Review Article

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Escitalopram Poisoning & Toxicity with Analytic AL Aspects: A Review

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Abstract

Escitalopram is the therapeutically active S-enantiomer of RS-citalopram, a commonly prescribed SSRI. The R-enantiomer is essentially pharmacologically inactive. Escitalopram is used for the treatment for major depressive disorder (MMD) and also an anxiety disorder. It is a selective serotonin reuptake inhibitor (SSRI). The drug enhances the activity of serotonin in the central nerves system. It has high selective inhibitor of serotonin and transporter protein. It process the rapid onset of the antidepressant and it effective and generally well tolerated treatment for MMD disorder. Significant difference can be seen between escitalopram and placebo and changes in the scores after 24 weeks of treatment. In this review paper, the HPTLC, is a simple, rapid, and accurate technique. This method is used to established and validated for simultaneous analysis of the escitalopram oxalate.

Keywords: Escitalopram; Generalized anxiety disorder; Obsessive compulsive disorder; Panic disorder; Pharmacodynamics pharmacokinetics social phobia; Premenstrual dysphonic disorder; Vasomotor symptoms of menopause.

INTRODUCTION

Escitalopram drug is used to treat depression and anxiety disorders. The depression is a mood disorder that causes mood feeling of sadness and loss of interest. It effects how people feel, think, behave and can lead to a variety of emotional and physical problem. Anxiety is your body natural response to stress & it is a feeling of fear. Anxiety symptoms are particularly common in patients with depression disorder and a family drug. The molecular formula for this drug is C_{22} H_{23} FN_2 O_5 and the structure is similar. The chemical formula for escitalopram is $C_2OH_{21}FN_{20}$. The symptoms are: Agitation, Insomnia, Confusion, Rapid heart rate, High blood pressure, Loss of muscle co-ordination.[1]

This drug will help to restore the balance of a certain natural substance for the body and it will effect for the brain. It indicates that escitalopram achieved high continvity in antidepressant drug therapy.Escitalopram is a 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile that has S-configuration at the chiral centre. It is the active nantiomer of citalopram.

It indicates that escitalopram achieved high continuity in antidepressant drug therapy. There is growing trend to develop the drugs that comprise

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a single enantiomer. As opposed to a mixture of enantiomer. The trend has largely been prompted by the need to develop the drugs with improved tolerability profiles. It will be support by the recommendations issued by the Food and Drugs Administrations (FDA) and European medicine agency for the development of chiral drug (FDA in 1992 and committee for the proprietary medical products (CPMP) IN 1993). Depression is a common debilitating. It has fatal disorder, which limits occupational and diminishes well being and the quality of life. It has the lifetime prevalence rate of about 17% & the approximately two thirds of patients with depression are women. And the 70% to 80% of cases it is a chronic recurring condition. According to the neurotransmitter receptor, the factors in the aetiology of depression may be dysfunction of the central serotonin 5 – HT_2 receptor. Variety of drugs have been developed with the aim of regulating serotonin levels in the brain in order to treat the affective disorders.[21,22]

SSRIs are the first drug to developed for the purpose on the molecular targeting & have proved useful in the management of major depressive disorder as well as anxiety disorder. Although the diagnostic and statistical manual of mental disorder (DSM) call it the anxiety distress specifier of major depressive disorder.

The efficancy of escitalopram in the treatment of MDD with the anxiety symptoms that has been established in short term (8-12 weeks) and the long term treatment with escitalopram in these patients is 24 weeks.[4,3,15,16]

Highlights of Escitalopram

The escitalopram oral tablet is available for the both generic and another one is brand name drug (Lexapro), and it is also available in oral solution. It is an interaction when a substance changes way to drug and it is harmful to prevent the drug. Escitalopram is used to treat the depression and generalized anxiety disorder. It may cause the sleepiness and tiredness and it may cause the other side effects. The more common adults' side effects for this drug are the slightly different from the more common side effect in children.[11]

IMPORTANCE

FDA Warning

This drug has a box warming and food is most serious warning to the drug administration (FDA). It alerts the doctors and patients about drug effects that cause dangerous.

