MediKredit® INTEGRATED HEALTHCARE SOLUTIONS (PTY) LTD

Medifile drug information bulletin

Jan/Feb 2006; 20(1)

◆ ABSTRACT

The first edition of Medifile for 2006 provides information on two new drug classes, Atomoxetine and Ezetimibe. Strattera® (Atomoxetine) is the first non-stimulant drug registered for the management of Attention Deficit Hyperactivity Disorder (ADHD). Ezetrol® (Ezetimibe) is an anti-hyperlipidaemic and selective cholesterol absorption inhibitor. The selective cholesterol absorption inhibitors are the first new class of cholesterol lowering drugs in 15 years. Both products were launched in South Africa in 2005.

◆ NEW TREATMENT AVAILABLE FOR ADHD: ATOMOXETINE

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) occurs in 3-10% of children.[1] It may persist into adolescence in about 85% of patients and into adulthood in as many as 31% of patients.[1] Boys have approximately a 9 times greater chance of having ADHD than girls.[1] Stimulants such as methylphenidate, amphetamine, and dextroamphetamine are the most common drugs used to treat ADHD. These are controlled substances in the USA and schedule 6 substances in South Africa due to their addictive properties and potential for abuse. Although these drugs are efficacious and relatively safe, 30% of patients fail to respond to them and some develop intolerable adverse effects. In addition, many parents have reservations about giving controlled substances to their children.[1,2] As a result considerable interest in other drug classes has emerged.[1,2]

Atomoxetine (Strattera®) which was registered with the MCC in June 2005 as a schedule 5 drug, is manufactured by Eli Lilly. It is the first and only non-stimulant registered for ADHD. It is approved for the use in children over the age of 6, adolescents and adults. Atomoxetine was originally called Tomoxetine but was changed to atomoxetine to avoid potential confusion and dispensing errors with Tamoxifen.[2,3,4]

PATHOPHYSIOLOGY

The pathophysiology of ADHD is thought to involve several neurotransmitters including norepinephrine, epinephrine and dopamine. Low levels of norepinephrine in the right dorsal and orbital sections of the prefrontal cortex have been linked to various symptoms of ADHD including increased motor activity, lack of self-control and decreased concentration.[1]

Atomoxetine is effective in treating ADHD as it is a *selective inhibitor of the presynaptic norepinephrine* transporter and increases norepinephrine concentrations.[1,2,3] Atomoxetine has a minimal affinity for other neurotransmitter transporters and receptors or other noradrenergic receptors.[2,3]

EFFICACY OF ATOMOXETINE IN TREATING ADHD

Atomoxetine compared to placebo

Several trials have been conducted in children and adults that indicate that atomoxetine is more effective than placebo in ADHD.

Spencer et al reported on 2 double-blind placebo-controlled trials both of which indicated a significant improvement in the ADHD-rating scale (RS) score.[1]

Michelson et al conducted an 8-week multicenter, placebo-controlled, dose-response, randomized study on 297 children and adolescents with ADHD.[2] Atomoxetine or placebo was administered twice daily in the following regimens:

- Placebo – 83 patients
- Atomoxetine 0.5mg/kg/day – 44 patients
- Atomoxetine titrated up to 1.2mg/kg/day – 84 patients
- Atomoxetine titrated up to 1.8mg/kg/day – 83 patients

At the higher doses of 1.2mg/kg/day and 1.8mg/kg/day, atomoxetine was superior to placebo on almost all measures, including the ADHD RS and CPRS-R (Conners' Parent Rating Scale-Revised). All doses of atomoxetine were well tolerated. There was no difference in efficacy of the two higher doses, which suggests that the lower dose of 1.2mg/kg/day is preferable.

Study limitations:

- It was not possible to establish the time to onset of the initial response, because at the two higher doses, the target dose was only reached by the third and fourth week of the study.
- A comparison of the degree of symptom reduction associated with atomoxetine with that of stimulants was not possible because no active comparator was included in the study.
- The data provides evidence of acute efficacy, but does not address the value of long-term therapy once patients have achieved a satisfactory initial response.
- A teacher's assessment was not part of the study and no direct conclusions about effects on behavior in the classroom can be drawn from this study.
- The participants of the study had very few co-morbid psychiatric conditions other than oppositional defiant disorder, which was not distributed evenly between the treatment groups.

