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Abilify® (aripiprazole)

Identifying Features:

The trade name for this third-generation antipsychotic is Abilify®, and its generic name is aripiprazole. The Food and Drug Administration approved Abilify® on November 15, 2002. It was originally approved for the treatment of Schizophrenia and is now also used for the treatment of Bipolar Disorder, specifically Acute Mania[1, 2]. There have been studies of an off-label use in children for Bipolar Disorder[3] and Asperger Disorder. Aripiprazole is available in tablet and as an oral solution. Tablets are available in 5, 10, 15, 20 and 30mg from Otsuka Pharmaceutical Co (Japan) or Bristol-Myers Squibb Company (USA). A 1mg/ml (150ml bottle) Oral Solution is available from Bristol-Myers Squibb Company. Aripiprazole is available in the United States, Australia, the United Kingdom and Switzerland[2].

Pharmacologic Actions:

Aripiprazole is a mixed D_2 agonist-antagonist. When there is a high concentration of endogenous dopamine, aripiprazole acts as an antagonist on the D_2 receptors. However when there is a low concentration of endogenous dopamine it has agonist activity. Aripiprazole also acts as a partial agonist on the 5-HT_{1A} receptor and as an antagonist on the 5-HT_{2A} receptor[1, 2]. The mechanism of action is unknown but it is thought that the action at these receptors gives it efficacy in Schizophrenia. Its activity is primarily through the parent drug but there is some activity seen with the major metabolite

dehydro-aripiprazole. Aripiprazole also has affinity for alpha$_1$ receptors and histamine receptors[2].

Therapeutic Dosing:

The usual adult dosage for Schizophrenia is 10 to 15 mg/day. It has been shown effective at doses of 10 to 30 mg/day but these higher doses seem have no greater efficacy than the lower doses. The dose should only be increased every two weeks. For Bipolar Disorder the usual adult dose is 30mg once daily[2]. The safety and efficacy has not been studied in children and adolescent patients, but in off-label use, patients 5 to 17 years of age were given doses that ranged from 5mg to 20mg[3]. There have been no studies to suggest an adjustment is needed in the elderly[2].

Pharmacokinetics:

Aripiprazole is well absorbed both in the tablet form and the oral solution, with a bioavailability of 87% and a peak is seen in 3 to 5 hours. The volume of distribution is 4.9 L/kg and aripiprazole and its metabolite are more than 99% protein bound. Metabolism includes three different pathways: dehydrogenation, hydroxylation and N-dealkylation. This occurs using the CYP3A4 and CYP2D6 enzymes. Known inhibitors and inducers of these enzymes warrant a dosage change accordingly. Aripiprazole is eliminated through hepatic metabolism and the half-lives of the parent drug and its active metabolite are 75 hours and 94 hours respectively. A steady state concentration is seen in 14 days[1, 2].

Adverse Effects:

Nausea and vomiting may be seen with initial therapy, but if given with a meal or snack side effects seem to be reduced. These effects seem to taper off after a week of treatment[1]. Other common (>10%) adverse effects include headache, dyspepsia, constipation, anxiety, agitation, insomnia, somnolence, akathisia and lightheadedness. Less common (<10%) adverse events include asthenia, accidental injury, peripheral edema, hypertension, myalgia, extrapyramidal syndrome, tremor, increased salivation, pharyngitis, rhinitis, coughing, weight loss and blurred vision. The long-term trial effects of the drug are similar to the short-term trial effects except for a higher incidence of tremor. Warnings for aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia and cerebrovascular events including stroke. There have been rare occurrences of hypersensitivity reactions such as anaphylactic reaction, angioedema, laryngospasm, pruritis or urticaria, therefore contraindications include those patients with a known hypersensitivity to Abilify®[2].

Fetal Effects:

Aripiprazole has a pregnancy category of C. In animal studies aripiprazole produced developmental toxicity that included possible teratogenic effects in rabbits and rats but there are no controlled studies in pregnant women and no data on whether it crosses the placenta. There is no third trimester study data. Therefore aripiprazole should only be used during pregnancy if the benefits outweigh the potential risk to the fetus. Aripiprazole was excreted in the milk of rats during lactation, but it is not known if it is excreted in human milk. It is recommended that women who are on aripiprazole not breast-feed[2].

Toxicity:

There are four case reports, and two case series found in the literature. Of these, one of the case series was not available from the library. Three of the four case reports were of children 3 years old or less and the other was of a 27 year old woman. The case series involved two children 6 years old or less and three teenagers, two who were 15 and one who was 16.

Toxic and lethal doses are not defined for aripiprazole.

Aripiprazole has affinity for $alpha_1$ receptors; this could explain some of the hypotension seen in patients with acute overdose. With its partial agonist effects in the nigrostriatal regions of the brain the incidence of extrapyramidal side effects should be reduced but in an overdose this may not be true. Nausea and vomiting is common with poisonings and is caused by gastrointestinal irritation. Affinity for dopamine receptors could produce increased heart rate and affinity for the 5-HT and dopamine receptors may be related to its CNS effects.

In the first case report by Carstairs, a 27 year old female ingested 330mg and showed signs of drowsiness. Aripiprazole levels (obtained by the manufacture) three hours post ingestion were 716ng/mL. She was observed and monitored for eight hours and had no other side effects[4].

The second case from Schonberger was of a 3 year old male (15.5kg) who ingested an estimated 11.9mg. He became lethargic with a flat affect, tremor, ataxic and had a Parkinsonian gait. Estimated peak serum levels (obtained from manufacture) were 136µg/mL. His symptoms resolved in 7 days with just observation[5].

Seifert wrote about a case of a 2.5 year old female that ingested 195mg. Her levels (obtained from the manufacture) 10 hours after ingestion were 1873ng/ml. She had a spontaneous emesis, became lethargic in less than one hour and was given 10g of activated charcoal three hours after ingestion. She then lost consciousness but did not require airway support. Upon wakening on the second day she had ataxia but symptoms resolved in 7 days[6].

The last case report included two 2 year old females that ingested 90mg and presented 3 hours post ingestion, neither was given activated charcoal. One of them vomited several times and became hypotensive one hour after ingestion. The other became irritable and both showed somnolence and had tachycardia. Each was given IV fluids and the vomiting, tachycardia and hypotension resolved with in 6 to 8 hours. Their mental status returned to normal in about 24 hours[7].

In the case series by Lofton five patients were exposed to aripiprazole. Three were teenagers, a 15 year old female, a 15 year old male and a 16 year old female. They ingested 120mg, 300mg and an unknown amount respectively. The second was given activated charcoal and each were observed from 4 to 7 hours and remained asymptomatic. The other two patients were a 2 year old female and a 6 year old male. The 2 year old ingested 40mg and vomited several times over a 14 hour period. She also

had significant lethargy that lasted about 30 hours. The 6 year old ingested 20mg and became lethargic and had drooling and flaccid facial muscles. He was given diphenhydramine 25mg and his symptoms improved[7].

There does not seem to be a correlation between drug concentration and adverse effects. Serum drug concentrations are not readily available to all institutions and can only be determined by the manufacture.

Treatment:

Treatment seems to be mainly supportive. Airway support does not seem to be needed for patients who lose consciousness. IV fluids can be given to those who present with hypotension. Diphenhydramine may also be beneficial depending on the patient. Most patients just need to be observed and effects of aripiprazole seem to resolve within 6 to 8 hours. The longest symptoms were observed were for 7 days, and there was complete resolution. Activated charcoal can be used to decrease absorption. There are no known antidotes for this medication.

References

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