Suicide Warning

In this, the escitalopram like any other antidepressants it can increase the risk of suicidal thinking and behavior when it takes to treat the depression and other psychiatric disorders. In this, the more risk will be in children, teenagers or young adults, within few months of treatment or the dose is changed. Family members, caregivers should pay more attention on them because mental changes, mood, thoughts or feelings, behaviors will be changed.[13, 10]

Serotonin Syndrome

It is a serotonin syndrome which may occurs when people take drug. It occurs when dangerously high levels of a natural brain chemical are present and other name called the serotonin very high in dangerous. If people take this drug with the other drug then automatically it increases the levels of serotonin. The serotonin syndrome causes the symptoms like irritability, agitation, seizures, confusion, rigid muscles, tremors, hallucinations.[9,13]

Bleeding

By using the escitalopram can increase the risk in bleeding for taking the aspirin, no steroid anti-inflammatory drugs (NSAIDs) and other anticoagulants. If it is bleeding or any unusual bruising then immediately contact with pharmacist or doctor.[19]

Stopping the drug quickly

If people stop taking this drug in short period of time then our side effects will be withdrawal with the irritability, agitation, feeling restless, changes in sleep habits, nausea, dizziness, anxiety, electric shock, shaking, confusion, high or low mood swings. So while people are stopping the drug first they have to contact with the doctor then doctor will slowly decrease the dose by level to level then they will not get any side effects.[18,19]

Side effects of Escitalopram

In these common side effects of escitalopram happens in more than 1 in 100 people. They are:

- Feeling sick
- Headaches

- A dry mouth
- Sweating a lot
- Being unable to sleep
- Feelings sleepy
- Feeling tired or weak[19]

Electrical Direct Current Therapy Versus Escitalopram for Depression

In the single center, double–blind, no inferiority trial involving the adults with unipolar depression, randomly assigned patients to receive tDCS plus oral placebo, sham tDCS plus escitalopram or sham tDCS plus oral placebo. The tDCS was administrated in 30 min; 2-MA prefrontal stimulations are sessions for the 15 consecutive week days and 7 weekly treatments. The escitalopram was given the dose of 10 mg per day, and for 3 weeks 20 mg per day. In this the primary outcome measure changes in the 17 items Hamilton depression rating scale (HDRS-17) in this the score for the higher depression of the range is (0 to 52). In non-inferiority of tDCS versus escitalopram was defined by a lower boundary to the confidence interval for the difference in the decreased score that was at least 50% difference in the score with the placebo versus escitalopram.

For example: A total of 245 patients underwent randomization, with 91 patients assigned to escitalopram, 94 patients assigned to tDCS and 60 patients assigned to placebo. All these people are suffering from depression, and people recognized that the escitalopram patients had more sleeping disorder.[23]

Electroconvulsive Therapy

There is another treatment for people who struggle with severe treatment and resistant depression. This treatment involves administering electric impulses to create controlled seizures while the patient is under the sedation. From this therapy the maximum numbers of people helps 80% to 90% are receive it and which is significant. Most of them may suffer by continue that. In this the form of treatment has a stigma attached to it and changes in the way were implemented decades ago and have the significantly decreased side effects and improved its effectiveness.[20]

Pharmacological

Escitalopram has a higher selective and dose dependent for the inhibitory effects on the SERT. In this pharmacological of the antidepressant action arises from its inhabitation of the serotonin reuptake into presynaptic nerve ending, which enhances serotonin activity in the central nerves system. The escitalopram revealed the radio ligand binding assays and it shows the high selectivity for the SERT and it compared to the citalopram and several other SSRIs. Escitalopram is the most typical SSRIs and it is the SSRI agents, because it is having the virtually no binding affinity for other transporters. The high affinity binding site is SERT which controls the serotonin reuptake in nerve ending. The low affinity binding site is allosteric site in which induces the structural changes in SERT and later it stabilize and prolong binding of escitalopram to the primary site.[17]

Pharmacokinetic

The half-life of receptor occupancy for escitalopram was calculated to be the approximately 130 hours, and it is much half-life of the plasma concentration that which has the approximately 30 hours. It shows binding occupancy of escitalopram on cerebral SERTs relative to its concentration changes in plasma. An allosteric action was involved in the prolonged occupancy, and the escitalopram was metabolized in the liver and mainly by cytochrome. The escitalopram inhibits liver metabolic enzymes and primarily with the minimal inhibition of the other enzymes. It was higher than its effective blood concentration and in this regard its interactions with other drugs would be the presumably will be the minimal.[17]

Analytical Aspects

Escitalopram is an easy drug to extract from the depression and to detect the range of therapeutic and to detect the overdose levels. It has been measured by variety biological specimens by using some analytical techniques.

