

Citalopram Drug Interactions

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Abstract

Citalopram is an antidepressant belonging to selective serotonin reuptake inhibitors. Citalopram produces its activity by inhibiting the reuptake of serotonin in the synaptic clefts. So, concomitant administration of drugs (opioids, Monoamine oxidase inhibitors) which are having affect on serotonin or other monoamine levels in the synaptic cleft may produce some adverse effects as a pharmacodynamic interaction. Citalopram is metabolized by CytochromeP450 (CYP) 2C19 and CYP2D6 to desmethylcitalopram and further by CYP3A4 to di-desmethylcitalopram. Some drugs may either induce (carbamazepine and rifapicin) or inhibit (buspirone, tramadol, Tricyclic antidepressants) these enzymes and affecting the citalopram levels producing either therapeutic failure or serotonin toxicity. Similarly, citalopram mildly inhibits CYP2C19, CYP2D6 and CYP3A4 and thus affects the plasma levels of the drugs (imipramine, β -blockers, trazodone) which are metabolized by the above enzymes. So, in this review we tried to summarize both the interactions of citalopram with other drugs and other drugs interaction with citalopram and their probable mechanisms which may be helpful for the psychiatrists or physicians to judge the appropriate therapy when the patient is to be co-administered with citalopram.

Key words: Citalopram; Drug interactions; Pharmacodynamic; Pharmacokinetic.

INTRODUCTION

Citalopram is an antidepressant drug belonging to selective serotonin reuptake inhibitor (SSRI) class. Citalopram selectively inhibits serotonin (5HT) reuptake into the presynaptic neurons. This leads to elevated serotonin levels in the synaptic clefts. Serotonin acts on different types of serotonin receptors to produce antidepressant and other pharmacological effects. Citalopram is demethylated by CYP2C19 and CYP2D6 to N-desmethylcitalopram and N-desmethylcitalopram is further demethylated to di-desmethylcitalopram by CYP3A4.¹ Both of its metabolites are inactive. Some drugs which induce or inhibit these enzymes can also alter the plasma concentrations of citalopram by altering its liver metabolism. Citalopram is an inhibitor of CYP2D6 and also a weak inhibitor of CYP2C19 and CYP3A4. Hence, the plasma concentration of drugs which are substrates of these enzymes may be affected. And some drugs which have the potential to affect the synaptic levels of serotonin may affect the outcome of citalopram therapy. Thus, pharmacokinetic and

pharmacodynamic drug interactions are likely to occur with citalopram. Citalopram is frequently prescribed to treat the depressive patients when compared to other SSRI class antidepressants such as fluoxetine, sertraline, fluoxetine and paroxetine. Fluoxetine, sertraline, fluoxetine and paroxetine can cause severe adverse drug interactions with other drugs when compared to citalopram.² Hence, all the drug interactions identified with citalopram were reviewed to know its interaction potential especially when used to treat the depressive patients with or without co-morbidity.

Interaction Potential of citalopram

Citalopram has the potential to interact with many drugs through the pharmacodynamic and pharmacokinetic mechanisms. Its pharmacodynamic interaction is due to elevated levels of 5HT in the synaptic cleft. Such citalopram pharmacodynamic interaction was observed with non-steroidal antiinflammatory drugs (NSAIDs), antimigraine, anxiolytics, tricyclic antidepressants, monoamineoxidase inhibitors, beta blockers and opioids. Pharmacokinetically, citalopram inhibits different drug metabolising CYP450 isoenzymes. This mechanism increases the plasma levels of desipramine, trazadone,

aripiprazole, haloperidol, clozapine, reserpine, metoprolol and perhexiline. Citalopram plasma levels can be decreased by carbamazepine and rifampicin, which induce CYP2C19, CYP3A4 and CYP2D6 enzymes.^{3,4} The interaction of many drugs with citalopram is individually explained with respect their effect on clinical outcome.

