Aripiprazole Lauroxil

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Aripiprazole lauroxil is a prodrug of aripiprazole and is administered as an intramuscular injection. Once administered, aripiprazole lauroxil is first converted to N-hydroxymethyl aripiprazole by enzyme-mediated hydrolysis and is hydrolyzed again to aripiprazole. Aripiprazole was originally reported to be a partial agonist at D2and 5HT1Areceptors, with a combination of antagonistic activity at 5HT2Areceptors.

Keywords: schizophrenia ; schizophrenia treatment ; aripiprazole lauroxil ; long-acting injections ; aristada

1. Introduction

1.1. Dosing Information

Aripiprazole lauroxil is an FDA-approved atypical antipsychotic indicated for the treatment of schizophrenia. Aripiprazole lauroxil can only be administered by intramuscular (IM) injection (deltoid 441 mg only or gluteal region 441 mg, 662 mg, 882 mg, 1064 mg) from a licensed healthcare professional. This method nullifies the need for daily oral administration and will help improve adherence to treatment in patients who are nonadherent with taking daily medications [1]. If a patient has never taken aripiprazole, oral tolerability must be established before aripiprazole lauroxil can be administered [2]. The half-life of oral aripiprazole is approximately 75 h, and it may take 2 weeks for some patients to reach tolerability status [3]. Oral dosage reflects how much injection dosage is given. If the patient were taking 10 mg per day, then they would receive a 441 mg injection every month. If the patient were taking 15 mg per day, then they would receive 662 mg every month, 882 mg every 6 weeks or 1064 mg every 2 months. If the patient were receiving 20 mg or higher, then they would receive a 882 mg injection every month. Oral aripiprazole should be administered for 21 consecutive days after the first aripiprazole lauroxil injection. The patient should be counseled on adverse reactions and side effects of the medication and counseled to go to the emergency room. Aripiprazole lauroxil can be given as a monthly dose of 441 mg, 662 mg, or 882 mg based on the needs of the patient. These doses are equal to 300 mg, 450 mg, and 600 mg of aripiprazole, respectively. All doses should be administered in the gluteal muscle except for the 441 mg dose, which can be given in the deltoid muscle dependent on patient preference [2][4].

1.2. Contraindications and Adverse Effects

Aripiprazole lauroxil is contraindicated in patients with a known hypersensitivity reaction to aripiprazole and is not approved for the treatment of elderly patients with dementia-related psychosis (boxed warning). Aripiprazole lauroxil is also associated with other adverse effects, including cerebrovascular accidents, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, dyslipidemia, orthostatic hypotension, leukopenia/neutropenia, seizures, cognitive and/or motor impairment, hyperthermia, and dysphagia [2]. Patients with a history of leukopenia or neutropenia should be monitored for the first few months of therapy and receive regular complete blood counts to ensure a normal white blood cell level. There is not sufficient data to determine the risks of birth defects or miscarriage in pregnant women using aripiprazole lauroxil, but withdrawal symptoms and extrapyramidal side effects have been observed in infants exposed to antipsychotics during the third trimester [5].

1.3. Mechanism of Action

Aripiprazole lauroxil is a prodrug of aripiprazole and is administered as an intramuscular injection. Once administered, aripiprazole lauroxil is first converted to N-hydroxymethyl aripiprazole by enzyme-mediated hydrolysis and is hydrolyzed again to aripiprazole [6][7]. Aripiprazole was originally reported to be a partial agonist at D_2 and $5HT_{1A}$ receptors, with a combination of antagonistic activity at $5HT_{2A}$ receptors [2][7]. At present, it has been demonstrated that aripiprazole can act as an antagonist, partial agonist, or full agonist at D_2 receptors [7]. Antagonistic activity at $alpha_1$ receptors explains some of the adverse reactions that have been reported, such as orthostatic hypotension [8]. Contrary to other second-generation antipsychotics, aripiprazole displays a higher affinity for the dopamine receptor than the serotonin receptor. When the

