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THE NEED OF PHARMACOVIGILANCE OF DISULFIRAM - A REVIEW

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ABSTRACT

A good pharmacovigilance practice is the need of time to ensure that the drugs in the market are fulfilling the purpose for what they are meant. Similarly, the literature survey highlights the miracle drug i.e. disulfiram which is showing promising results and giving a sigh of relief to the families from the rural areas of our country by enabling the alcohol dependent patients to quit alcohol. . Disulfiram is a drug used to support the treatment of chronic alcoholism by producing an acute sensitivity to alcohol. Disulfiram is also being studied as a treatment for cocaine dependence, as it prevents the breakdown of dopamine. Several studies have reported that it has anti-protozoal activity as well. There is no tolerance to disulfiram: the longer it is taken, the stronger its effects. The adverse drug reactions (ADRs) of disulfiram are themselves used as a treatment for alcoholism. So, the more we get pharmacovigilant about the drug the more it will be fruitful for us to treat the patient. Hence, we can call disulfiram as one of the life saving drugs for the alcohol addicts knowing the consequences of excessive consumption of alcohol.

Keywords: Pharmacovigilance, disulfiram, alcoholism, adverse drug reaction.

INTRODUCTION

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problem. It aims in making best use of medicines for the treatment or prevention of diseases. Though it is not intended to harm the patients during medicine use process, unfortunately some medicines often cause problems. Significant harm to even a few patients not only destroys the credibility of the medicine but the patients too, loose trust on the care professional or the health system.[1] It is the process of identifying and responding to the issues of drug safety through effects usually adverse.[5]

Need for Pharmacovigilance Systems

To be eternally vigilant to ensure that medicines, which are developed for treatment of diseases, actually do not do more harm than good, is one of the important pre-requisites for the progress of medicine. Already, at least in the U.S.A., figures as high as 3 to 5% of hospital admissions have been attributed to iatrogenic diseases, that is., those caused by drugs. The science and systems used for systematically identifying and correlating drugs and side-effects and taking corrective actions fall under the discipline of

Pharmacovigilance.[2] Key objectives pharmacovigilance can be briefly defined as the process of evaluating and improving the safety of medicines.[11]

Pharmacovigilance Process

Finding the risks of drugs

Medicines have helped to bring improved health and longer life to human beings. Medicines affect the lives of hundreds of millions of people every day. But they are not without risk, and have caused, do cause and will continue to cause harm to many people. There are also large numbers of people who experience no evident effect at all from the drugs they take.[3, 4] Pharmaceutical companies are required by law in all countries to perform clinical trials, testing new drugs on people before they are made generally available. The manufacturers or their agents usually select a representative sample of patients for whom the drug is designed — at most a few thousand — along with a comparable control group. The control group may receive a placebo and/or another drug that is already marketed for the disease.[3, 4]

Clinical trials do, in general, tell us a good deal about how well a drug works and what potential harm it may cause. They provide information which should be reliable for larger populations with the same characteristics as the trial group - age, gender, state of health, ethnic origin, and so on.[3, 4] Good Pharmacovigilance will identify the risks and the risk factors in the shortest possible time so that the harm can be avoided or minimized. The integration of Pharmacovigilance may be crucial to the success of public health programmes involving medicines. Under the stimulus and coordination of World Health Organization (WHO) and its Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre), National programmes are built up to make it a true international necessity.[1]

The specific aims of pharmacovigilance are to:

Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions. Improve public health and safety in relation to the use of medicines; contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.[6]

Pharmacovigilance is mainly governed by:

The pharmaceutical industry (prime responsibility), competent (regulatory) authorities, WHO collaborating Centre for International Drug Monitoring (in Uppsala), Council for International Organization of Medical Sciences - CIOMS Working Groups on drug safety plays an advisory role in harmonization of pharmacovigilance practices.[1]

