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Study of effect of Omeprazole on pharmacokinetic and antidepressant activity of Sertraline

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ABSTRACT

The interaction processes of Sertraline with Omeprazole have been investigated practically. Some studies reported that depression and peptic ulcer disorders present in same patient. Therefore both the disorders are managed clinically by administrating numbers of drugs for long duration. In such scenario, there is a possibility that one drug may alter the effects of other drugs. On the literature survey, it has been found that both the drugs are metabolized by common enzyme CYP2C19. The omeprazole is an effective inhibitor of CYP2C19, therefore the effect of omeprazole on sertraline might be increases the side effect of sertraline.i.e pharmacokinetic interaction might be possible, The study of the effect of omeprazole on pharmacokinetics and antidepressant activity of sertraline is very much important. Since both the drugs are metabolized by the common enzymes CYP2C19.

Keywords: Depression, Peptic ulcer, Sertraline, Omeprazole, CYP2C19.

1. INTRODUCTION

1.1. Health Status

Status of Health and Health System in India:

The health policies in India have well formulated in terms of National Policies for Health, Nutrition, Education, Children. The constitutional amendments from time to time and their ratification by the State assemblies also provide the guidelines to planners and administrators to direct there sources to the priority areas.[1] With increase in the number of aged people, there will be higher incidence and prevalence of diseases like Hypertension; IHD, Diabetes, Cancers and the whole range of geriatrics problems. The prevalence of mental disorders is estimated to be 10-15 per cent. [1]

Current Health Status of Women in India:

The health of women depends on their emotional, social and physical well-being which are determined by different social, political and economic contexts of their lives. India being large country, has a diverse population- socially, culturally and economically; As education holds the key to development, women education should be considered more seriously. Comparing the health indicators and empowerment indicators across states. [2]

Mental and Physical Health Status in India:

In India, there is an increasing including incidence and prevalence of Depression & other mental disorders.[3]Depression is ranked fourth among the disabling disease affecting people worldwide and is the most common psychological problem in patients with End Stage Renal Disease (ESRD). [3]

The burden of mental illness has been underestimated worldwide. [4] Depression is rated as the fourth leading cause of disease burden in 2000, and it is accounted for 4·4% of total disability adjusted life years (DALYs). [5]

1.2. Depression

Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. Today, depression is estimated to affect 350 million people. A recent World Health Assembly called on the World Health Organization and its member states to take action in this direction. [6]

Depression is quite widespread within the age group. While it is a tragic disease at any age, it is doubly tragic that so many young people in the prime of their lives should fall victim to this disease. Suicide is the second leading cause of death among people between the ages of 10 and 20years. [7]

1.2.1 Symptoms of Depression

The main symptom of depression is "dysphoric mood," or a subjective feeling of being depressed. This, however, is neither necessary nor sufficient for a clinical diagnosis. In place of dysphoric mood, for example, a patient may present vague somatic complaints, such as:

- Headache or backache.
- In clinical depression, dysphoric mood is accompanied by certain cognitive or perceptual symptoms.
- The patient may feel low esteem, for example, or guilt feelings.
- Many depressed people find themselves unable to concentrate. Slowed thinking and indecisiveness are common.
- There may be occasional anxiety, or "panic attacks."
- Clinicians may observe in depressives certain vegetative signs.

1.2.2. Causes of Depression

There is no single cause or obvious set of factors that can explain why the depression occurred. However, the depression is the result of the interaction of a complex set of factors, some economical, some political & some social factors. Individuals who have been victims of trauma or abuse are also at increased risk of depression. In addition to the risk factors described, some medications can cause depression-like symptoms, including sedatives, narcotics, and pain relievers.[8,9]

1.2.3. Global Burden of Depression

Disability and Mortality:

Depression is a significant public health problem because it is relatively common and its recurrent nature profoundly disrupts patient's lives. Though estimates from developing countries are not available, depression costs the US economy more than US$ 43 billion annually in medical treatment and lost productivity. [10,11] Patients with depression spend more days away from work, become medically ill more often, suffer greater physical disability, and die at a younger age than the general population. [11]

1.2.4. Prevalence of Depression

Depression is an illness that affects both the mind and the body and is a leading cause of disability, workplace absenteeism, decreased productivity and high suicide rates. Depression is the most common psychiatric disorder in general practice and about one in ten patients seen in the primary care settings suffer from some form of depression. In a study by the World Health Organization (WHO) conducted at 14 sites, the most common diagnosis in primary care was depression. Depression is estimated to affect 340 million people globally. [12]

1.2.5. Etiology

The theories and models of depression are categorized into several major schools: psychoanalytic, behavioral, sociological, existential, cognitive, self-control, and biological.[13]

1.2.6. Classification of depression

Major Depression:

Major depression is characterized by a combination of symptoms that last for at least two weeks in a row, including sad and/or irritable mood, that interfere with the ability to work, sleep, eat, and enjoy once-pleasurable activities. Difficulties in sleeping or eating can take the form of excessive or insufficient of either behavior. Disabling episodes of depression can occur once, twice, or several times in a lifetime. [14]

Dysthymia:

Dysthymia is a less severe but usually more long-lasting type of depression compared to major depression.

Bipolar Disorder (Manic Depression):

Another type of depression is bipolar disorder, which encompasses a group of mood disorders that were formerly called manic-depressive illness or manic depression. [14]

However, certain risk factors make more vulnerable to depression like: [15]

- Loneliness
- Lack of social support
- Recent stressful life experiences
- Family history of depression
- Marital or relationship problems
- Financial strain
- Early childhood trauma or abuse
- Alcohol or drug abuse
- Unemployment or underemployment
- Health problems or chronic pain, etc., [15]

1.2.7. Treatment for Depression

There are three main types of treatment for depression they are:

- *Pharmacotherapy:* Pharmacotherapy includes Antidepressants, Phototherapy
- (St. John's wart), Narcoleptics and Lithium.
- *Psychotherapy:* Psychotherapy for depression includes Cognitive behavioral therapy (CBT), deep psychology-based and psychoanalytic psychotherapy, Interpersonal psychotherapy (IPT).
- *Supportive measures:* Supportive therapy comprises light therapy, aerobic and endurance training, Electroconvulsive therapy (ECT).

Tri cyclic and Tetra cyclic Antidepressants:

Amitriptyline, Amoxapine, Clomipramine, Dothiepin, Doxipin, Lofepramine, Imipramine, Irondale, Nortriptyline, Protriptyline, Trimipramine. [17-19]

Selective Serotonin Reuptake Inhibitors:

Citalopram, Escitalopram, Fluoxatine, Fluoxatine, Paroxetine, Sertraline. [17, 18, 19]

Monoamine Oxidase Inhibitors:

Isocarboxazide, Moclobemide, Phenezine, Traylcypromanie. [17, 18, 19]

Other Antidepressants:

Bupropion, Reboxetine, Venalafaxine, Nefazodone, Mirtazapine, Trazodone. [17, 18, 19]

Tri cyclic and Tetra cyclic Antidepressants:

In severe, recurrent, or chronified depression, as well as for elderly depressed patients, a primary combination of these two treatment modalities may be advantageous.[17] Tricycle antidepressants when administered chronically have a modulator effect on NMDA receptors. [18]

The results seem to apply to major depressive disorder and heterogeneous depression (commonly seen in primary care) and suggest that treating depression with antidepressants is an appropriate activity in primary care. [20]

There is an increased risk of suicide in patients who have chronic physical illness and pain. Particular caution is required with elderly patients in this category. [21]

Exercise Treatment for Major Depression On completion of the baseline assessment, participants was randomly assigned to one of three treatments:

- ✓ Exercise
- ✓ Medication, or
- ✓ Combined exercise and medication.[22]

1.3. Peptic Ulcer

Ulcer is deep lesions penetrating through the entire thickness of the gastrointestinal tract (G.I.T) mucosa and muscularis mucosa. Peptic ulcer has unquestionably been a disease of the 12th century. There are different types of ulcers most common are peptic ulcer, gastric ulcer which appeared to be due to damage to the lining of the stomach, and duodenal ulcer, which was associated with excessive acid secretion by the stomach. [23]

1.3.1. Symptom Profile of Peptic Ulcer Disease

Retrosternal Pain, Heartburn, Dysphagia to Solids, Dysphagia to Liquids, Vague persistent, Abdominal pain, Dyspepsia, Weight loss. [24]

Causes

- Exercise increases gastric pressure and causes highly acidic stomach fluid to reflux into the higher non-glandular and poorly protected lining of the stomach.
- Stabled horses generally had higher gastric pressures as compared to horses trained from the paddock.
- Horses that are exercised on an empty stomach are likely to have an increased risk of highly acid reflux than horses given a small roughage meal of hay or chaff prior to exercise.
- Some herbal preparations, such as Devil's Claw and White Willow Bark, used as natural anti-inflammatory remedies, may also increase the risk of gastric ulcers in horses given these products to ease discomfort and mild arthritic pain. [25]

1.3.2. Types of ulcer [23]

Peptic ulcer:

Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. The causative agent is infection caused by bacteria H.pylori or reacton to certain medicines like non-steroidal anti-inflammatory drugs (NSAIDs). Symptoms of peptic ulcer include weight loss, poor appetite, bloating, nausea, and vomit and black stools that indicate gastrointestinal bleeding. The term combined ulcer was applied if lesions were seen both proximal and distal to the pyloric ring during the same examination. Scars or deformities were accepted as signs of former ulcer. Outcomes described as possible ulcer were interpreted as

ulcers. Malignant ulcers (n=2) were excluded from calculations. [26]

1.3.3. Prevalence of peptic ulcer

From clinical experience and retrospective hospital based surveys, it has been suspected that peptic ulcer is widely prevalent in India, more common among the population of South India than North India and the clinical behaviour of peptic ulcer in India is different from that in the West. [27]

1.3.4 Etiology [28]

Helicobacter pylori infection and the use of a non steroidal anti-inflammatory drug (NSAID) are the principal factors associated with PUD. Similarly, etiologic factor in 88% of patients in our study was H pylori and/or NSAID use. [28]

1.3.5. Pathophysiology

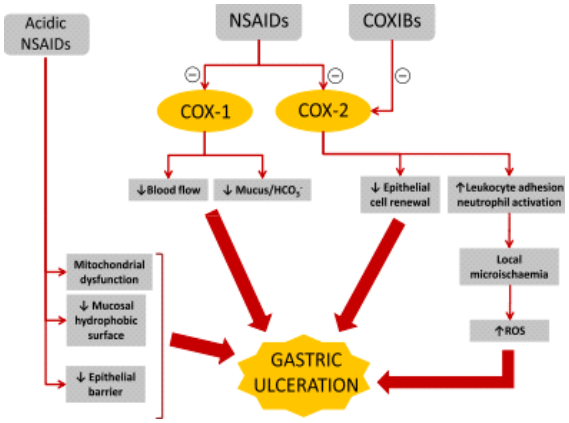


Figure 1: Pathophysiology of Peptic Ulcer.

This infection may lead to impaired production of somatostatin by D cells, and in time, decreased inhibition of gastrin production, resulting in increased acid production and reduced duodenal bicarbonate production. [29, 30]

1.3.6. Treatment for Peptic Ulcer

Classification of Anti-Ulcer drugs: [31]

Reduction of gastric acid secretion:

- H2 antagonists: Cimetidine, Ranitidine, Famotidine, Roxatidine
- Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole,Esmoprazole
- Anticholinergic: Pirenzepine, Propantheline, Oxyphenonium.
- Prostoaglandin analogues: Misoprostol

Neutralization of gastric acid (antacids):

- Systemic: Sodium bicarbonate, Sodium citrate
- Non-systemic: Magnesium hydroxide, Magnesium trisilicate, Aluminium hydroxide, Gel calcium carbonate

Ulcer protective's:

Sucrulfate, Colloidal Bismuth Sub citrate (CBS)

Anti-H.pylori drugs:

Amoxicillin, Clarithromysin, Metronidazole, Tinidazole, Tetracycline. [31]

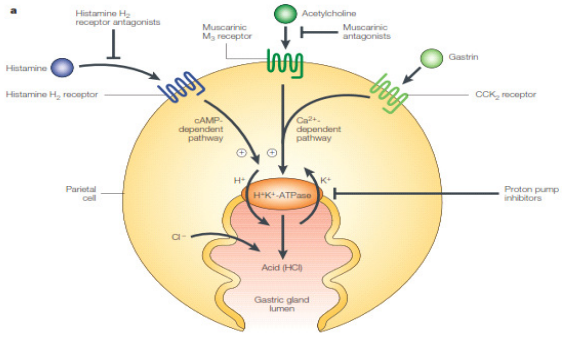


Figure - 2: Effect of various anti-ulcer drugs on parietal cell.

1.4. Need for Study

People with depression suffer overly from various medical disorders and die prematurely.[32] Men and women view depression differently, men are more likely to express their symptoms of depression through substance abuse, such as alcoholism, and antisocial behaviours.

Some of antidepressants are norepinephrine reuptake inhibitors (NRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine inhibitors (MAOs). TCAs are major class of drugs to the area of depression but a number of SSRIs were introduced and all of the SSRIs show a clear improvement in safety margin compared to TCAs and Are much safer in over dose. The SSRIs are effective in treating the major depression. [33]

Sertraline, Belongs to the Pharmacological Class Of Antidepressants Called Selective Serotonin Reuptake Inhibitors (SSRIs), [34,35] which is used in the treatment of depression and metabolised by CYP2C19. [36] Cytochrome P450 is important for metabolism of many drugs. Although this class has more than 50 enzymes CYP1A2, 2C9, 2D6, 3A4, 2C19 etc and they metabolized number of drugs. [36]

Similarly peptic ulcer is a disorder requires a variety of relatively specific medical conditions in which injury by gastric acid thought to play an important role. Currently there are several different proton pump inhibitors available

for clinical use, omeprazole,, lansoprazole, rabeprazole etc. [34]

Among these omeprazole is selectively inhibits gastric mucosal carbonic anhydrase, which may contribute to its acid suppressive properties.[34] Omeprazole is also metabolised by CYP2C19. [33]

Some studies reported that depression and peptic ulcer disorders present in same patient.[35] Therefore both the disorders are managed clinically by administrating numbers of drugs for long duration. In such scenario, there is a possibility that one drug may alter the effects of other drugs.

On the literature survey, it has been found that both the drugs are metabolized by common enzyme CYP2C19.[36,33]The omeprazole is an effective inhibitor of CYP2C19, therefore the effect of omeprazole on sertraline might be increases the side effect of sertraline. [33] i.e pharmacokinetic interaction might be possible.

The study of the effect of omeprazole on pharmacokinetics and antidepressant activity of sertraline is very much important. Since both the drugs are metabolized by the common enzymes CYP2C19. Any alteration on the effect of sertraline is harmful to the patient. Since, it effects the mutual depression of the patient. The study on antidepressant activity will help to predict the extent of mechanism of action of drug interaction and also help to support the pharmakodynamic interaction.

To our knowledge, there is no such scientific studies have been conducted. So it is very much significant and justified to conduct to demonstrate the possible interaction between Omeprazole & sertraline, and to predict their pharmacokinetic and pharmacodynamic parameters to find out possible mechanism of drug- interaction.

2. Objectives of the Study

The present study was designed to evaluate the effect of Omeprazole on pharmacokinetic and antidepressant activity of Sertraline in experimental animal models and hence to investigate the possible interaction between above two drugs.

The study is divided into 4 parts

- To study the effect of omeprazole on pharmacokinetic parameters of sertraline in healthy albino rabbits.
- Evaluate the effect of omeprazole treatment on anti-depressant activity of sertraline in healthy albino rats by despair swim test.
- Evaluate the effect of omeprazole treatment on anti-depressant activity of sertraline in healthy albino rats by serotonin syndrome method.
- To suggest the alterations if required in the dose and frequency of administration of sertraline

3. LITERATURE SURVEY

3.1. Drug-drug interaction

Drug interaction is the phenomenon which occurs when the effects of one drug is modified by the prior or concurrent administration of another (or the same) drug(s). Drug interaction arise either from alteration in the absorption, distribution, biotransformation or excretion of one drug by another or from combination of their action or effects.

Drug interaction has been used for years as a beneficial aspect in drug therapy. **[37]**

3.1.1. Drug - interaction occurs by following machanisms,

How Drug Interact

A. Chemical reactions between drugs

B. Pharmacodynomics

Modification of intestinal absorption:

- Alteration of pH
- Effect of transfort systems
- Complex formation
- Miscellaneous
- changes in circulation(e.g.epinephrine and local anesthetics)
- precipitation(e.g. procaine and penicillin)

Displacement of drugs from storage tissue component:

- Drug-drug displacement
- Drug-endogenous substance (hormone or neurohormone)

Modification of drug action of receptor site:

- physiological antagonism
- Competitive inhibition
- non-equilibrium antagonism
- non competitive antagonism
- partial agonist

Biotransformation:

- enzyme inhibitors
- enzyme stimulators

- complex mechanisms

Alteration of excretion

- change urinary pH
- direct effect on kidney
- complex reactions

C. Physiological factors affecting drug interactions:

- age
- body temperature
- nutritional state
- pathological state
- sex, species, genomics, strain, etc.