Citalopram interactions with other drugs

Non steroidal anti inflammatory drugs

All selective serotonin reuptake inhibitors (SSRIs) (example, citalopram) increase the risk of upper gastrointestinal bleeding. This effect is potentiated by concurrent use of NSAIDs in depressive patients who are under treatment of SSRIs. The risk of upper gastrointestinal bleeding was found to be increased in the range of 5.2% to 12.2% when SSRIs and NSAIDs were administered together.⁵ SSRIs inhibits the serotonin transporter, which is responsible for the uptake of serotonin into platelets. Serotonin released from platelets in response to vascular injury promotes the vasoconstriction and changes the shape of the platelets leading to aggregation. SSRIs also inhibit the pulmonary endothelial metabolism of serotonin. It could thus be predicted that SSRIs would deplete platelet serotonin, leading to a reduced ability to form clots and a subsequent increase in the risk of bleeding.^{5,6}

Anticoagulants

Citalopram can increase the maximum prothrombin time when co-administered with oral anticoagulants (e.g., warfarin, acenocoumarol). Citalopram (40 mg/day) increased the normal maximum prothrombin time by 6.4% in a patient who was taking warfarin. It was considered as clinically insignificant as there was no evidence of bleeding.⁷ But, in another 63-year-old patient who was taking acenocoumarol (18 mg/week), citalopram (20 mg/day) addition resulted in the spontaneous gingival haemorrhage after 10 days. The haemorrhage, however, stopped five days after citalopram was withdrawn. This suggests the ability of citalopram including other SSRIs to increase the risk of bleeding by inhibiting serotonin levels and thus causing decreased platelet aggregation.^{8,9}

Atypical antidepressants

Citalopram can increase the plasma concentrations and pharmacodynamic aspect of trazodone. Citalopram increased the mean plasma concentrations of trazodone by 30% when compared to the trazodone monotherapy in depressive patients. This interaction is perhaps due to

inhibition of CYP3A4 metabolising enzymes responsible for the metabolism of trazodone. Increased trazodone plasma levels may result additive serotonergic effects like serotonin syndrome.^{10,11}

Antiparkinsonian drugs

Citalopram can decrease the bioavailability of selegiline. The bioavailability of selegiline was reduced by 30% in the presence of citalopram in a study involving 18 healthy subjects who were given citalopram 20 mg or a placebo daily for 10 days followed by four days with concurrent selegiline (10 mg/day). However, there was no change in the serum concentrations of the three main metabolites of selegiline and also vital signs or frequency of adverse events. The study concluded that there is no clinically relevant interaction between selegiline and citalopram.¹²

Cardiovascular drugs

Concurrent use of **metoprolol** and citalopram resulted in the twofold increase in the plasma levels of **metoprolol**. This may decrease its cardioselectivity. This interaction is due to inhibition of CYP2D6 and 2C19 isoenzymes by SSRIs. These metabolizing enzymes are involved in the metabolic clearance of beta-adrenergic blockers such as carvedilol, labetalol, metoprolol, nebivolol, propranolol and timolol.^{10,13} In another case study, citalopram raised perhexiline levels when concurrently administered in an elderly man.¹⁴ *In vitro* studies with human liver microsomes found that fluoxetine and paroxetine are potent inhibitors of metoprolol metabolism and fluvoxamine, sertraline and citalopram less potent. These results suggest the need for monitoring of the changes in the cardiovascular dynamics when SSRIs and cardiovascular drugs are concurrently administered.¹⁵

Anxiolytics

Citalopram was found to have no effect on alprazolam plasma levels, although the time to maximum alprazolam concentration was delayed by 30 minutes. The prolongation of time of maximum plasma concentration of alprazolam (T_{max}) is probably due to the effect of citalopram on the absorption of alprazolam. It is possible that citalopram may have a yet undiscovered effect on P-glycoproteins in the gut or some other effect on the gut wall to produce such effect.¹⁶