HPTLC determination of Escitalopram

Escitalopram is a unique among the SSRIs in that it stabilizes its binding to the high affinity binding site of the serotonin transporter protein via allosteric effects at the low affinity binding site. The chromatographic separation was performed on the modular HPLC. The separation was isocratically with a Lichrosorb C18, 250 mm x 4.6 mm, 5um column eluted with a mixture of methanol, acetonitrile as the mobile phase at flow rate of 1 ml/ min. detection was carried out by absorbance at 270 nm. The analysis was carried out at an ambient temperature and injection volume was 20ul.

Preparation of standard solutions; 10mg of accurately weighted standard escitalopram was dissolved and made up to mark with the mobile phase in a 100ml volumetric flask, to get primary stock solution of 200 ug/ml. The dilutions were made to obtain 5, 10, 25, 50, 75, 100 ug/ml using mobile phase. All solutions were filtered through 0.45 um membrane filter prior to use.

Sample preparation; a commercially available tablet formulation containing escitalopram 10mg was analyzed using this method. The content of 20 tablets as taken and powdered, the powder equivalent to 10 mg of escitalopram was accurately weighted and transferred into a 100ml volumetric flask. 70 ml of mobile phase was added and wait for 10 min with occasional shaking to disperse and dissolve the contents. The volume was made up to 100 ml with the diluted suitably using mobile phase to obtain 50 ug/ml solutions.[24]

Liquid Chromatographic Conditions

Chromatography conditions were obtained using a stainless steel column. In this the C 18 250 mm x 4.6mm 5um. It was maintained at the 40°C, and the analytical wavelength was set at 240mm and the samples are of 20 u1 were rejected to the HPLC. The mobile phase was acetonitrile and the phosphate buffer in the ratio is of 90:10, and the PH value is 4 at a flow of the rate of 1 ml/min. The mobile phase was filtered through 0.22um filter and it is degassed for 10 min by the sonication.[24]

Rp-Hplc Method for Simultaneous Estimation of Escitalopram

In this method, the mobile phase consist of methanol, phosphate buffer PH-5 was pumped at a flow rateof 1 ml/mm. elution was monitored at 254 nm and the injection volume is 20ul. Using the ICH guidelines, doing the validation method. Methanol and phosphate buffer used for mobile phase were filtered through 0.22 um membrane filter and it is degassed by the ultra sonication for 15 min. Then the standard stock solution was prepared by dissolving etizolam and escitalopram oxalate in 100 ml of methanol to get a solution containing 100ug/ mL of etizolam and 1mg/ml of escitalopram oxalate. The working standard solution was prepared by dilution 20ml to get solution containing 20ug/ml of etizolam and 200ug/ml of escitalopram oxalate.

Taking the 20 tablets containing escitalopram oxalate equivalent to escitalopram 5mg and etizolam 0.5 mg were accurately weighted, that means the weight was determined and the tablets were powdered in a glass mortar. An amount of powder equivalent to two tablets was dissolved in 50 mL of methanol and was solicited for 20 min. Then the result mixture was filtered through 0.45u membrane filter and later analyzed it.[25]

CONCLUSION

The escitalopram is most effective drug and tolerated antidepressant for the short term treatment is acute and major depressive disorder in adults. Depression occurs commonly in causing suffering, increased risk of suicide, functional impairment, added health care costs and it losses of productivity. While taking the treatment people should be very careful and not take over dose of drugs and suddenly not stop drugs because it create more side effects and it goes to depression. The quantitative determination of ESCin pharmaceutical formulation is efficient and sensitive. The HPLC method was found to be simple, rapid, accurate and sensitive. Mental health refers to a person's psychological, emotional, social wellbeing, by this they will influences by they feel and they think and behave. Escitalopram is contraindicated in combination with irreversible monoamine oxidase inhibitors (MAOIs) and a period of at least 2 weeks should be allowed between discontinuation of escitalopram and commencement of an irreversible MAOI and vice versa.

CASE REPORT

A 22-year-old gravidity 1 and parity 1 (G1P1) Caucasian mother gave birth to a 3030-g male newborn via spontaneous vaginal delivery at 40 weeks gestational age at a distant hospital. Nuchal chord and considerable amounts of amniotic fluid tinged with meconium made delivery difficult. At 1 and 5 minutes, the APGAR scores were 8 and 9, respectively. The maternal screening was negative for rubella, chlamydia, syphilis, hepatitis B antigen, gonorrhea, the human immunodeficiency virus, and group B streptococci. Herpes simplex virus status was unclear. Mother had a major history of depressive disorder in the past, and she had escitalopram 20 mg treatment throughout her pregnancy.