D. Others

- Increase or decrease synthetics
- Effect on transport mechanism, e.g. insulin and glucose [37]

During the past few years a revolution has taken place in our understanding of drug interactions, as a result of advances in the molecular biology of the CYP enzyme system. Several factors directly or indirectly influence the CYP activity. Many drug interactions are a result of induction or inhibition of CYP enzymes. [38]

There are basically two mechanisms responsible for drug interactions: (i) modification of the pharmacological response without altering the concentration of the drug in the tissue fluid, i.e. pharmacodynamic interaction or (ii) by altering the concentration of the drug in the tissue/tissue fluid, i.e. pharmacokinetic interaction. [39]

3.1.2. Pharmacodynamic Interactions

The most common interactions encountered in clinical practice are pharmacodynamic. [40]

When two drugs with similar pharmacological effects are administered with each other, they may alter the sensitivity of the effect or organ, resulting in a synergistic or antagonistic effect. Usually, the drug effects result due to binding of the drug to the receptor site. The drug may act on the same or different receptors or processes, and may produce similar biological effects. [39]

The quantity of the drug available at the receptor site depends on: (i) the amount of drug available in the body. (ii) Its accessibility at the receptor site and (iii) affinity constant of the drug for the receptor. Further, the magnitude of the response depends on the concentration of the free drug at the receptor site. [39]

Many instances of antagonism are beneficial, *For example:* naloxone is a specific antagonist that reverses the action of morphine by competing with it for occupancy of the opioid μ-receptor. By contrast, antipsychotic drugs reduce the efficacy of levodopa in Parkinson's disease by blockade of dopamine receptors in the corpus striatum. [40]

The most commonly encountered interactions in practice are pharmacodynamic interactions. Clinically significant pharmacodynamic drug interactions with psychotropic drugs are discussed below. [41]

3.1.3. Pharmacokinetic interactions

In pharmacokinetic interaction, there is a change in the concentration of the drug at the target site of clinical effect and could be due to alteration in drug absorption, distribution, metabolism and excretion. [41]

Interaction at the site of absorption:

Important clinical effects caused by changes in drug absorption are rarely seen in general medical or psychiatric practice. [40]

In the gut the drugs may interfere with each other's absorption by the following mechanisms: (i) chemical interaction, (ii) effecting gut motility, (iii) changing gut flora. In addition absorption of drug from the injection site may be affected by the simultaneous administration of another drug. [39]

Example: For undesirable interaction is the decreased absorption of phenothiazines or sulpiride when they are taken concurrently with antacids, leading to a reduced antipsychotic effect.[40]

Interaction at the site of distribution:

The mechanism by which drug interaction alters drug distribution include: (i) competition for plasma protein binding site, and (ii) displacement from tissue binding sites. [39]

Interaction during metabolism:

Many drugs are eliminated by metabolism. The microsomal reactions that have been studied the most involve cytochrome P450 family of enzymes, of which a few are responsible for the majority of metabolic reactions involving drugs. These include the isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. [42]

The metabolism of drug can be stimulated or inhibited by two drugs administered concurrently. This metabolism can be stimulated by enzyme induction, and inhibited by enzyme induction. [39]

Interaction during excretion:

Some drug interactions of clinical significance, of both beneficial and potentially harmful, occur in the kidney. Interference by drugs with active transport system, with kidney tubule fluid pH and with blood flow to the kidney can alter the excretion of other drugs. [39]

For a drug with a narrow therapeutic window, only a small change in response may precipitate a clinically significant interaction, whereas for a drug with a wide margin of safety, large changes in, say, its pharmacokinetics will have no clinical consequence. [43]

Co-existence of depression with peptic ulcer:

Depression is an important risk factor to consider because of its direct and indirect relationship to peptic ulcer disease. Depression has a direct effect on peptic ulcer disease by improvement of the gastric damage after successful antidepressant treatment. [44]

The prevalence of psychiatric morbidity among patients of peptic ulcer disease and to study the patients of peptic ulcer disease with psychiatric morbidity in comparison to patients of peptic ulcer disease without psychiatric morbidity on following variables: socio-demographic variables and attributes/risk factors of peptic ulcer disease. [45]

Management:

Anti-depressants are probably the most widely used treatment for depression but they are successful in relieving the psychological symptoms in only about 30% of patients. Most gastroenterologists will have had experience in treating functional gastro-intestinal disorders with antidepressants. However, there is a paucity of studies to guide the use of such drugs in IBD. Data from a single open label study of paroxetine (20–40 mg) in eight depressed IBD patients reported a significant improvement in depression and social disability scores and an unspecified positive effect on IBD activity after eight weeks of treatment. At Digestive Disease Week in 2008, the results of a randomized controlled trial in patients with ulcerative colitis using imipramine were presented. Unfortunately, the encouraging findings were compromised by several aspects of trial design, the most important of which was that clinical response was assessed using symptom scores depending heavily on bowel frequency. [46]

3.2. Sertraline

Sertraline is an antidepressant and antipanic agent that is a potent and selective inhibitor of serotonin reuptake into the presynaptic terminal. Selective serotonin reuptake inhibitors (SSRIs) depress the firing of neurons in the raphe nucleus, which in turn may affect norepinephrine neurons of the locus coeruleus. Selective serotonin reuptake inhibitors (SSRIs) depress the firing of neurons in the raphe nucleus, which in turn may affect norepinephrine neurons of the locus coeruleus. Increased firing of locus coeruleus neurons leads to desensitization of the postsynaptic and presynaptic-receptors, and it has been demonstrated that sertraline leads to subsensitivity of adrenoceptors in rat brain. This blunted -adrenoceptor responsivity of the noradrenergic receptor-coupled adenylate cyclase system occurs after repeated doses of many antidepressants and has been described following electroconvulsive therapy. This effect may also partially account for the effectiveness of sertraline as an antipanic agent, as noradrenergic neurons of the locus coeruleus as well as the serotonergic system have been implicated in anxiety. In contrast to the findings of down regulation of adrenoceptors, an increase in adenylate cyclase activity has been demonstrated following chronic antidepressant treatment and electroshock in rat hippocampus and cortex. [47]

3.2.1. Basic pharmacology

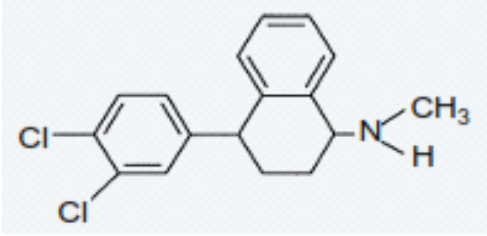


Figure - 3: structure of sertraline.

The structure of sertraline [(1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1naphthalenamine], its metabolite desmethylsertraline [(1S-cis)-4-(3,4-dichlorophe-nyl)-1,2,3,4tetrahydro-1-naphthalenamine], and part of the metabolic sequence are shown in Fig. 4.[78]

3.2.2. Basic pharmacokinetic properties

Like paroxetine, sertraline possesses two chiral centers. Only one (1S, 4S) enantiomer of sertraline is contained in the marketed formulation.

Absorption, Distribution:

Absorption from the gastrointestinal tract is almost complete, but rather slow, with a time to reach the maximum plasma concentrations of 6–8 hr. The reason for this delay is not clear, but the enterohepatic cycle may play a role. The *C*max in humans exceeds 20 L/kg, which points to extensive nonspecific binding to tissue. At least in

rats, brain concentrations of sertraline are 40 times higher than in plasma. Linear pharmacokinetics is suggested for sertraline. After single doses between 50 and 200 mg, *t*½ is similar for single dose and steady-state conditions. [47]

Metabolism

Although the hepatic metabolism is the most important elimination pathway, with only 0.2% of an oral dose being excreted unchanged in the urine, information on the metabolism of sertraline is rather limited. N-demethylation is the main metabolic step in the biotransformation of sertraline.

The N-demethylated metabolite is more slowly eliminated and has a 3 times longer $t_{1/2}$ (60–100 hr) than its parent drug. Hence, the plasma concentration of *N*-desmethylsertraline is 1–3 times that of sertraline. Since *N*-desmethylsertraline has only 5–10% of the serotonin reuptake inhibitor potency of sertraline, a contribution to clinical effects of sertraline can be neglected. The N-demethylation correlates with the activity of CYP3A4, suggesting that this enzyme is involved. Conclusive data on enzymes responsible for the metabolism of sertraline, however, are still lacking. Because it is a substrate of a CYP3A, the metabolism of sertraline in the gut may be important. However, the gut metabolism of sertraline has not been examined and little has been reported on other pathways, including oxidation at the side chain to a carbamaic acid and oxidative deamination to a ketone derivative (Fig 4) . [47]

Compared to other SSRIs, a relevant portion of oral sertraline is excreted in the feces (50%). This point to an extensive transport of metabolites or their conjugates into the bile or fecal elimination from the enterohepatic circle.[47]

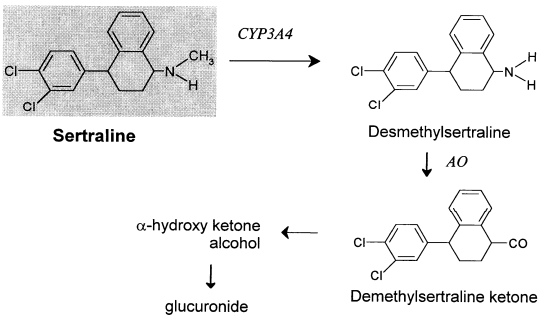


Figure - 4: Metabolism of sertraline and enzymes suggested catalyzing Phase I reactions: CYP3A4 and amine oxidase (AO). [47]