Antipsychotics

Escitalopram and citalopram in 6 patients taking aripiprazole elevated the plasma levels of latter by 39% and 34% respectively than that was found in patients

taking aripiprazole alone.¹⁷ Aripiprazole is metabolized by CYP3A4 and CYP2D6 isoenzymes. In two individual studies in schizophrenics citalopram did not affect the plasma levels of clozapine.^{18,19} But in another study initiation of citalopram 20 mg/kg therapy in a schizophrenic patient who was regularly under clozapine treatment raised the plasma levels of clozapine. The patient reported sedation, hypersalivation and confusion. Total clozapine serum levels were found to be 1097 ng/ml. The total clozapine level dropped to 792 ng/ml when the citalopram dose was reduced to 20 mg daily and the symptoms resolved over the following 2 weeks.²⁰ In a case study it was reported that a man with idiopathic priapism for 4 hours every 1-2 months experienced a prolonged bouts lasting for 6-8 hours when he was given resperidone. Then he experienced almost daily erections when he was given with citalopram with reduced resperidone dose which lasted for 12 hrs.²¹ Another study found that paroxetine, fluoxetine and sertraline increased olanzapine levels by about 32%, but citalopram had no effect.²² SSRIs including citalopram inhibit CYP2D6 isoenzyme involved in the metabolism of the antipsychotics to cause such interactions.

Tricyclic antidepressant

The contradictory reports are available about the pharmacokinetic interaction outcome associated between tricyclic antidepressants and citalopram. In five patients who were taking amitriptyline, clomipramine or maprotiline, addition of citalopram (20 to 60 mg/day), did not change the plasma tricyclic antidepressant levels.²³ But, in a study in eight healthy volunteers citalopram caused 50% increase in the area under the curve of desipramine, a primary metabolite of imipramine. This was attributed to the strong ability of desmethylcitalopram to inhibit CYP2D6 enzymes involved in the hydroxylation of desipramine.²⁴ Similarly, in another study, the levels of imipramine metabolites, desmethylclomipramine and 8-hydroxydesmethylclomipramine was found elevated.^{25,26} However, citalopram was successfully substituted for paroxetine in a case of tricyclic antidepressant toxicity during coadministration of desipramine and paroxetine.²⁷

Chemotherapeutic agent

Pharmacokinetic interaction was observed between the chemotherapeutic drugs and citalopram. A 74-year-old man who had been taking citalopram for two months developed rhabdomyolysis after undergoing initial treatment with irinotecan for gastrointestinal cancer. All

medications were discontinued. But, rhabdomyolysis was found exacerbated upon restarting citalopram to treat the depression. When citalopram was discontinued, he improved over the next five days. It was thought that the levels of citalopram might have increased because citalopram and irinotecan share at least one metabolic pathway through CYP3A4 enzymes. The cytochrome enzymes system may also have been compromised in the cancer patient.²⁸

Other drugs interaction with citalopram

Anti-migraine drugs

Concurrent administration of triptan (e.g., Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) and citalopram results in serotonin syndrome. Serotonin syndrome occurs due to excessive serotonergic effect. The symptoms include restlessness, hallucinations, loss of coordination, tachycardia, rapid changes in blood pressure, hyperthermia, over reactive reflexes, nausea, vomiting, and diarrhoea. Triptans are the agonists of 5HT_{1B/1D} receptors. SSRIs cause the accumulation of serotonin at the synaptic clefts.^{29,30} Combined use of these drugs results in serotonin syndrome due to additive serotonergic effect at the synaptic level. The clinicians should be aware of this drug interaction for better patient care.³¹

Appetite suppressant

Serotonin syndrome may occur when appetite suppressants such as sibutramine, dexfenfluramine or fenfluramine are co-administered with citalopram. A 43-year-old depressive woman taking citalopram 40 mg daily was given sibutramine 10 mg daily to treat obesity. Within a few hours of taking the first dose of sibutramine, symptoms of serotonin syndrome developed and continued for three days till she continued to take sibutramine. Sibutramine inhibits the reuptake of norepinephrine, dopamine, and 5HT. Dexfenfluramine and fenfluramine are nonspecific serotonin agonists that enhance the release of serotonin and also inhibit serotonin reuptake.^{32,33} The combination of these drugs may thus leads to excessive serotonergic effects.³⁴

Anxiolytics

On administration of buspirone and citalopram, serotonin syndrome and hyponatraemia were produced in an isolated case. Buspirone is metabolised by the same CYP3A4 isoenzymes responsible for the metabolism of citalopram. This may have caused increase in the plasma concentrations of citalopram leading excessive

serotonergic effect.³⁵ There are no pharmacodynamic interactions noted in clinical studies in which citalopram was given with benzodiazepines^{36,37} But, alprazolam significantly elevated the plasma levels of citalopram by 13%.³⁸ Hence, caution is required when these drugs are required to be administered.