extracellular concentration of dopamine is high, such as in the mesolimbic circuit, aripiprazole can compete with dopamine as a partial antagonist. If the extracellular dopamine concentration is low, namely in dopamine circuits involved in cognition and working memory, aripiprazole can bind and partially activate other dopamine receptors. This unique mechanism of action gives aripiprazole the name “dopamine stabilizer” as it should ideally maintain dopamine levels in the tuberoinfundibular and nigrostriatal pathways to avoid hyperprolactinemia and extrapyramidal side effects [9][10]. Aripiprazole is also a partial agonist for D_2 receptor-mediated recruitment of the β-arrestin-2 signaling pathway. This pathway appears to be critical in minimizing extrapyramidal side effects while maintaining antipsychotic efficacy [7]. Targeting the β-arrestin signaling pathways is promising in the design of future antipsychotic drugs [9].

2. Pharmacokinetics and Pharmacodynamics

2.1. Absorption and Distribution

After injection of aripiprazole lauroxil, aripiprazole is released into the systemic circulation after 5–6 days, and maximum concentration is reached approximately 41 days after administration. To bridge the gap created by slow absorption into the systemic circulation, patients should take oral aripiprazole for 21 days following the first injection [11]. An alternative regimen consisting of a nano-crystalline milled version of aripiprazole lauroxil and a 30 mg single dose of oral aripiprazole achieved the desired therapeutic dose in the same time frame as a 441 or 882 mg injection plus the 21-day oral initiation regimen [4]. Following absorption, aripiprazole displays broad extravascular distribution and has a volume of distribution of 268 L [8].

2.2. Metabolism

Once injected, aripiprazole lauroxil dissolves slowly and is cleaved by esterases into N-hydroxymethyl aripiprazole and lauric acid, which is a fatty acid found in human breast and cow’s milk. Through water-mediated hydrolysis, N-hydroxymethyl aripiprazole becomes aripiprazole and formaldehyde. The amount of formaldehyde formed by the metabolism of aripiprazole lauroxil is a minute amount compared with the amount produced by basic metabolism and a regular diet [11]. Aripiprazole lauroxil undergoes metabolism in the liver by CYP3A4 and CYP2D6 to dehydro-aripiprazole [11][8]. Pharmacokinetic differences may be present in individuals who are poor metabolizers of CYP2D6, and healthcare providers may need to adjust the dose based on patient response to treatment [5].

2.3. Elimination

The mean elimination half-life of aripiprazole lauroxil after administration of the final dose of 441 mg, 882 mg, and 1064 mg ranges from 53.9 to 57.2 days. Similar to the other long-acting injectables available, aripiprazole lauroxil has an extended pharmacokinetic profile due to an elimination rate that is faster than the absorption rate [12]. Thus, the calculated half-life for the injection of aripiprazole lauroxil is greater than the half-life of oral aripiprazole, which has a mean of 75 h [2]. After aripiprazole lauroxil is converted into its active metabolite, there is no measurable amount of prodrug present, making it unlikely that the rate of conversion or distribution of aripiprazole lauroxil is the cause of the slow elimination rate [12].

3. Conclusions

Schizophrenia consists of positive symptoms, negative symptoms, and cognitive dysfunction. Several theories regarding pathogenesis have been proposed, including the neurodevelopmental theory and dopaminergic imbalance. There are several risk factors that contribute to the development of schizophrenia, including genetic factors, history of cannabis use, and childhood trauma. The pharmacological treatment of schizophrenia is largely based on mitigating dopaminergic imbalance.

First-generation antipsychotics work by non-selectively blocking D_2 receptors in the CNS. While effective at mitigating positive symptoms, FGAs lead to unwanted extrapyramidal symptoms and elevated prolactin levels due to non-selectivity. FGAs have not been shown to reduce negative symptoms or improve cognitive impairment. Second generation antipsychotics also work by blocking dopaminergic receptors. SGAs have been shown to produce less extrapyramidal symptoms and can treat both positive and negative symptoms; however, SGAs show no improvement in cognitive dysfunction. Third generation antipsychotics, including aripiprazole, can be characterized as D_2 partial agonists or D_2-biased ligands.