Pharmacovigilance in India

Pharmacovigilance is fastest emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary .This may ensure the safer use of drugs.[7] Historically, Indian market has always, except in very few cases, seen the launch of only products, which have been earlier approved and marketed in U.S.A., Western Europe or Japan. Until now, the time lag between the first marketing of a new drug in a foreign country and India has been on an average around 4 years, and hardly any new drug was introduced for the first time in India. In

that kind of scenario, it was not too critical that there was in place a system of pharmacovigilance in India, since reports of side-effects from outside India would have helped our regulatory agencies to assess the rationale of continuing the drug in the Indian market. Thus in the past, action on marketed drugs has been triggered on the basis of reports on the harmful effects of drugs marketed abroad. In a few cases, drugs, which have been banned or withdrawn in foreign markets, were allowed to be kept in the market in India. For example, Chloramphenicol, Phenyl Butazone, Clioquinol, Phenformin, Cisapride, all continue to be prescribed in India on the basis of a conscious decision by the Regulatory Agency that the benefit to risk ratio is in favor of the former.[8] The evolution of a new Patent regime in the Indian Pharmaceutical Industry (the Post-2005 scenario) as a consequence of India being a founder member of WTO, and her obligations under Trade Related Intellectual Property Rights and Services (TRIPS), makes it incumbent that India can no longer copy patented products and market them without license from the innovator company. The leading Indian companies realizing the compulsions of the new regime have already initiated investments of substantial resources for the discovery and development of new drugs needed for both Indian and International markets. This in turn means that during the coming years R&D by the Indian Pharmaceutical companies will hopefully lead to new drugs based on pre-clinical and clinical data generated mostly in India. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess the incidence and prevalence of adverse reactions from drug usage, and therein lays the importance of a properly designed pharmacovigilance system in India. For an effective Pharmacovigilance system to be functional and efficient all the stakeholders need to be alert and attentive throughout the lifetime of the drug in the market.[8]

Need for ADR reporting

The most frequent question that arises in pharmacovigilance is the need to monitor the adverse reactions of the drugs, even though their safety profiles have already been studied adequately before their commercial release. The answer to this question is to make the drugs safer. In addition, the formal therapeutic trials are conducted in carefully controlled conditions; in highly selected and limited number of patients, so that the exact safety profile of the drug in the real life situations is not known. Children, pregnant women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release. Another important drawback of clinical trials is that they can only report adverse reactions that appear within the finite duration of trial. Delayed reactions would be missed. Reporting of adverse drug reactions is done by mainly two methods - spontaneous and intensive. Though plagued by numerous problems like low yield of reports, sub-optimal quality and imperfect nature, these have often served to be a useful source of data or provided early warning signals for the drug related regulatory actions.[9] At the time a drug is approved knowledge about its risk is incomplete. Tests in animals are necessary and useful to discover toxic effects, but do not allow sufficient conclusions about human safety. Clinical studies focus on demonstrating efficacy statistically instead of comparing benefits and ADRs with those of existing drugs. The small number of patients involved in, and unsatisfactory length of, clinical studies limit the value of their findings. Thus, pre-approval clinical data include only information about the most common ADRs. In addition, specific doses are used and patients who may be at greater risk

from ADRs are usually not studied during the development of a drug, e.g. young children, elderly people, pregnant or lactating women, patients concomitantly using other drugs or other therapies, patients with complicated disease conditions, sub-populations carrying known and relevant genetic polymorphism and patients of different racial and/or ethnic origins.[10] Thus, clinical studies give very limited information about risk and efficacy in real life conditions. Reporting of harm related data from clinical studies needs improvement.[11] Here arises the research question that, why Pharmacovigilance of Disulfiram? Now the answer to this is very simple as we move into the details of the drug. Disulfiram is a drug used to support the treatment of chronic alcoholism by producing an acute sensitivity to alcohol. Trade names for disulfiram in different countries are antabuse and antabuse manufactured by Odyssey Pharmaceuticals. Disulfiram is also being studied as a treatment for cocaine dependence, as it prevents the breakdown of dopamine (a neurotransmitter whose release is stimulated by cocaine); the excess dopamine results in increased anxiety, higher blood pressure, restlessness and other unpleasant symptoms. Several studies have reported that it has anti-protozoal activity as well.[12]

Pharmacology:

Mechanism of action: Disulfiram inhibits aldehyde dehydrogenase, the oxidative enzyme of acetaldehyde, a metabolite of alcohol. The latter is accumulated in the blood, thus producing unpleasant symptoms of disulfiram-alcohol reaction when a patient has taken small amounts of alcohol.