Monoamine Oxidase Inhibitors

Serotonin syndrome was observed in a 34-year-old depressive patient when he was switched to citalopram 20 mg daily from moclobemide 100 mg administered thrice a day for several months.³⁹ Moclobemide and citalopram when taken in overdoses produces serotonin syndrome and may even lead to death.^{40,41,42} Limited animal data on the effects of combined use of SSRIs and monoamine oxidase inhibitors suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioural excitation. In contrast these reports, citalopram does not appear to have any influence on the wet-dog shakes response induced by the combination of a monoamine oxidase inhibitor and L-tryptophan, which is a precursor of 5HT.⁴³

Selective Serotonin Reuptake Inhibitors

The depressive patients, who did not respond to citalopram, have responded when another SSRI was co-administered. Fluvoxamine was (50 to 100 mg/day) co-administered in seven depressive patients who failed to respond to citalopram (40 mg/day) for three weeks. All patients responded. It was found that plasma S-citalopram levels rose to two to threefolds due to stereoselective inhibition of the metabolism of S-citalopram by fluvoxamine.⁴⁴ In non-responding depressive patients, the interaction of SSRIs results in the beneficial outcome.

Lithium Carbonate

A study conducted in healthy individuals concluded that there was no pharmacokinetic change when citalopram and lithium carbonate were co-administered.⁴⁵ But, the depressive patients who did not respond to citalopram alone have responded well in combination with lithium carbonate without any signs of adverse effects.⁴⁶ Even then the manufacturers cautioned the patients about excessive serotonin effects with the co-administration of citalopram and lithium.^{10,47} Lithium may enhance the pharmacologic effects of citalopram through the hyperstimulation of the brainstem 5-HT_{1A} and 5-HT_{2A} receptors.⁴⁸

Antiepileptic drugs

Approximately 30% plasma levels of citalopram were reduced when it was given along with carbamazepine. Because, carbamazepine induces CYP3A4 isoenzyme involved in the metabolism (*N*-demethylation) of citalopram.⁴⁹ In contrast, increase in the plasma levels of citalopram was observed when carbamazepine was replaced with oxcarbamazepine.⁵⁰

Opioid analgesics

The symptoms of serotonin syndrome and hallucinations were observed when the opioid analgesics were administered along with citalopram. A 70-year-old woman with mild recurrent depressive disorder who was taking citalopram 10 mg daily for three years showed the symptoms of serotonin syndrome when started taking tramadol 50 mg daily for pain relief following an operation. It was observed that CYP2D6 and CYP2C19 levels were lowered.⁵¹ A 44 year old woman who was on citalopram treatment for 9 months developed the signs of serotonin syndrome after 24 hours of meperidine administration.⁵² A 65-year-old patient chronically treated with citalopram developed serotonin syndrome following initiation of fentanyl. It was concluded that development of serotonin syndrome is due to its property of inhibition of reuptake of serotonin causing overstimulation of the 5-HT_{1A} and possibly the 5-HT₂ receptors, resulting in manifestations of the serotonin syndrome.⁵³ Visual hallucination occurred in a 90-year-old woman taking hydrocodone when her antidepressant was changed from citalopram 10 mg daily to escitalopram 10 mg daily.⁵⁴ The seizures or myoclonus associated with citalopram treatment appeared to be decreased in the threshold when concurrently administered with dextropropoxyphene.⁵⁵ In all the above cases, the symptoms of serotonin syndrome and hallucination have stopped on discontinuing the administration of the opioids.⁵⁴ Meperidine, fentanyl and other opioids are weak serotonin reuptake inhibitors. On co-administration of these drugs with citalopram may produce higher levels of serotonin in the synaptic cleft, which may result in the development of serotonin syndrome and other adverse outcome.⁵³