In a subsequent study on children (n=171) Michelson reported that over a 6-week period once daily dosing of atomoxetine at a mean dose of 1.3mg/kg/day produced significantly greater response to therapy compared with placebo.[1,3] He also reported a significant improvement in the inattention and hyperactivity/-impulsivity subscores in 2 double-blind, placebo-controlled trials of 400 adults.[1]

Atomoxetine compared to Methylphenidate

Several trials have been conducted in which atomoxetine is compared with methylphenidate. The majority of these studies have been sponsored by Eli Lilly.[5]

◆ Atomoxetine compared to immediate-release Methylphenidate

A randomized, open-label study was conducted on 228 patients for a 10 week period to determine the comparable efficacy of atomoxetine and methylphenidate. (Atomoxetine: 184 patients; Methylphenidate: 44 patients). Boys aged 7-15 and girls aged 7-9, who met the DSM IV diagnostic entry criteria for ADHD and a severity score of at least 1.5 standard deviations above norms for age and gender on the ADHD RS, were included in the study. Atomoxetine was given in the morning and late afternoon and did not exceed 2mg/kg per day. Methylphenidate was given once to three times per day and the total daily dose did not exceed 60mg.

Both atomoxetine and methylphenidate had similar reduction of hyperactive-impulsive and inattentive symptom domains as measured by the Hyperactivity/Impulsivity and Inattention subscales of the ADHD RS.

These two drugs were well tolerated and there was no statistically significant difference in discontinuation of therapy due to adverse effects. Somnolence and vomiting were more frequently reported among patients taking atomoxetine. Abnormal thinking occurred more often with methylphenidate. Although insomnia was more frequently reported among patients randomized to methylphenidate in two previous double blind studies, no statistical significance was reached in this study.

The interpretation of this study is limited due to the following facts:

- It was an open label study – outcome could have been influenced by patient or investigator's expectations.
- Fewer patients were assigned to methylphenidate.
- As the study utilized a gradual dose titration design, it was not possible to assess the onset of treatment effects.
- A relatively large amount of patients in both groups withdrew from the study for no accountable reason.
- The two treatment groups were not well matched for gender.

♦ Atomoxetine compared to sustained release Methylphenidate[5]

Comparative efficacy between atomoxetine and controlled/sustained release methylphenidate was evaluated in a Lilly-sponsored double-blind, randomized, parallel-group study. Atomoxetine was compared to Concerta® and placebo in 516 patients aged 6-16 over a 6 week period. Both drugs showed statistically significant superiority over placebo (P=0.003 and P<001 respectively for atomoxetine and Concerta® vs. placebo) in reducing the symptoms of ADHD on the ADHD RS. In the total study population, Concerta® resulted in a statistically significantly greater reduction in ADHD symptoms from baseline compared with atomoxetine (P=0.016).

Study Limitation:

- Eli Lilly has reported that as atomoxetine was not an FDA-approved medication at the time of the study, it was not feasible to exclude patients who could not tolerate atomoxetine or responded poorly to it. However, patients were excluded if they were unable to tolerate stimulants or had previously responded poorly to them and this may have affected the study outcome in favor of Concerta®.[5]

The FOCUS trial, a 3-week open-label trial conducted on 1323 children sponsored by McNeil Pharmaceuticals, also compared the efficacy and tolerability of atomoxetine and Concerta®. As with the Lilly study, both drugs produced statistically significant improvement in ADHD symptoms. There was a statistically significantly greater reduction in ADHD symptoms from baseline with Concerta® compared to atomoxetine.[5]

Study Limitations:

- Patients with poor previous response to ADHD treatment were excluded, which may favour Concerta®.
- The study duration was only 3 weeks with maximum doses only achieved in week 2.

Definitive assessments of comparability between atomoxetine and methylphenidate await larger, double-blinded studies.