Elimination:

The elimination rate constant is higher in young males than in females or subjects t½ 65 years (0.031/hr vs. 0.022/hr for young females vs. 0.019/hr in the elderly). In young men, is 30% shorter (22.4 hr) than in females or aged patients (32.1-36.7 hr). This suggests sex- and age-dependent differences *t* ½ either in the tissue distribution (lower relative fat volume in young men) or in the metabolism of sertraline. Similar age and sex differences have been shown for the N-demethylated metabolite. The pharmacokinetics are not significantly different between healthy controls and patients suffering from renal impairment. In patients with liver cirrhosis, the clearance of sertraline is markedly reduced. This is consistent with the finding that the main route of sertraline clearance is hepatic metabolism. [47]

3.2.3 Pharmacodynamics

The pharmacodynamic properties of the SSRIs, including sertraline, have been previously reviewed Biogenic amine reuptake. In vitro studies have demonstrated that sertraline is 2–10 times more potent in inhibiting serotonin reuptake than fluvoxamine, fluoxetine, and clomipramine. In addition to animal in vitro and behavioral data, human blood α platelet serotonin inhibition has been used as a measure of inhibitory effect. When healthy male volunteers took oral doses of sertraline between 50 and 200 mg/day, platelet serotonin reuptake was inhibited in a dose-dependent manner, with the compared affinity constant of serotonin also increasing in a dose-dependent manner. Sertraline indirectly down regulates postsynaptic -adrenoceptors, but it has only weak effects on direct norepinephrine and dopamine reuptake. dopamine reuptake, sertraline is more potent compared to a number of common antidepressants (bupropion, venlafaxine, nefazadone, paroxetine, norfluoxetine, nortriptyline, desipramine). It is about 60 times more potent at inhibiting serotonin than either norepinephrine or dopamine reuptake. [47]

Table - 1: Pharmacokinetic parameters of SSRIs and clinically relevant interactions with CYP isoenzymes. [47]

Name	Daily dose (mg)	$t_{1/2}$	Time to reach steady state	V_d (L/kg)	Linear kinetics	CYP inhibition
Sertraline	50-150	26 hr	5-7 days	20	Yes	Minimal

3.2.4. Clinical Studies

Sertraline is one of the most widely used and studied SSRIs. In addition to the literature on the use of sertraline in the treatment of (primary) mood and anxiety disorders, there has been a surge of literature pertaining to its use for the treatment of mood symptomatology, associated with neurological and medical conditions, such as Parkinson's disease, diabetes mellitus and HIV infection-related mood disorders.

- ✓ Melancholic features [47]
- ✓ Dysthymia disorder
- ✓ Anxiety Disorders
- ✓ Obsessive-compulsive disorder
- ✓ Social phobia

Panic disorder Post-traumatic stress disorder

Side Effects: The incidence of side effects with sertraline is related to both dose and dosage of the drug. [47] Gastrointestinal side effect such as nausea, dyspepsia, diarrhea other effects, including tremor, dry mouth, dizziness, and somnolence or insomnia. [47] Sexual dysfunction. [47]

3.2.5. Cytochrome P450 enzyme system

At least five isoforms of CYP (2B6, 2C9, 2C19, 2D6, and 3A4) are involved in the metabolism of sertraline, but since the contribution of any individual isoform does not exceed40% of the overall metabolism, concurrent administration of a drug that inhibits one of these iso-forms is unlikely to cause a marked increase in the plasma concentration of sertraline. Sertraline mildly inhibits the CYP2D6 iso enzyme, resulting in 10%–50% elevation inplasma levels of a co-administered CYP2D6 substrate (e.g., dextromethorphan taken withsertraline). However, its effect on CYP1A2, CYP3A3_4, CYP2C9, and CYP2C19 appears minimal. There are few studies of the effect of sertraline on the 2C9_10 enzyme substrates. There is little evidence of conversion by genetically determined CYP2D6 'extensive metabolizers' to phenocopies of CYP2D6 'poor metabolizers' following treatment with daily dosages of sertraline in the range from 50–100 mg_day, but in general, much remains to be delineated about isoenzyme metabolism and SSRIs. Desmethyl sertraline has a mild effect on cytochrome P450 enzymes similar to that of sertraline. This effect is probably not meaningful at usual antidepressant doses, but may be relevant at high doses or in unusually sensitive individuals. Cytochrome P450 3A isoenzyme activity may be greater in young and postmenopausal women; this system is relevant to the metabolism of sertraline, and there are data describing sex- and age-related differences in plasma concentrations of sertraline. [47]

3.3. Omeprazole

Omeprazole, the first proton pump (H^+/K^+ -ATPase) inhibitor, has been used for over a decade in the treatment of acid-related diseases. Like subsequent proton pump inhibitors omeprazole is metabolized primarily by a polymorphically expressed enzyme within Cytochrome P450 (CYP), CYP2C19. Omeprazole is a racemic composition of its two optical isomers, S-omeprazole (esmoprazole) and R –omeprazple, which have demonstrated stereoselective metabolisms.[50]

3.3.1 Basic Pharmacology

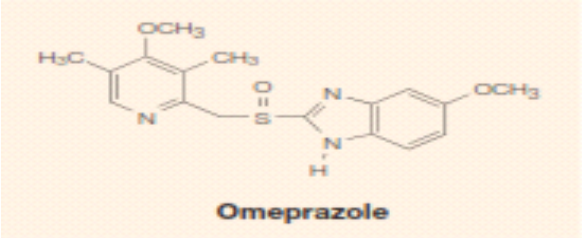


Figure - 5: Structure of Omeprazole.

3.3.2. Mechanism of action of omeprazole

The success of omeprazole in the clinic can be ascribed to the very effective inhibition of gastric acid secretion achieved through specific inhibition of the gastric H+K+-ATPase. This proton pump is located in the secretory membranes of the parietal cell of the gastric mucosa and constitutes the final step of acid secretion. Therefore, blockade of this pump results in a more specific inhibition of acid secretion compared with blockade of the more widely distributed H and cholinergic receptors. Furthermore, as omeprazole interacts with the final step of acid production, the inhibition of gastric acid secretion is independent of how acid secretion is stimulated an important advantage over other pharmacological approaches to inhibiting acid secretion. For example, the inhibition of acid secretion by H2-receptor antagonists can be overcome by food induced stimulation of acid secretion via gastrin or cholinergic receptors.[48]

3.3.3. Pharmacokinetic of Omeprazole

Radioactive Omeprazole was orally administrated at a dosage of 10 mg/kg to make full inhibition, and the drug concentration in the plasma level and the inhibition of acid secretion were measured at timed intervals. Then, the stomachs were isolated at a given time and the pump enzyme was separated from each stomach. Radioactive omeprazole bound to the enzyme was counted, and the quantity of the enzyme was determined. Maximum binding of omeprazole to

the pump enzyme with full inhibition of acid pumping was 2.5 nmol/mg of the enzyme, which was fully agreed with the reported data. As shown in table 3, the inhibition of acid secretion decreased as the binding amounts of omeprazole decreased. The relationship was linear.Plasma level of the drug was not correlated with the inhibition or binding amounts except administration beginning time. Drug concentration in the blood abolished fast with the elimination half-life about 7-10 minutes in rats, while the inhibition prolonged since the inhibition was achieved by covalent binding of activated omeprazole. [49]

Table - 2: Pharmacokinetic property of omeprazole

Parameter	Omeprazole 20 mg
T_{max} (hr)	1 - 4
C_{max} (µmol/L)	0.23- 23.2
AUC (µmol/hr/L)	0.58-3.47
V (L/kg)	0.13- 0.3
CL (mL/min)	400- 620
$t_{1/2}$ (hr)	0.5- 1.2

3.3.4. Healing Effect

Omeprazole (40 mg daily) was significantly better than continued treatment with standard doses of cimetidine (0-8 g or 1 g daily) or ranitidine (300 mg daily) in healing peptic ulcer that was refractory to these doses of H2 receptor antagonists. Though pain control was not a primary objective and patients with extremely severe pain were not included, omeprazole gave better symptom relief than did further H2 receptor antagonist treatment. [52]

3.3.5. Clinical Studies

Omeprazole was found to be significantly superior to previous treatment regimens of H2 receptor antagonists in patients with duodenal and gastric ulcers. A particularly notable superiority of omeprazole compared with the H2-receptor antagonist ranitidine was found in GERD patients, in which the healing rates were about twice as high with omeprazole.[48] Omeprazole, a gastric acid pump inhibitor which has greater anti-secretary activity than histamine H2 receptor antagonists has been widely used in the treatment of reflux oesophagitis, Zollinger–Ellison syndrome and peptic ulcer disease. [51]