Antipsychotic Drugs

Both pharmacokinetic and pharmacodynamic interactions were observed between the typical and atypical classes of antipsychotics and citalopram. Levomepromazine increased the initial steady-state

plasma levels of desmethylcitalopram, the primary metabolite of citalopram, between 10 and 20%. This pharmacokinetic interaction was due to potent inhibition of the CYP2D6 isoenzymes activity by levomepromazine. Cytochrome P450 2D6 isoenzymes are involved in metabolism of desmethylcitalopram.⁵⁶

Urinary obstruction was observed in a 65 year old schizophrenic woman under treatment of aripiprazole when co administered with citalopram. The mechanism of urinary retention has been attributed to its cholinergic and central serotonergic effects. Aripiprazole is a partial agonist of dopamine D₂ receptors and 5-HT_{1A} serotonin receptors. It blocks 5-HT₂ serotonergic, α₁-adrenergic and histamine-H₁ receptors.⁵⁷

The serotonin syndrome developed in a patient with bipolar affective disorder who was taking lithium carbonate and citalopram when olanzapine was added. The syndrome was due to serotonergic side effects of olanzapine together with serotonergic effects of citalopram. These symptoms resolved on cessation of olanzapine administration.⁵⁸ Similarly, serotonin syndrome was reported in a 42 year old woman who was taking citalopram along with quetiapine. It was mentioned that serotonin syndrome was a consequence of increased brainstem and spinal cord 5-HT_{1A} receptor modulation occurring with 5-HT_{2A} receptor antagonism.⁵⁹ These reports suggest that the psychiatrists are required to be alert about the adverse outcome associated with the combination of antipsychotics and citalopram.

Tricyclic antidepressants

In a study conducted in 18 patients who were taking citalopram and tricyclic antidepressants, the serum levels of citalopram was found increased by 44%.⁶⁰ This interaction was related to the ability of tricyclic antidepressants to inhibit mildly CYP2C19 enzymes involved in the metabolism of citalopram.⁶¹

Chemotherapeutic agents

In another case report, 85-year-old woman taking citalopram developed the symptoms of serotonin syndrome after linezolid was started. Symptoms were resolved over 72 hours upon discontinuing citalopram.⁶² Linezolid is a reversible non-selective inhibitor of monoamine oxidase. It has the potential to interact with adrenergic and serotonergic agents.⁶³

In 55-year-old man who was taking citalopram 40 to 60 mg daily reported a decrease in therapeutic efficacy (increased crying and panic attacks) after starting

rifampicin 600 mg twice daily. His condition improved when the rifampicin was stopped. Rifampicin is a potent inducer of the hepatic CYP450 enzymes system, particularly CYP3A4 isoenzymes involved in the metabolism of citalopram. Induction of the CYP enzymes may have decreased citalopram plasma levels to result in the therapeutic failure.⁶⁴ Concomitant administration of citalopram with fluconazole, an antifungal produces serotonin syndrome which may be of life threatening intensity. This interaction is concluded as the outcome of fluconazole's potent CYP3A4 isoenzyme inhibiting property.⁶⁵

DISCUSSION

All selective serotonin reuptake inhibiting antidepressants interact with many drugs. Of these antidepressants, interaction potential of citalopram is less.² Nevertheless, citalopram was found to interact with many drugs. Reviewing of such drug interactions helps psychiatrists to take the precautionary steps while treating the patients with such interacting combinations.

Citalopram increases serotonin levels in the brain to produce antidepressant effect.¹ It is prescribed either alone or in combination with drugs of different therapeutic classes to treat the patients with depression with or without co-morbid illnesses. Citalopram acts by elevating serotonin levels in the synapse and it inhibits the cytochrome isoenzymes like CYP2C19, CYP2D6 and CYP3A4 involved in the metabolism of many drugs. This may lead to pharmacodynamic and pharmacokinetic drug interactions due to citalopram. In contrast, other drugs also potentially interact with citalopram by pharmacodynamic and pharmacokinetic mechanisms. These reports suggest that the citalopram behaves like a precipitant and/or index drug to result in drug-drug interactions.