Absorption: Rapidly absorbed from the GIT; peak plasma concentrations after 8-10 hrs (oral).

Metabolism: Reduction to diethyldithiocarbamate by the glutathione reductase system in the erythrocytes.

Excretion: Urine (as metabolites); exhaled gas (carbon disulphide).

Dosage: Disulfiram is supplied in 200 mg, 250 mg, and 500 mg tablets. The usual initial dose is 500 mg for 1 to 2 weeks, followed by a maintenance dose of 250 mg (range 125 mg–500 mg) per day. The total daily dosage should not exceed 500 mg.[13]

How does Disulfiram work?

Under normal metabolism, alcohol is broken down in the liver by the enzyme alcohol dehydrogenase to acetaldehyde, which is then converted by the enzyme acetaldehyde dehydrogenase to the harmless acetic acid. Disulfiram blocks this reaction at the intermediate stage by blocking the enzyme acetaldehyde dehydrogenase. After alcohol intake under the influence of disulfiram, the concentration of acetaldehyde in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone. As acetaldehyde is one of the major causes of the symptoms of a "hangover" this produces immediate and severe negative reaction to alcohol intake. Some 5–10 minutes after alcohol intake, the patient may experience the effects of a severe hangover for a period of 30 minutes up to several hours. Symptoms include flushing of the skin, accelerated heart rate, shortness of breath, nausea, vomiting, throbbing headache, visual disturbance, mental confusion, postural fainting, and circulatory collapse. Disulfiram should not be taken if alcohol has been consumed in the last 12 hours. There is no tolerance to disulfiram: the longer it is taken, the stronger its effects. As disulfiram is absorbed slowly through the digestive tract and eliminated slowly by the body the effects may last for up to two weeks after the initial intake; consequently, medical ethics dictate that patients

must be fully informed about the disulfiram-alcohol reaction.[14]

Adverse Drug Reactions:

The most common adverse drug reactions are drowsiness, headache, tiredness, fatigue, metallic or garlic taste in the mouth, vision changes, decreased sexual ability, mental or mood changes, trouble in breathing, increased heart rate, muscle weakness, numbness or tingling of hands and legs and several others. Whereas the moderately common occurring ADRs are severe dizziness, poor memory, dark urine, bad body odor. Also there are some rarely occurring ADRs such as yellowing of eyes, skin and nails, which are the symptoms of jaundice, severe allergic reactions such as skin rash, itching, swelling specially on the face, tongue or throat.[15]

There are also certain special instructions to be followed while consuming disulfiram.

Do not drink any alcoholic beverages while taking disulfiram, during the 12-hours period before you take your first dose, and for several weeks after stopping the drug. Always carry an identification card stating that you are taking disulfiram and indicating the doctor to be contacted in an emergency. Disulfiram makes some patients drowsy. Do not drive a car or operate dangerous machinery until you know how this drug affects you. Do not stop taking disulfiram without consulting your doctor. Special dietary instructions should be followed. Avoid sauces, vinegars, and all foods and beverages containing alcohol. If you remember a missed dose within 12 hours of when you should have taken it, take the missed dose. However, if it is more than 12 hours since you should have taken it, omit the missed dose and take only the next dose at its regularly scheduled time. Do not take more than one dose in a 12-hour period.[16]

CONCLUSION

The survey of literature showed that there is a need to be pharmacovigilant about disulfiram and such other drugs used for the treatment of alcoholism. As we now know that the adverse drug reactions of disulfiram is the key for the treatment of the alcoholics there must be more action taken for the ADR reporting of this miracle drug. The percentage of population quitting alcohol due to the disulfiram treatment is much greater than the other remedies. So, if more attention is focused on the pharmacovigilance of the drug it may be possible to report more such ADRs which might be beneficial for treatment of alcohol dependent patients.

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