3.3.6 Adverse effects [52]

- Diarrhea
- loose stools and
- constipation

3.4. Reported Interactions of sertraline

- Glenda macqueen, Leslie born, and Meir Steiner reported a case study that, Sertraline and dextromethorphan metabolized by same isozyme. sertraline mildly inhibits the CYP2D6 isoenzyme, resulting in 10%–50% elevation in plasma levels of dextromethorphan when co-administered. [47]
- Amany and Tohamy studied and reported that, Sertraline and erythromycin are metabolized through CYP3A4 which is one of the cytochrome P-450 enzymes in liver and are responsible for the metabolism of large number of endogenous substrates and therapeutic agents. This shows increased Genotoxicity after multiple combined treatment with sertraline and erythromycin may indicate increased risk of toxicity-based drug-drug interaction. This toxicity may be due to the ability of sertraline and erythromycin to inhibit the activity of CYP3A4 which lead to a prolonged storage period of drugs in the body and hence increased toxicity. [53]

3.5. Reported Interactions of omeprazole

- Behave, and co-workers were studied the effect of low dose of amlodipine in combination with low dose of Omeprazole on the above parameters such as volume, pH, acidity of gastric secretion and ulcer index were observed. Combination of omeprazole (1mg/kg) and amlodipine (0.25mg/kg) also produced a significant ($p<0.01$) decrease in the values of all the parameters. With a significant increase in the pH values as compared to the control values as well as to the groups that received either omeprazole or amlodipine alone. Amlodipine produced significant antiulcer effects in pylorus-ligated model .combination of low dose of Amlodipine with low dose of either famotidine or omeprazole produced significant antiulcer effects. It was suggested that the patients who received Amlodipine therapy for some other clinical conditions are less prone to develop peptic ulcers; and even if ulcer develop, they would require lower doses of antiulcer agent like Omeprazole.
- Pharmacokinetic Interaction: The proton pump inhibitors (PPIs) are all substrates of CYP2C19 and in theory could interfere with the metabolism of citalopram by competing for the enzyme. Competitive inhibition is dose-dependent, reversible and tends to have only oldest effects. Recent evidence suggests that omeprazole, specifically the enantiomer of Omeprazole, is a mechanism-based

inhibitor of 2C19. Mechanism-based inhibition irreversibly inactivates enzyme and is more likely to have a significant clinical effect than competitive inhibition. Pharmacodynamic Interaction: Use of PPIs for more than one year may deplete magnesium, potassium and calcium. These electrolyte deficiencies are risk factors for TdP (Torsades de Pointes). Adding citalopram to long-term PPI therapy could, in theory, increase this risk.

4. MATERIALS AND METHODS

4.1. Material selection

4.1.1. Experimental animals and treatment

Cage cards were utilized to identify the strain of animal, sex, and number, name of the principal investigator and title of research protocol. Temporary identification of individual animal was accomplished by dyeing the fur.

4.1.2. Chemicals

- **Sertraline:** Pure sample of Sertaline was procured as a gift sample from Mylan Laboratories Limited, New Dhelli
- **Omeprazole:** Pure sample of Omeprazole was procured as a gift sample from Mylan Laboratories Limited, New Dhelli
- **5-Hydroxytryptophan:** Yarrow Chem. Products, Mumbai.
- **Normal saline**
- **Tween-80**
- **Distilled water**
- **Surgical spirit**

All the chemicals used were of analytical grade.

4.1.3. Apparatus:

- Laboratory Centrifuge Remi R8C.
- Aquity Ultra Performance Liquid Chromatography.
- Electronic balance.Ohous corp. pine brooki, NJ USA, AR0640-N13123
- Rabbit holder, Disposable syringe, 22 & 26 gauge Needles, Spatula, Sterilized cotton, Oral cannula, Variable micropipette [0-100 µL], Volumetric flask, Measuring cylinder, Mortar and pestle, Eppindroff tubes, Centrifuge tubes, Refrigerator, Membrane [Nylon-65] syringe filter.

4.2. Methods

4.2.1. Preparation of sertraline standard solution

Sertraline pure sample was dissolved in 2% Acacia after triturating with 2 gm of Acacia in little quantity of water. Final volume was made up in 100 ml volumetric flask using water, stock solution was prepared to get 1mg/ml concentration.

4.2.2. Preparation of Omeprazole standard solution

Omeprazole pure sample was dissolved in 1% of Tween-80, which was prepared by triturating 1ml of surfactant Tween-80 in little quantity of water and make up in 100 ml volumetric flask with distilled water, stock solution was prepared to get 1 mg/ml concentration.

4.2.3. Preparation of 5-hydroxytryptophan standard solution

5-Hydroxytryptophan was dissolved in saline (0.9%) after triturating with 10% Tween-80. Final volume was made up in volumetric flask using saline. Stock solution was prepared to get 2 mg/ml concentration.

4.2.4. General procedures

Method for oral administration of drug in rabbits:

The rabbits were fixed in wooden stalls and an oral gag was placed in between the jaws and held in position by holding upper and lower jaw using the left hand. One end of the feeding tube was moistened with glycerin and introduced into the mouth through the central hole of the gag. One end of the feeding tube was pushed slowly such that it enters the esophagus. The other end of the feeding tube was connected to a syringe, 2-3 ml of distilled water was administrated initially to ensure that the incubation is in right position. The drug solution was administrated similarly and this was followed by 3ml-distilled water to ensure the administration of correct dose of the drug. The oral feeding tube was then gently removed and the animal was removed from the wooden stall immediately and is tilted with its head down, which prevents the entry of any fluid into the respiratory tract. The gag and the oral feeding tube were cleaned.

Blood sampling technique in rabbit:

Blood samples were collected from the marginal ear vein. For this, the rabbits were kept in wooden stalls, with their heads-protruding out. The marginal ear vein was located by gentle trucking and tapping of the ear, this made the vein more visible. After disinfecting the site, 22 gauge needle was inserted into the ear vein and blood was collected from the hub of the needle directly into a blood collecting tube. A cotton ball was pressed on the top of the injection site before

pulling out the needle, and clip was applied on the top of the cotton ball for 2-3 minutes to stop further bleeding.

4.3. Experimental procedure

4.3.1. Effect of Omeprazole treatment on Pharmacokinetic Parameters of Sertraline in healthy albino rabbits.

Four male albino rabbits weighing between 2 to 2.5 kg were taken and marked suitably. Rabbits were fasted for 18 hours before commencing the experiment. During this period, the rabbits were allowed to take adequate water. Fasting was continued till the completion of the experiment. After fasted for 18 hours, the blood was collected (at '0' hour) before the administration of sertraline. Later all the rabbits received Sertraline (20mg/kg) solution orally, the time of administration was noted.

Blood samples were collected thereafter at prefixed time intervals i.e. 0.1, 2, 4, 8, 12 and 24 hours after dosing in blood collection tube and kept aside for 30-40 minutes. Serum samples were obtained after centrifugation at 3000 r.p.m. for 15-20minutes. The transparent supernatant liquid (serum) obtained was transferred into a clean dry eppindroff tubes. Serum samples were stored at -20°C for analysis.

After blood collection animals were left for a washout period of 15 days with normal diet. The next part of this experiment was conducted on the same group of animals. All the rabbits received Omeprazole (8mg/kg) orally once a day for one week. On the 7th day, 6 hours after administration of the drug, the rabbits were fasted for 18 hours. On the 8th day, Omeprazole (8mg/kg) was administered orally to all the animals, the time of administration was noted. After 60minutes of Omeprazole administration, Sertraline (20mg/kg) was given orally. Blood samples were collected in a blood collection tube at prefixed time intervals i.e. 0,1, 2, 4, 8, 12 and 24 hours after Sertraline dosing, serum was separated from blood and stored at -20°C for analysis.

The serum concentration of Sertraline was estimated by High Performance Liquid Chromatography method.[70] Sertraline estimation method: in this method, the estimation of Sertraline is carried out using a reversed phase C_{18} column (Gracesmart RP-18), mobile phase (Acetonitrile/0.25 M potassium phosphate (pH 2.7) 30:70 v/v) and UV detection at a wavelength of 235 nm. Flow rate maintained at 1.0 ml/min.

The results are tabulated in table 3, and depicted in figure 6. The amount of Sertraline present in serum was calculated using the following equation:

The serum concentration of Sertraline before and after treatment Omeprazole were applied to software Ramkin to calculate pharmacokinetic parameters like AUC0-t, AUMC0-t, Cmax, Tmax, *t* ½ and MRT. The results are presented in table 4, and the changes in pharmacokinetic parameters are depicted in figure 7.

The chromatogram obtained for standard sertraline are depicted in figure 8, and the chromatogram obtained for the serum sertraline at 8th hour of day 1 (i.e. before Omeprazole treatment) are depicted in **figure 9**. The chromatograms obtained for serum Sertraline concentration at 8th hour of day 21st (after Omeprazole treatment) are depicted in **figure 10**.

Evaluation:

Pharmacokinetic data of sertraline was measured assuming complete oral absorption. All the experimental results were expressed as mean ± SEM and assessed by student't' test using parametric statistics, IBM PC version 1.01, LONDON SOFTWARE, INC. A value of $P<0.05$ was considered statistically significant.