Pharmacokinetically, citalopram affects the plasma concentrations of other drugs. It has increased the plasma levels of atypical antipsychotics, trazodone and β-adrenergic receptor blockers to the different extent by inhibiting the CYP450 isoenzymes mentioned elsewhere. Citalopram elevated the plasma levels of aripiprazole up to 34% in six patients.¹⁶ And metoprolol plasma levels were increased by twofold.¹³ But, the patients from both the studies did not report any side effects. Citalopram (40mg daily), on co-administration with clozapine in schizophrenics reported sedation, hypersalivation and confusion with the clozapine serum levels of 1097 ng/ml. And the symptoms resolved when

the dose is reduced to 20mg daily with clozapine serum levels of 792 ng/ml.¹⁹ In another case study, initiation of treatment with citalopram in a man who was regularly taking resperidone, resperidone plasma levels were elevated and resulted in idiopathic priapism.²⁰ Similarly, citalopram increased the plasma concentrations of trazodone up to 30% in depressive patients and produced serotonin syndrome.¹¹ These reports suggest the pharmacodynamic changes due to pharmacokinetic interaction with certain drugs.

In contrast, the bioavailability of selegiline was decreased by 30% in presence of citalopram in a study involving 18 healthy subjects.¹² In another study, citalopram delayed the time to maximum alprazolam concentration by 30 minutes perhaps by affecting its absorption.¹⁵ Nevertheless, there was no pharmacodynamic change or therapeutic failure observed in such patients. These drug interactions were considered as clinically insignificant.

The drugs that alter the activity of CYP3A4, CYP2D6 and CYP2C19 enzymes involved in the metabolism of citalopram can thus alter the plasma levels of citalopram. Buspirone and alprazolam have increased the plasma concentrations of citalopram in depressive patients by inhibiting CYP3A4 isoenzyme. In an isolated case, buspirone and citalopram co-administration lead to serotonin syndrome and hyponatraemia.^{35,38} In another study, concomitant administration of citalopram with fluconazole produced serotonin syndrome of life threatening intensity. Because, fluconazole potently inhibits CYP3A4 isoenzymes.⁶⁵

In a patient citalopram 10 mg daily for three years showed the symptoms of serotonin syndrome when started taking tramadol 50 mg daily for pain relief following a surgical operation. Tramadol inhibits CYP2D6 and CYP2C19 enzymes.⁵¹ Similarly, levomepromazine increased the initial steady-state plasma levels of desmethylcitalopram (10 to 20%), the primary metabolite of citalopram, by potently inhibiting CYP2D6 isoenzymes activity. The interaction was not considered as clinically significant.⁵⁶ The serum levels of citalopram was found raised by 44% in eighteen patients who were taking combination of citalopram and tricyclic antidepressants (example imipramine).⁶⁰ Imipramine reportedly inhibits CYP2C19 enzymes to a milder extent.⁶¹ Depressive patients who did not respond to citalopram (40 mg/day) alone responded when fluvoxamine (50 to 100 mg/day) co-administered for

three weeks. The plasma concentration of citalopram was increased by two to three folds due to selective inhibition of CYP3A4 and CYP2C19 enzymes by fluvoxamine.⁴⁴ These reports suggest that the drugs that interact with citalopram by inhibiting CYP450 enzymes from mild to severe extent may produce excessive serotonergic reactions. These reactions may be life-threatening for many patients but, sometimes, beneficial to non-responsive depressive patients. Hence, psychiatrists must be cautious and reduce the doses of index drug, if needed, while prescribing such interacting drug combinations.