SAFETY DATA ON ATOMOXETINE

Study to determine the difference in sleeping patterns between Atomoxetine and Methylphenidate[6,7]

A randomized, double-blind, crossover trial of 85 patients was conducted to determine sleep difficulties related to immediate-release methylphenidate therapy and atomoxetine. Patients aged 6-14 years were treated with each medication for 7 weeks. A twice daily dose of atomoxetine, titrated up to the lesser of 1.8mg/kg/day or 120mg/day, and a three times daily dose of methylphenidate with maximum titration to 1.8mg/kg/day or 60mg/day, whichever was less, were administrated to the patients. Atomoxetine was significantly better (p<001) than methylphenidate in the change from baseline to endpoint in *time to onset of sleep* as measured by actigraphy. The increase in sleep onset was 3.36 minutes versus 30.14 minutes for atomoxetine and methylphenidate respectively.

Other safety issues

- A secondary endpoint of the above study was the safety/tolerability of treatment.[7] **Table 1** shows reported differences in adverse events in atomoxetine versus methylphenidate.

- Recent analyses of clinical trial data from 11 trials conducted in children and adolescents showed that ***suicidal ideation*** *was more often observed in patients treated with atomoxetine* (0.37%) compared to those taking placebo (0%) in the age group 7-12 years. There was one suicide attempt in the atomoxetine group but no completed suicides.[8,9]

Based on this, Health Canada has requested that the manufacturer incorporates a warning in the product monograph of Strattera® stating that atomoxetine has the potential for behavioural and emotional changes, including risk of self harm.[8]

In September 2005 the FDA issued a Public Health Advisory advising healthcare providers and caregivers that children and adolescents treated with atomoxetine should be closely monitored. Any signs or symptoms of clinical worsening, irritability, agitation, suicidal ideation or behaviours, or any changes in behaviour (particularly during the initial few months of treatment or when the dose is changed) should be closely observed.[9]

The current South African package insert states that Strattera® may increase the risk of mood swings including emotional lability and hostility, and that the drug lacks effectiveness as a treatment modality in depression.[10] The updating of the package insert has been referred to both the Medicine Control Council and the National Adverse Event Monitoring Centre. Eli Lilly is awaiting feedback and has indicated that they will include the warning in the package insert as soon as possible.[7]

- In December 2004 the FDA posted a new warning of potential of **severe liver injury** due to Strattera®. The warning was as a result of two cases of severe liver injury in patients (one teenager and one adult) treated with atomoxetine for several months. Both these patients however recovered on discontinuation of the drug.[11]

Table 1: Reported differences in adverse events experienced with Atomoxetine and Methylphenidate[7]

Adverse effect	Outcome	Statistical significance
Insomnia	More frequent with methylphenidate	P<0.001 (Highly significant)
Anorexia*	More frequent with methylphenidate	P=0.03 (Significant)
Somnolence	More frequent with atomoxetine	P=0.057 (Trend)
Increase in diastolic blood pressure	Greater with atomoxetine	P<0.001 (Highly significant)
Increase in pulse	Greater with atomoxetine	P=0.056 (Trend)

* Both treatments resulted in a slight decrease in weight, but the changes were similar

Strattera® product labelling has been updated to state that patients with jaundice or laboratory evidence of liver injury should discontinue atomoxetine and should not restart it. If symptoms of liver dysfunction present, (nausea and vomiting, dark urine, jaundice, pruritis or unexplained "flu-like" symptoms) a laboratory test should be done to determine liver enzyme levels. Routine monitoring of hepatic function is however not indicated due to the idiosyncratic nature of the hepatic injury.[10]

BENEFITS OF ATOMOXETINE

- Atomoxetine is a non-stimulant Schedule 5 drug. Methylphenidate is a stimulant Schedule 6 drug. As such, a new prescription is required each time methylphenidate is dispensed. Prescriptions for Strattera®, on the other hand, may be repeated for 6 months.[10,12]
- Atomoxetine is not associated with stimulant or euphoric properties, limiting its potential for substance abuse.[1,13]
- It provides the doctor with a choice of an alternative where other therapy failed or treatment was discontinued due to side effects or allergy.[1]
- Patients treated with atomoxetine have a quicker onset of sleep than patients using methylphenidate.[6,7]
- Atomoxetine is not contraindicated in patients with co-exiting motor activity abnormalities (such as tics) and anxiety.[13]
- Atomoxetine may be taken once daily.

