prescribed drug from a selected class (consumption Report) by approching pharmacy stores company representatives & pharma companies web portal.

Consumption of Valproic acid -;

Valproic acid is used in treatment of epilepsy 'bipolar disorder, maigrain.

Valproic acid is available in tablet or capsule Or sprinkles given by oral route of administration. The delayad released tablet are available 125 mg, 250 mg, 500mg.The extended released dosage form contain 280 mg 500mg.

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The oral dosage form of capsule are available in strength 125 mg. For treatment of epilepsy -:

- The medicine of valproic acid can use monotherapy Or adgunctiv therapy in the complex partial seizures type.
- The range of dosage form started from 10-15 mg /kg / day which are not above 60 mg / kg days.

In the treatment of mania -:

Maine is a bipolar disorder CNS.

In mania treatment the initial dose started 250mg thrice (3) a day.

For the extended Released dosage form initial dose is 25 mg /kg Once a day with Fastly range increase 60mg/kg/day effect for achiving desired the clinical effect

For Migrain prophylaxis -:

In the migrain prophylaxis treatment valproic acid initial dose given 250mg twice a day for one week .

The extended released dosage from range started from 500mg once day or daily for one week.

The dose can be improve or given upto one thousand 1000 mg / day the dose of 1000mg /day should given if needed. For one roomy once day or daily.

The dose can be improve or given upto one thousand 1000 mg / day. the dose. I day should given if needed.

Therapeutic range -:

1) For epilepsy -: 50 to 100 mcg/ ml total valproic.
2) Mania -: 50 to 150 mcg /ml total valproic.

- It takes for two weeks to reach maximum conc. Dose modifications -:

- In renal impairment -: No changes needed
- Hepatic impairment -: Administered in low dose. The VPA contraindicated in sever hepatic impairment.

Identification Of Adverse Effect Of Selected DrugDrug:-

Identification of adverse effect of selected drug using different search engines.(eg.Medscape,.com,drugs .com etc)

ADR of Valproic Acid 1)On CNS

- sedation,drowsiness
- Dizziness
- Tremor,
- Anorexia
- Nystagmus,
- Dilopic
- Dysathria.
- Nervousness
- Agitation (Mainly in children) 2)On Gastrointestinal System
- Nausea
- Vomiting
- Anorexia
- Wait gain
- Hyper Anemia
- Fluminaut Hepatitis 3)Haematopoetic system
- Thrombocytopenia (mainly dose related) 4)Allergic Reaction
- Skin rashesh
- Photosensitivity
- Erythema multiforme 5)On Reproductive system
- Menstrual Disturbances

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- Spina Bifoda Can Ensure
- Increased risk of neural tube defect (Up to 20 fold)when given during preganancy.

6) Other Adverse effects

- Weight gain
- Hair loss
- PCOD
- Bone loss
- Ankles swelling
- Hepatotoxicity

Adverse drug reaction monitoring form -:

Preparation of ADR monitoring form as per guideline given by AMCS Example Indian pharmacopia Commission

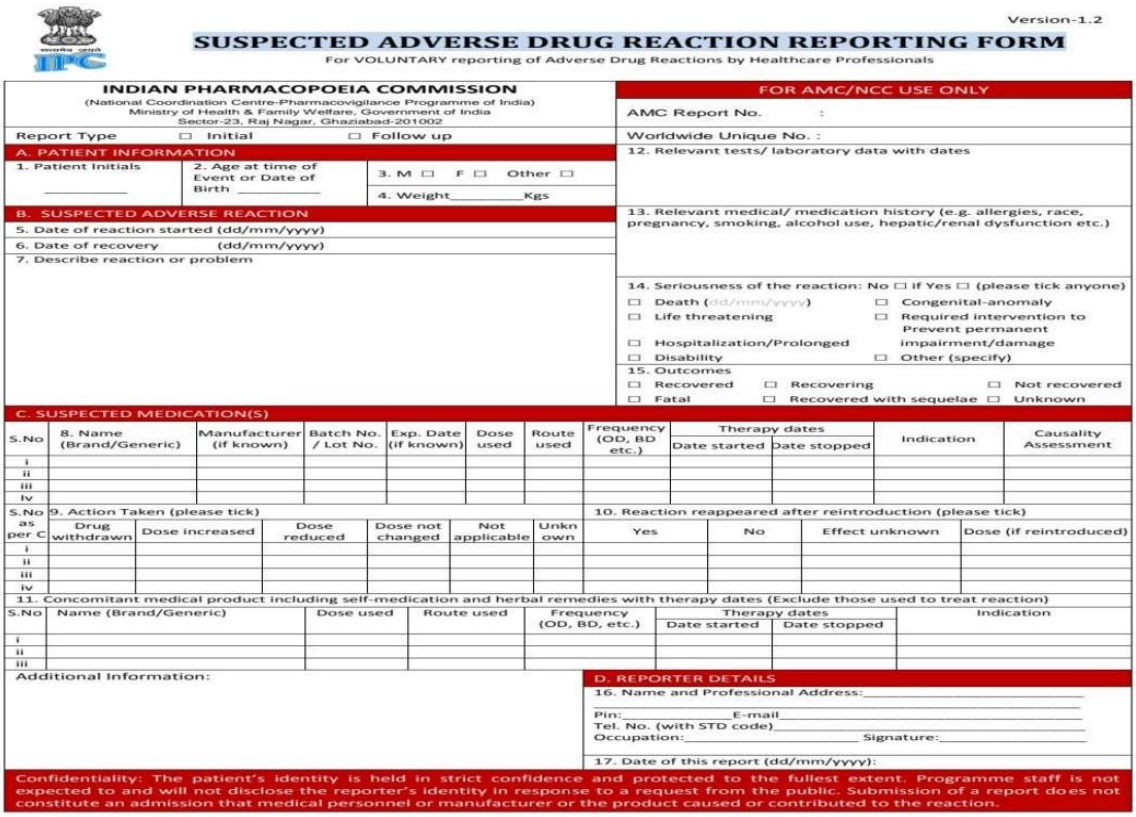
Process of induction of AMCS undbeginer PVPIspeech

1. MCI approved Medical College or institute and hospitals
2. furnishing the letter of intent
3. Duly forwarded by head of the institution
4. NCC – PvPI
5. Examining the stability by NCC
6. NCC excepting as AMCS under communicating to Following

A. Ministry of Health and family welfare Government of India

B. CDSCO

C. WHO-UMC Sweden



Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY
AMC Report No. :
Worldwide Unique No. :

Report Type ☐ Initial ☐ Follow up

A. PATIENT INFORMATION
1. Patient Initials _____
2. Age at time of Event or Date of Birth _____
3. M ☐ F ☐ Other ☐
4. Weight_____Kgs
12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION
5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem
13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)
14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)
☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent
☐ Hospitalization/Prolonged impairment/damage
☐ Disability ☐ Other (specify)
15. Outcomes
☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates Date started	Therapy dates Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick) Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unkn own	10. Reaction reappeared after reintroduction (please tick) Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates Date started	Therapy dates Date stopped	Indication
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS
16. Name and Professional Address:_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____
17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

II. CONCLUSION

Pharmacovigilance is track to identify the selection of safe dug during treatment of disease. The review artical help to ensure safety ,efficacy of valporic acid during treatment. The drug not given in case, patient with hepatic

disorder and pregnant lady. This article suggest safe dose and use of valporic acid.

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