In contrast, the dose of citalopram is required to be increased in patients who are also prescribed with CYP450 enzymes inducers such as carbamazepine and rifampicin. Carbamazepine and rifampicin potently induces CYP3A4 isoenzyme involved in the metabolism (*N*-demethylation) of citalopram. Carbamazepine was found to decrease (30%) the plasma levels of citalopram.⁴⁹ Less therapeutic efficacy (increased crying and panic attacks) of citalopram (40 to 60 mg daily) was observed in a 55-year-old depressive man when rifampicin (600 mg twice daily) was co-administered. The depressive condition improved when rifampicin administration was stopped.⁶⁴

Pharmacodynamically, citalopram interacts potentially with many drugs from different therapeutic classes. Conversely, other drugs also interact with citalopram through the same mechanism. Serotonin reuptake inhibiting property of citalopram is responsible for such interactions. Citalopram including other SSRIs increase the risk of bleeding when administered with NSAIDs and oral anticoagulants by inhibiting serotonin levels and thus causing decreased platelet aggregation.^{8,9} Meperidine, fentanyl and other opioids weakly inhibit serotonin reuptake. Serotonin syndrome, visual hallucinations and decrease in the threshold of the myoclonous were observed when the opioids were concurrently administered with citalopram.^{52,53,54,55}

Appetite suppressants like sibutramine, dexfenfluramine and fenfluramine have nonspecific serotonin agonistic activity that enhance the release of serotonin and also inhibit serotonin reuptake. These drugs produce serotonin syndrome when administered with citalopram.^{32,33,34} Patients who did not respond to citalopram alone responded well with lithium carbonate combination.^{45,46} It was related to hyperstimulation of the 5-HT_{1A} and 5-HT_{2A} receptors by lithium in the

brainstem.⁴⁸ Similarly, olanzapine and quitapine with citalopram produced serotonin syndrome as a consequence of increased brainstem and spinal cord 5-HT_{1A} receptor modulation occurring with 5-HT_{2A} receptor antagonism.^{58,59} Fatal serotonergic effects were observed when citalopram was co-administered with monoamine oxidase inhibitor moclobemide and chemotherapeutic agent linezolid due to activation of 5-HT_{1A} receptor.
40,41,42,62,63

These findings indicate that the outcome of pharmacodynamic interactions of citalopram is clinically significant. The consequences of excessive serotonergic effects may even produce death in the affected patients or prolonged hospital stay. Long hospital stay due to adverse interaction consequences may increase economic burden for the affected patients. To avoid such adverse consequences awareness about patient's conditions, adverse interactions including their management is required. In addition, withdrawal of an offending drug may be necessary to resolve exaggerated serotonergic symptoms.

In spite of the adversities which are mentioned above, citalopram was found to be safest of its class. It was found to be safe in the treatment of hypertension as it is a weaker inhibitor of CYP2C19.¹⁵ It was found to be a substitute for the treatment of paroxetine in tricyclic antidepressant toxicity.²⁷ Citalopram did not affect the plasma levels of antipsychotic olanzapine which was found in case of fluoxetine, sertraline and paroxetine.²² Overall intensity of pharmacokinetic interactions of citalopram is minimum and which can be managed clinically. But, the pharmacodynamic interactions which were observed with drugs with serotonergic activity were found sometimes fatal. So, it is necessary that close monitoring of serotonin syndrome symptoms is required when these drugs are co administered and it is better to avoid this combination. Citalopram is producing some interaction on co administered with some drugs the outcome of which is its increased therapeutic efficacy.

CONCLUSION

Citalopram has the potential to interact with many drugs by pharmacokinetic and pharmacodynamic mechanisms. Many drugs similarly interact with citalopram. The nature of these interactions may vary from mild to severe. Close monitoring of these drug interactions consequences is required. This helps to avoid or manage the citalopram implicated interactions in the affected patients and thus reducing the cost associated with these

interactions and reducing the time of hospitalization. The interaction capacity of citalopram was less compared to other SSRIs in concurrent treatment with some antihypertensives, tricyclic antidepressants and antipsychotics. The interaction consequences of citalopram are some time manageable and even some times it gives an outcome which is beneficial. But pharmacodynamic interactions cannot be managed as the consequences of it were very severe which may even cause death. So close monitoring of the symptoms of pharmacodynamic interaction was required and even it will be better if these combinations with pharmacodynamic interactions is avoided.

ACKNOWLEDGMENT

The authors sincerely thank Dr. H.G. Shivakumar, Principal, J.S.S. College of Pharmacy, Mysore, for his support and encouragement. Our gratitude also goes to J.S.S. University, Mysore, for providing all the necessary facilities.

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