Aripiprazole can act as an antagonist in areas with high dopamine levels and an agonist in areas with low dopamine levels, thus giving it the name “dopamine stabilizer.” The use of aripiprazole has also been shown to minimize

extrapyramidal symptoms when compared with first- and second-generation antipsychotics. Aripiprazole lauroxil is a prodrug of aripiprazole and is given as an IM injection, which helps improve treatment rates in patients who are not compliant in taking once-daily oral medication. AL is metabolized by CYP3A4 and CYP2D6 in the liver. The use of AL is contraindicated in patients with known aripiprazole hypersensitivity and in dementia-related psychosis. Side effects are known to include weight gain, akathisia, neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension due to $alpha_1$ blockade, leukopenia, and neutropenia. The use of AL has shown significant statistical and clinical efficacy in treating the symptoms of schizophrenia.

References

1. Fellner, C. Pharmaceutical Approval Update. Pharm. Ther. 2015, 40, 807–808.
2. Federal Drug Administration. Aristada Drug Insert. 1998; 50, pp. 1–25.
3. Federal Drug Administration. Abilify Drug Insert Interactions. 2002; 50, pp. 1–25.
4. Hard, M.L.; Wehr, A.Y.; Sadler, B.M.; Mills, R.J.; von Moltke, L. Population Pharmacokinetic Analysis and Model-Based Simulations of Aripiprazole for a 1-Day Initiation Regimen for the Long-Acting Antipsychotic Aripiprazole Lauroxil. Eur. J. Drug Metab. Pharmacokinet. 2018, 43, 61–69.
5. Raedler, L.A. Aripiprazole Lauroxil (Aristada): Long-Acting Atypical Antipsychotic Injection Approved for the Treatment of Patients with Schizophrenia. Am. Health Drug Benefits 2016, 9, 40–43.
6. Rohde, M.; MØrk, N.; Håkansson, A.E.; Jensen, K.G.; Pedersen, H.; Dige, T.; Erling, B.J.; Holm, R. Biological conversion ofaripiprazole lauroxil—An N-acyloxymethyl aripiprazole prodrug. Results Pharma Sci. 2014, 4, 19–25.
7. Allen, J.A.; Yost, J.M.; Setola, V.; Chen, X.; Sassano, M.F.; Chen, M.; Peterson, S.; Yadav, P.N.; Huang, X.-P.; Feng, B.; et al. Discovery of β-arrestin-biased dopamine D 2 ligands for probing signal transduction pathways essential for antipsychotic efficacy. Proc. Natl. Acad. Sci. USA 2011, 108, 18488–18493.
8. Cruz, M.P. Aripiprazole lauroxil (Aristada): An extended-release, long-acting injection for the treatment of schizophrenia. Pharm. Ther. 2016, 41, 556.
9. Stępnicki, P.; Kondej, M.; Kaczor, A.A. Current concepts and treatments of schizophrenia. Molecules 2018, 23, 2087.
10. Miyamoto, S.; Duncan, G.E.; Marx, C.E.; Lieberman, J.A. Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol. Psychiatry 2005, 10, 79–104.
11. Hard, M.L.; Mills, R.J.; Sadler, B.M.; Turncliff, R.Z.; Citrome, L. Aripiprazole lauroxil: Pharmacokinetic profile of this long-acting injectable antipsychotic in persons with schizophrenia. J. Clin. Psychopharmacol. 2017, 37, 289–295. Available online: (accessed on 1 June 2021).
12. Hard, M.L.; Mills, R.J.; Sadler, B.M.; Wehr, A.Y.; Weiden, P.J.; von Moltke, L. Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase I Study and a Population Pharmacokinetic Model. CNS Drugs 2017, 31, 617–624.