4.3.2. Effect of Omeprazole treatment on antidepressant activity of Sertraline in healthy albino rats

4.3.2.1. Despair swim test

Purpose and rationale:

Behavioral despair was proposed as a model to test for antidepressant activity by Porsolt, et al. It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behaviour of immobility. This behaviour reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression.

Experimental procedure:

Six Male albino rats weighing between 160-180 grams were used. All rats were brought to the laboratory one day before the experiment and were housed separately in cages with free access to food and water. Rats are individually forced to swim inside a vertical Plexiglas cylinder (height: 40cm; diameter: 18cm) containing 15cm of water maintained at 25^{0}C.

Rats placed in the cylinder for the first time are initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2–3 min activity begins to subside and to be interspersed with phases of immobility or floating of increasing length. After 5–6 min immobility reaches a plateau where the rats remain immobile for approximately 80% of the time.

After 15 min in the water the rats are removed and allowed to dry in a heated enclosure (32 °C) before being returned to their home cages. They are again placed in the cylinder 24 hr later and the total duration of immobility is measured during a 5 min test.

An animal is judged to be immobile whenever it remains floating passively in the water in a slightly hunched but upright position, its nose just above the surface.

In the first part of experiment, animals were administered with Sertraline (20mg/kg, p.o.). The time of the drug administration was noted for all the animals. The animals were forced to swim and the duration of immobility was measured for a duration of 5 min. at 1^{st} , 2^{nd} , 4^{th}, $8^{th,}$ 16^{th} and 24^{th} hour after drug administration. All the rats were left for washout period of 15 days.

In the next part of the experiment, the same group of animals after a gap of 15 days were administered with Omeprazole (8mg/kg, p.o.) once a day for one week. On the 8th day, Omeprazole (8mg/kg, p.o.) were administered to all the animals, and the time of administration was noted. After 60 minutes of Omeprazole administration, Sertraline (20mg/kg, p.o.) was administered, the test was repeated and the total duration of immobility for duration of 5 min was measured at 1^{st}, 2^{nd}, 4^{th}, 8^{th}, 16^{th} and 24^{th} hour after Sertraline administration. The results obtained are tabulated in table 5 and depicted in figure 11.

Evaluation:

The data are expressed as mean ± SEM for each treatment group. The data obtained from each response measures were subjected to students't' test using parametric statistics, IBM PC version. 1.01. London. A value of $P<0.05$ was considered statistically significant.

4.3.2.2. Serotonin syndrome test [71, 72]

Purpose and rationale:

Compounds which stimulate serotonin receptors or which increases dramatically the serotonergic transmission in the CNS cause a series of behavioral changes in rats which is called the serotonin syndrome such as head weaving, increased locomotion, forepaw treading, tremor, hind limb abduction, flat posture and lower lip retraction. With increasing knowledge about the subtypes of serotonin receptors these symptoms were defined to be associated with 5-HT receptors and their specific agonists.

The behavioral motor syndrome (5-HT syndrome) can be elicited by injecting, the serotonin precursor L-5-hydroxytryptophan, 5-HT agonists like 5-methoxy-N,N dimethyltryptamine (5-MeODMT) or quipazine. 5-HT-releasing compounds like p-chloroamphetamine or fenfluramine have also been shown to induce the 5-HT syndrome.

The serotonin syndrome in rats has been used to study the interaction of drugs with central 5-HT system of rats. It is also used for the screening of the psychoactive drugs and this method offers several advantages like this is fast, require no elaborate equipment and provide information on CNS permeability etc.

Experimental procedure:

Six male albino rats weighing between 160-180 grams were selected and housed in cage with free access to food and water. In the first part of experiment, rats were administered with Sertraline (20 mg/kg, p.o.). The time of the drug administration was noted for all the animals. After 30minutes of sertraline administration, 5-hydroxytryptophan (5-HTP) (50 mg/kg, i.p.) and fluoxetine (30 mg/kg, i.p.) were administered to all the rats. Each rat was scored during 0, 15, 30, 45 and 60 minutes after the injection. The severity of the symptoms were scored as following scale, forepaw treading (0=absent; 1=weak; 2=continuous), head weaving (0=absent; 1=weak; 2=continuous), hind limb abduction (0=absent; 1=present), All the rats were left for washout period of 15 days.

In the next part of the experiment, the same animals after a gap of 15 days were administered with Omeprazole (8mg/kg, p.o.) once a day for one week. On the 8th day, Omeprazole (8mg/kg, p.o.) was administered to all the animals, and the time of administration was noted. After 60 minutes of Omeprazole administration, Sertraline (20mg/kg, *p.o.*) was administered. Again after 30minutes of Sertraline administration, 5-hydroxytryptophan (50mg/kg, *i.p.*) and fluoxetine (30 mg/kg, *i.p.*) were administered to all the rats. Severities of symptoms were scored as mentioned earlier. The results obtained are tabulated in the table 6 and depicted in figure 12.

Evaluation:

The data are expressed as mean ± SEM for each treatment group. The data obtained from each response measures were subjected to students't' test using parametric statistics, IBM PC version. 1.01. London. A value of $P<0.05$ was considered statistically significant.

5. RESULTS

Table - 3: Data showing the Serum concentration of Sertraline before and after Omeprazole treatment in healthy albino rabbits.

S. No	Time in hour	Serum Sertraline concentration in µg/ml ± SEM	
		Drug therapy	
		Sertraline Sertraline + Omeprazole 20mg/kg-orally	Sertraline + omeprazole 20mg/kg + 8mg/kg-orally
1	0	0.0 ± 0.0	0.0 ± 0.0
2	1	0.462 ± 0.042	0.714 ± 0.007
3	2	0.867 ± 0.036	1.239 ± 0.119
4	4	1.228 ± 0.110	1.942 ± 0.030
5	8	2.106 ± 0.05	2.823 ± 0.064
6	16	0.963 ± 0.048	1.239 ± 0.031
7	24	0.6523 ± 0.04	0.860 ± 0.021

Table - 4: Data showing the pharmacokinetic parameters of Sertraline before and after Omeprazole treatment in healthy albino rabbits.

Pharmacokinetic parameters	Drug Treatment	
	Sertraline 20mg/kg	Sertraline + Omeprazole (20mg/kg+8mg/kg)
C_{max} (µg/ml)	2.240	2.872
T_{max} (hr)	8	8
AUC_{0-t} (µg/ml/hr)	30.33	38.851
AUM $_{0-t}$ (µg/ml/hr*hr)	405.77	523.657
$t_{1/2}$ (hr)	16.013	19.30
MRT (hr)	24.79	28.43

C_{max} - Concentration maximum, T_{max} - Time of maximum concentration, AUC - Area under curve, AUMC - Area under first order moment curve, $t_{1/2}$ - Terminal half life, MRT - Mean residential time.

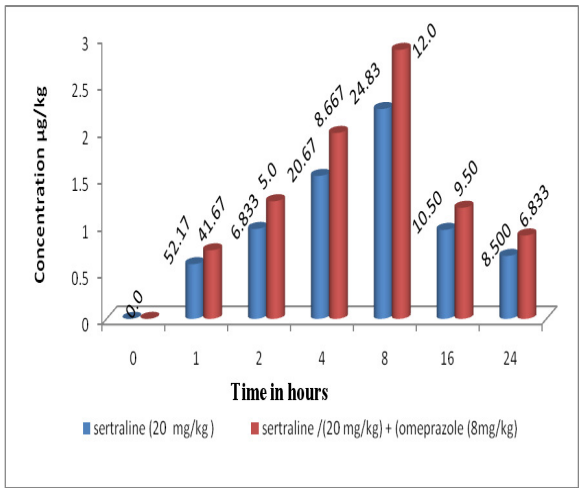


Figure - 6: Graphical representation showing the serum concentration Sertraline before and after Omeprazole treatment in healthy albino rabbits.