DISADVANTAGES OF ATOMOXETINE

- When compared with other ADHD treatment drugs, Strattera® is more expensive.
- Changes in blood pressure are a concern and require further investigation.[7]
- Information on the risk of serious adverse effects, particularly in the case of overdose, is lacking.[1]
- Potential adverse effects include severe hepatic injury and suicidal ideation.[8,9,11]

CONCLUSION

A limited number of studies indicate that atomoxetine appears to be as effective as immediate release methylphenidate[1,4,7] However available data indicate that controlled release methylphenidate produces a greater reduction in ADHD symptoms than atomoxetine.[5,7] As conclusive data is lacking more studies are required to compare atomoxetine with stimulants and amphetamines.[1,4,5,7]

Because of the lack of comparative studies, higher cost, and limited clinical experience, atomoxetine may be considered a second-line agent for the treatment of ADHD in children and adults.

References

1. Caballero J, Nahata MC. Atomoxetine Hydrochloride for the Treatment of Attention-Deficit/Hyperactivity Disorder. Clinical Therapeutics 2003;25(12):3065-3083.
2. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the Treatment of Children and Adolescents with Attention-Deficit/hyperactivity Disorder: A Randomized, Placebo-Controlled, Dose-Response Study. Pediatrics 2001;108(5):1-9.
3. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochivil C, et al. Once-Daily Atomoxetine Treatment for Children and Adolescents with Attention Deficit Hyperactivity Disorder: A Randomized, Placebo-Controlled Study. Am J Psychiatry 2002 November;159(11):1896-1901.
4. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, et al. Atomoxetine and Methylphenidate Treatment in Children With ADHD: A Prospective Randomized, Open-Label Trial. J. Am Acad. Child Adolesc. Psychiatry 2002 July:41(7):776-784.
5. Eli Lilly. Data on file – Strattera®: Comparison to Methylphenidate in ADHD treatment. Summary of Study 5; 2005 August 22.
6. Sangal RB, Owens J, Allen A, Kelsey D, Sutton V, Schuh K. Effects of Atomoxetine and Methylphenidate on Sleep in Children with ADHD. Sleep. Abstract Supplement 2004(27):A90.
7. Eli Lilly. Data on file – Strattera®: Comparison to Methylphenidate in ADHD. Summary of Study 4; 2005 August 22.
8. WARNING for atomoxetine regarding the behavioural and emotional changes, including risk of selfharm. Drugs & Health Products. Health Canada; 2005 September 28.
9. FDA Issues Public Health Advisory on Strattera® (Atomoxetine) for Attention Deficit Disorder. FDA News. P05-65; 2005 September 30.
10. Eli Lilly. Strattera® Package insert 2005 June.
11. New Warning for Strattera®. FDA Talk Paper. T04-60; 2004 December 17.
12. Medicines and Related Substance Control Act 101 of 1965 after amendment by the Medicines and Related Substances Control Amendment Act (Act 90 of 1997).
13. Strattera® (atomoxetine HCl) in the Management of Attention-Deficit/ Hyperactivity Disorder. U.S. Pharmacist 2005 June:3-11.

◆ EZETIMIBE: A NEW CHOLESTEROL LOWERING DRUG

INTRODUCTION

The World Health Organization's World Health Report of 2003 indicated that cardiovascular disease is responsible for 13% of the disease burden among adults over 15 years.[1] As increased low-density lipoprotein cholesterol (LDL-C) level is associated with an elevated risk of coronary heart disease, management of hyperlipidaemia is essential in reducing this disease burden. The control of hyperlipidaemia is a challenge for many healthcare providers, particularly in light of the updated NCEP guidelines' lower goals of LDL-C. New classes of lipid-lowering agents are therefore welcome.

Ezetimibe, launched as Ezetrol® in South Africa in 2005, is the first agent in a new class of lipid-lowering agents that selectively inhibits cholesterol absorption.

The rest of this article is available at www.safpj.co.za

Contributor: Marzelle Fivaz
Editorial Advisor: Dr J Noble

MediKredit Integrated Healthcare Solutions (Pty) Ltd ("MediKredit") 132 Jan Smuts Ave, Parkwood, PO Box 692, Parklands 2121, South Africa

Tel: (011) 770-6000 Fax: (011) 770-6325
E-mail: Medifile@medikredit.co.za
Supplement to the SA Pharmaceutical Journal - January/February 2006

Published by Medpharm Publications (Pty) Ltd. / Tel: (012) 664 7460,
E-mail: enquiries@medpharm.co.za