There were no additional drugs used during pregnancy. The mother denied using drugs, including nicotine, alcohol, and illegal substances.

Despite initial APGAR results, the newborn showed signs of probable seizures including a faint cry, non-responsive pupils, bradycardia, hypertonia, lethargy, and suspected convulsions. The infant was brought to our facility for additional examination and management after undergoing an initial septic workup evaluation. The infant, who had hypertonia, irritability, high pitched wailing, and posturing, arrived at our facility at around nine hours of age.

A chest radiologic scan was performed due to shallow breathing and potential meconium aspiration, and the results showed streaky perihilar densities consistent with residual lung fluid. Empiric drugs like gentamicin and ampicillin were kept on hand to handle sepsis and meningitis. Creatine kinase (CK) was isolatedly elevated at 735 international units/L during tests to rule out ischemic damage. Other relevant laboratory results, such as serum creatinine of 0.8 mg/dL, aspartate transaminase of 77 units/L, alanine transaminase of 20 units/L, and lactic acid of 1.9 mmol/L, were assessed and found to be within normal ranges.

To exclude any possibility of an ischemic brain injury or cerebral edema, head ultrasonography was conducted. There was no sign of hydrocephalus, edema, or germinal matrix bleeding. The baby was given 20 mg/kg of phenobarbital (PB) for suspected seizures at 20 hours of age after developing a loud, high pitched cry and significant hypertonicity. At around 22 hours of life, a head computed tomography showed a small extra-axial area of hyperdensity in the left posterior fossa next to the skull. This area was most likely a small subdural hematoma next to the left transverse venous sinus.

There were no interictal anomalies found in the normal electroencephalogram tracings. A maintenance regimen of PB was started at 4 mg/kg/day on day three of life (DOL). When the patient began having recurrent seizures later that evening, levetiracetam (10 mg/kg) was given to the child in a large dose, and a maintenance regimen (10 mg/kg/day) was initiated. On DOL 3, blood and cerebrospinal fluid cultures were still negative, thus antibiotics were stopped. Clinical seizure activity stopped on DOL 4, which was the final day. A blood sample was sent to an outside lab for parent drug citalopram and desmethylcitalopram testing at the time that escitalopram toxicity was suspected, around DOL 5.

The infant showed sporadic bradycardia, according to information from a distant institution. The bouts did not seem to coincide with the timing of suspected seizure activity, despite the patient's bradycardia. Additionally, the patient had persistent tachycardia the entire time they were in the hospital. The patient's echocardiography showed a patent foramen ovale with a left to right shunt, which was a normal finding. At 40 hours of life, an electrocardiogram (ECG) was done, and it showed a prolonged QTc interval of 531 milliseconds (normal range: 450 milliseconds). Continuous ECG recordings showed no signs of atrioventricular block and a normal sinus rhythm with normal heart rate variability.

Intermittent episodes of bradycardia persisted, and a QTc prolongation was seen through DOL 7. On DOL 11, an ECG was normal, and no additional bradycardia events were noticed. The patient also displayed lethargy and a feeble scream in addition to the intermittent seizure activity/hypertonia and bradycardia that were seen. This turned into an ear-piercing wail and uncontrollable crying. Irritability symptoms persisted until DOL 7, at which point PB was stopped. The baby was sent home with levetiracetam (10 mg/kg/day) on DOL 12 and was also referred to a pediatric neurologist. Citalopram and desmethylcitalopram concentrations upon discharge were both less than 10 ng/mL (normal range, 30-200 ng/mL).

This case study reports an infant that was exposed to 20 mg of escitalopram while still in the womb. The patient had QTc prolongation, lethargy, tachycardia, hypertonicity, and then hypotonicity, all of which were signs of probable poisoning. It is advised to keep a close eye out for NBS and QTc prolongation symptoms for around 5 days after in-utero exposure to citalopram or escitalopram. Consisting of cardiac, autonomic, neuromuscular, and autonomic neuromuscular findings (i.e., muscle tone, tremors), as well as changes in mental status, monitoring parameters for newborns exposed to escitalopram in utero should include conduction disturbances, dysrhythmia, and ECG alterations. Escitalopram is regarded to be a safer alternative to citalopram, although it should still be suspected that there may be a chance of CNS and cardiac damage in the newborn after in-utero exposure.[26]

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