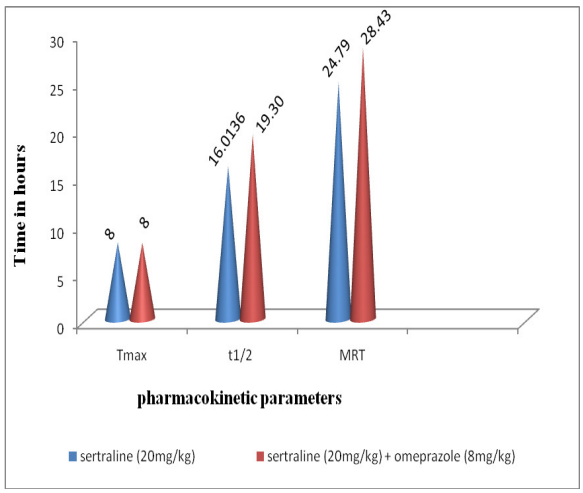


Figure - 7(a)

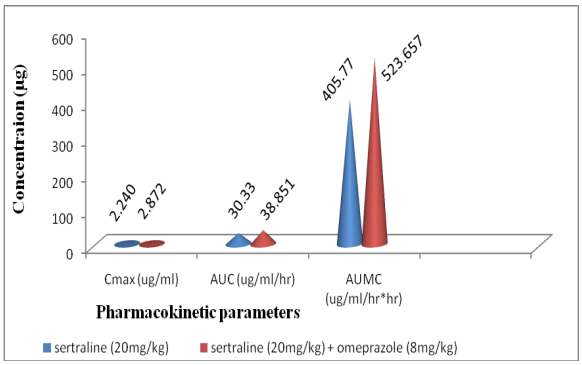
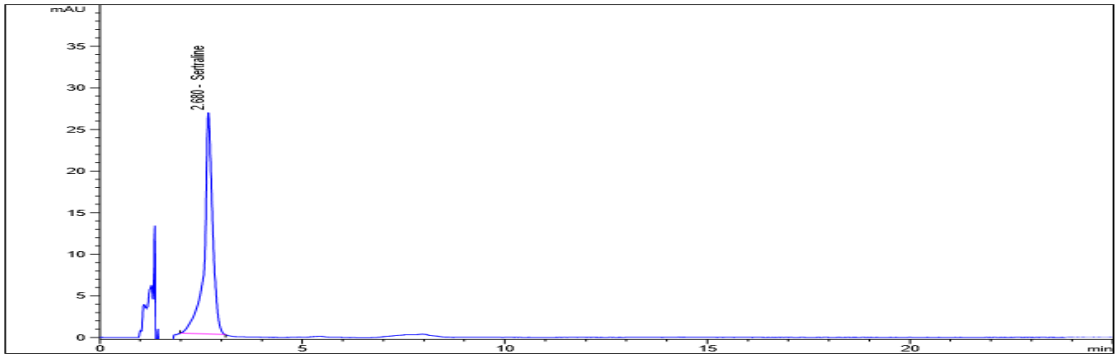


Figure 7 (b)

Figure 7: The graphical representation of the effects of Omeprazole on the pharmacokinetic parameters of Sertraline in healthy albino rabbits as shown in figure (a) and (b) respectively.

BANGALORE TEST HOUSE

Sample Name	:SERTRALINE HCL	Seq Line	: 2
		Location	: P1-A-01
Injection Date	:9.07.2013 1:57:27 PM	Inj. No.	: 1
Acq Operator	:VB	Inj. Vol.	: 40µl
Sample Info	:SERTRALINE HCL		->
Method Info	:ASSAY		
File Name	:D:\CHEM32\1\DATA\BP\SERTRALINE HCL 2013-07-09 13-29-38\ SERTRA0000002.D		



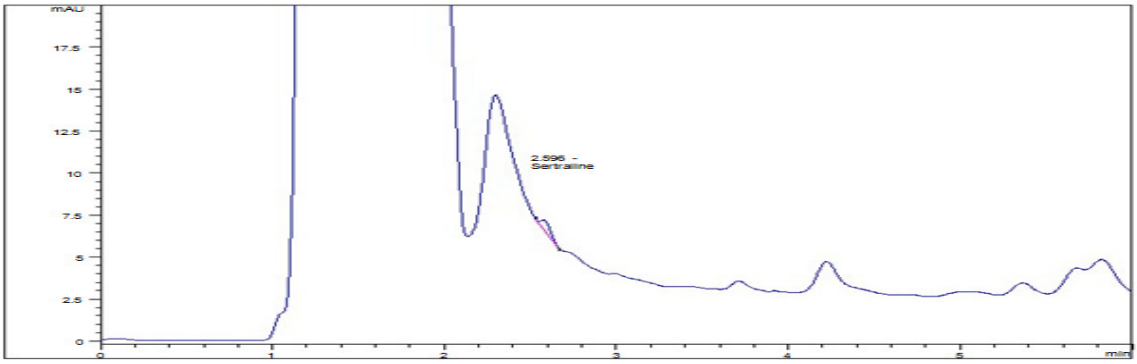
Signal DAD1 A, Sig=254,4 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %	Name
1	2.680	0.240	382.996	100.000	Sertraline

Figure - 8: Chromatogram of standard Sertraline.

BANGALORE TEST HOUSE

Sample Name	:SERUM	Seq Line	: 4
		Location	: P1-A-03
Injection Date	:9.07.20134:10:16 PM	Inj. No.	: 1
Acq Operator	:VB	Inj. Vol.	: 40µl
Sample Info	:B.No. MS-2 ND/2013/07/0051		->
Method Info	:ASSAY		
File Name	:D:\CHEM32\1\DATA\BP\SERTRALINE HCL 2013-07-09 13-29-38\ SERTRA0000007.D		



SignalDAD1 A, Sig=254,4 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %	Name
1	2.596	0.067	2.767	100.000	Sertraline

Figure – 9: Chromatogram of serum Sertraline sample (8th hour of 1st day of treatment).

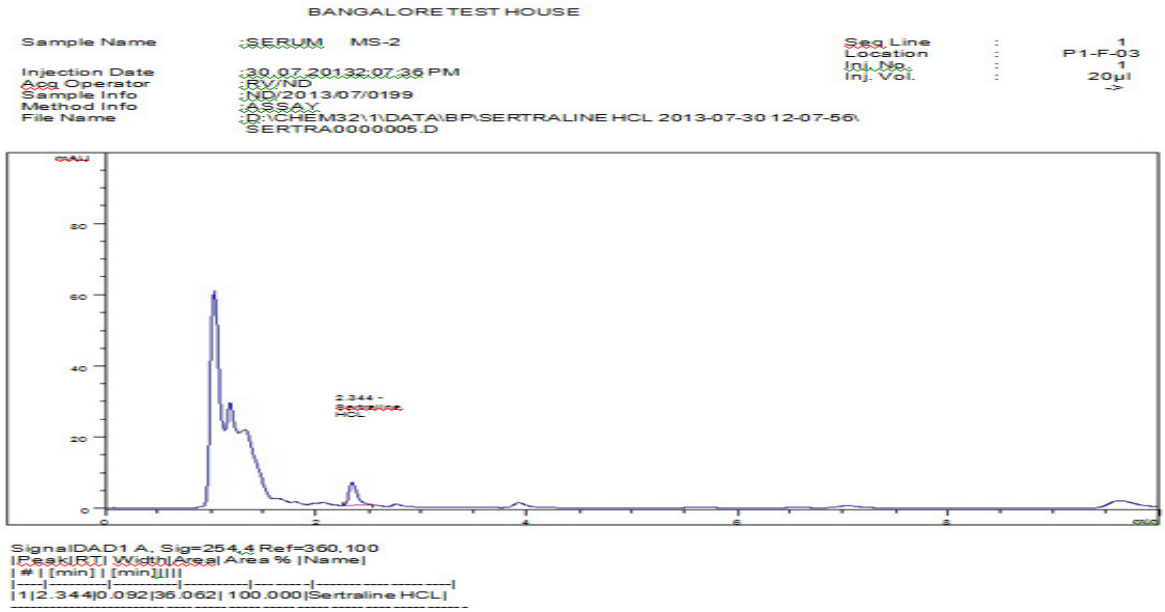


Figure - 10: Chromatogram of serum Sertraline sample (8th hour of 21st day of treatment)

Table - 5: Data showing the immobility time of Sertraline before and after Omeprazole treatment in healthy albino rats using despair swim test.

Sl. No.	Time Interval	Immobility time (seconds) in 5 minutes test (Mean ± SEM)	
		Drug Treatment	
		Sertraline (20 mg/kg, p.o.)	Sertraline + Omeprazole (20 mg/kg, p.o + 8 mg/kg p.o.)
1	1	52.17 ± 17.35	41.67 ± 16.22
2	2	6.833 ± 3.311	5.000 ± 2.40
3	4	20.67 ± 8.864	8.667 ± 3.14
4	8	24.83 ± 8.538	12.00 ± 7.27
5	16	10.50 ± 4.137	9.50 ± 3.03
6	24	8.500 ± 3.128	6.833 ± 2.38

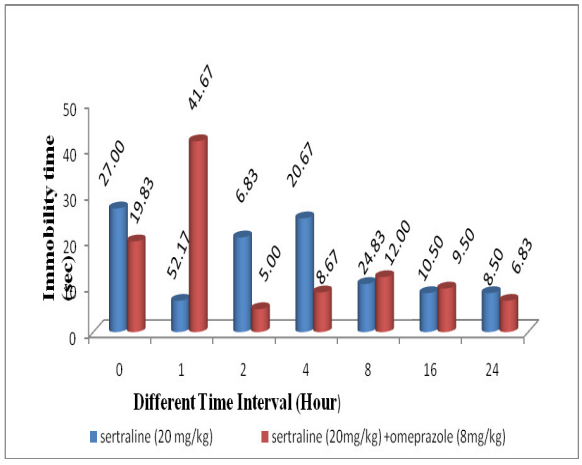


Figure - 11: Showing the immobility time of Sertraline before and after Omeprazole treatment in healthy albino rats using despair swim test.

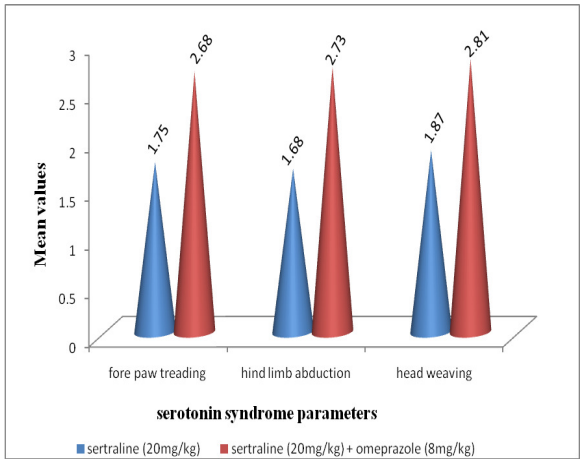


Figure - 12: Effect of Omeprazole treatment on Sertraline in rat Serotonin syndrome test.

Table - 6: Data showing the effect of Omeprazole treatment on Sertraline in healthy albino rats by using serotonin syndrome test.

Treatment	Dose	Fore paw treading score (Mean ± SEM)			
		15 min	30 min	45 min	60 min
5- HTP + FL	30 mg/kg, *i.p.*	0 ± 0	0.33 ± 0.21	0.66 ± 0.33	1 ± 0.44
Sertaline	20 mg/kg, *p.o*	1.25 ± 0.25	1.50 ± 0.28	1.75 ± 0.25	2.5 ± 0.28
Sertraline + Omeprazole	20 + 8 (mg/kg, *p.o.*)	1.50 ± 0.64	2.75 ± 0.25	3.00 ± 0.40	3.50 ± 28
Treatment	**Dose (mg/kg, *p.o.*)**	**Hind limb abduction score (Mean ±SEM)**			
		15 min	**30 min**	**45 min**	**60 min**
Sertaline	20	1.00 ± 0.42	1.50 ± 0.28	1.75 ± 0.25	2.5 ± 0.28
Sertraline + Omeprazole	20 + 8	1.75 ± 0.47	2.75 ± 0.2	3.0 ± 0.40	3.5 ± 28
Treatment	**Dose (mg/kg, *p.o.*)**	**Head weaving (Mean ± SEM)**			
		15 min	**30 min**	**45 min**	**60 min**
Sertaline	20	1.0 ± 0.40	1.75 ± 0.47	2.0 ± 0.0	2.75 ± 0.25
Sertraline + Omeprazole	20 + 8	1.75 ± 0.47	3.0 ± 0.0	3.0 ± 0.40	3.55 ± 0.28

6. DISCUSSION

Effect of Omeprazole on pharmacokinetic parameters of Sertraline:

The serum concentrations of sertraline before and after the treatment of Omeprazole are tabulated in table 3. The serum concentration of Sertraline at 1st hour was 0.584 mcg/ml and the peak concentration was at 8th hour i.e., 2.240 mcg/ml. It started declining at 16th hour. These results revealed that Sertraline was well absorbed by oral route.

The data of the effect of Omeprazole treatment on the pharmacokinetic parameters of Sertraline is tabulated in the table 4, it revealed that AUC and AUMC of sertraline have changed after Omeprazole treatment. The Cmax, AUC and AUMC of Sertraline are increased due to Omeprazole treatment. These results revealed the absorption of Sertraline is increased by Omeprazole treatment.

The Omeprazole treatment for one week significantly increased the serum concentration of Sertraline at 1st, 2nd and 4th. The peak concentration (C_{max}) of Sertraline is increased from 0.584 mcg/ml to 0.732 mcg/ml at 1st hour. The time of peak concentration (T_{max}) did not change. These results confirmed that the Omeprazole treatment enhanced the serum concentration of Sertraline at absorption site. The insignificant changes at T_{max} revealed that the omeprazole might not influence the metabolism of Sertraline.

The duration of action of Sertraline is not altered by Omeprazole treatment. It is also interesting to note that Omeprazole is metabolized by CYP2C19[33] and it is effective inhibitor of CYP2C19 whereas the Cytochrome P450 (CYP) isoenzyme CYP 2B6, 2C9, 2C19, 2D6, and 3A4 are responsible for the metabolism of Sertraline.[47,36] Theoretically we expected the interference of Omeprazole on Sertraline metabolism, since CYP2C19 is metabolizing both the drugs. It is also mentioned in the literature that Sertraline has the potential to interact with drugs. However our experimental results revealed that there is no significant change in the duration of action; hence the possibility of interaction at metabolism site is negligible.

The terminal half-life of sertraline is slightly increased from 16.0136 to 19.30 hours and the mean residential time from 24.79 to 28.43 hours, due to Omeprazole treatment. These increments may be due to strong protein binding property of Sertraline and Omeprazole.

Effect of Omeprazole treatment on antidepressant activity of Sertraline by despair swim test:

The results presented in the table 5, indicate that Sertraline exhibited immobility time of 27 seconds at 0th hour, peak effect at 2nd hour i.e. 20.6 seconds and 8.5 seconds at 24th hour. These results confirm its antidepressant activity tested in this animal model. Omeprazole treatment decreased the immobility duration in healthy albino rats significantly at 1st, 2nd, 4th, 8th, 16th and 24th hour i.e. 41.6, 5, 8.6,12, 9.5 and 6.8 respectively. The immobility time is significantly reduced at 1st, 2nd, 4th, 8th, 16th and 24th hour.

In the present study, we used the despair swim test to compare the effects of Omeprazole on Sertraline antidepressive effect by observing immobility time in rats. Porsolt, et al.[71] found that such immobility is reflective of a low-mood state in the rats, which is sensitive to antidepressant treatment.

Sertraline has been reported to decrease immobility time in rats. Present results showed that there was significant reduction in immobility time at 1st hour from 52 to 41.6 seconds, at 2nd hour from 6.8 to 5 seconds, at 4th hour from 20.6 to 8.6 seconds, at 8th hour from 24.8 to 12 seconds, at 16th hour from 11.1 to 9.5 seconds when Sertraline was co-administered with Omeprazole.

In the pharmacokinetic study performed earlier we observed that there was increase in serum concentration of Sertraline by Omeprazole treatment, and this may be the reason for potentiated effect of Sertraline.

Effect of Omeprazole treatment on anti-depressant activity of sertraline by serotonin syndrome test:

Observation of results presented in the table 6, shows that Sertraline treatment on rats with serotonin precursor has a significant effect on fore paw treading and head weaving. Rats treated with sertraline scored about 1.75 and 1.87 respectively for a maximum possible score of 12 each, but had very less effect on head weaving and a moderate effect on hind limb abduction, 1.87 for possible maximum score 12 and 1.687 for 6, respectively. While considering serotonin syndrome all together Sertraline had a moderate effect of 5.307 for 30 maximum score.

The Omeprazole treatment showed earlier onset of action of fore paw treading and head weaving when compared to Sertraline treatment alone. The severity of fore paw treading was much higher when compared with Sertraline treatment alone. Hind limb abduction and head weaving had a slight increased effect of 2.75 and 2.82 respectively. Overall serotonin syndrome had a significant difference, comparatively scored8.25 for maximum of 30

Serotonin syndrome is associated with increased serotonergic activity in the central nervous system (CNS). Serotonin syndrome is a potentially fatal complication of serotonergic drug therapy. Usually, serotonin syndrome occurs with the concomitant use of two serotonergic drugs..

Sertraline is well known SSRI, and Omeprazole is proved to have competitive inhibition of serotonin uptake in crude rat brain synaptosomes.

In the present study Omeprazole significantly potentiated the serotonin syndrome of Sertaline. This potentiating effect of Omeprazole may be due to its inhibition of serotonin reuptake mechanism along with its inhibitory effect on CYP2C19 isoenzyme. [33]

7. CONCLUSION

The effect of Omeprazole on pharmacokinetic and antidepressant activity of Sertraline on healthy albino rabbits and rats was studied. The results of the present study suggest that there is an interaction when Omeprazole is co-administered with Sertraline. The pharmacokinetic parameters of Sertraline were significantly changed in the rabbits pre-treated with Omeprazole. Significant increase in immobility time and severity in fore-paw treading of sertraline were also observed in rats pre-treated with Omeprazole.

These changes in the pharmacokinetic and antidepressant activity may be due to their potentiating effect in inhibiting serotonin uptake in brain synaptosomes and strong protein binding property of Sertraline and Omeprazole, or may be due to its inhibitory effect on CYP 2C19 isoenzyme.

The exact mechanism of this interaction cannot be predicted at this stage. Further more research into the effect of Omeprazole on serotonin concentration in brain synaptosomes, protein binding and the chronic treatment of Sertraline is required for predicting the molecular mechanism behind interaction.

The consumption of antidepressant and proton pump inhibitor in common among patient suffering from peptic ulcer and depression. The interfering effects of Omeprazole and Sertraline must be cautiously considered if patient is consuming Omeprazole and Sertraline together.

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