The Medicine Cabinet: Guanfacine

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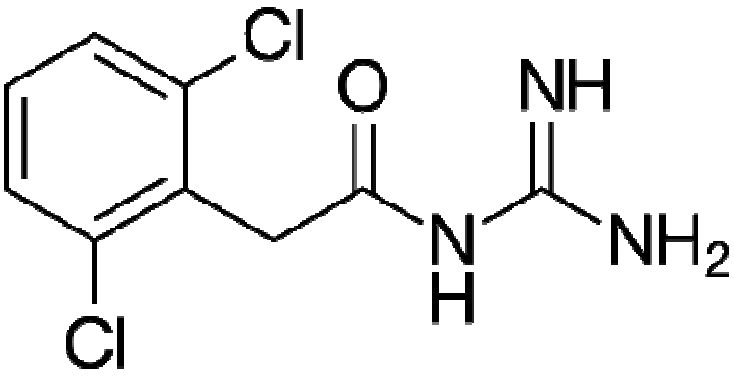

Guanfacine is an alpha 2 receptor agonist which has been in use as an antihypertensive in the immediate release form, from the 1980s in the USA. It is currently licensed in Australia as an extended release preparation for use in the treatment of ADHD as monotherapy or adjunctive therapy in children and adolescents 6-17 years. It primarily works on the alpha 2A receptor postsynaptically, (clonidine a similar medication works on alpha 2A, 2B and 2C and imidazole receptors). Guanfacine is significantly stronger affinity for the postsynaptic receptors than presynaptic whilst clonidine has stronger affinity for presynaptic. (See previous edition of MHCAIDD: Vol4, Issue 3/4, 2013)

The preparation (Intuniv®) is an extended release preparation and thus will not be able to be crushed, chewed or broken and should be swallowed whole and this is the preparation that will be on the Pharmaceutical Benefits Scheme (PBS). The Pharmaceutical Benefits Advisory Committee (PBAC) has approved it for listing on the PBS but the actual date at the time of writing is unknown but will be available until that date a private script could be utilised. It is available in 1mg, 2mg 3mg and 4mg strengths and boxes of 28 tablets.

Description of drug mechanism of action

Unlike clonidine, guanfacine acts only on the alpha adrenergic 2A receptor post synaptic primarily in the prefrontal cortex of the brain. This has been postulated as contributing to improvements in impulsivity, hyperactivity and inattention by the increase in noradrenaline release in the synapse without impairments to the dopamine neurotransmission. Treatment with a selective alpha 2A agonist would lead to increased signal via direct stimulation of postsynaptic receptors, resulting in increased ability to sit still and focus[1].

Side effects

In the clinical trials for licensing the main adverse effects were somnolence (strong desire to sleep), fatigue, abdominal pain, irritability and sedation[2]. Incidence of abdominal pain increases with dose but fatigue does improve. Other adverse effects would include a drop in blood pressure (hypotension) as well as dizziness, dry mouth, constipation and weakness[3] .

Other adverse effects that have been identified in the trials include weight gain, loss of appetite, wetting oneself, feeling or being sick, diarrhoea, indigestion or constipation, slow heart, beat low or high blood pressure and rash.

Dizziness and drop in blood pressure can be helped by not getting up from the lying position too quickly. Dry mouth can be relieved by sucking on ice. Taking guanfacine with food but not a fatty meal can also help with the nausea and feeling sick.

Drug interactions

Guanfacine is metabolised in the body by CYP 3A4 (most prolific of the drug metabolising enzymes) and thus when strong inhibitors of the enzyme such as fluoxetine, fluvoxamine and ketoconazole are also given then the clearance of guanfacine will be reduced causing the blood levels of guanfacine to raise.

Inducers of 3A4 such as the antiepileptics - carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone and high dose topiramate as well as St John's Wort especially those products with high levels of hyperforin will cause the guanfacine levels to rise and increase the risk of adverse effects[4].

Clinical trials in children

There has been several clinical trials conducted both placebo controlled trials and against comparator

atomoxetine. These trials have been used to support the application to PBAC for PBS listing as well as helping to extend the patent of the preparation in the USA.

Biederman trial was a multicentre USA double blind placebo controlled fixed dose escalation study in children 6-17 years. During 2003, a total of 365 patients were recruited to either placebo, or doses of 2mg, 3mg or 4mg and showed significant improvement in the Attention-Deficit/hyperactivity disorder rating scale IV (ADHD-RS-IV)[2]

Hervas study compared guanfacine to placebo as well as atomoxetine. The study was held over 58 sites in 11 countries from January 2011 to May 2013. Optimal dose of guanfacine used as 0.05-0.12mg/kg/d and the dose of atomoxetine was to a target dose of 1.2mg/kg/d. The total number in the study was 404 screened and 338 patients were randomised into 3 groups and 80% completed the study. There was a statistically significant improvement from baseline of the primary measure the ADHD-RS-IV. Although not designed for head to head study there was a greater mean change from baseline with guanfacine than atomoxetine[5].

Wilens trial for adolescents aged 13-17 years with a diagnosis of ADHD in a multicentre (48 USA sites) double-blind placebo controlled randomised study. Total of 314 adolescents (at least 25% female) entered the trial and received dosing 0.05 to 0.12mg/kg/d up to $\leq$ 7mg daily. Optimal response as with the other trials reduction of $\geq$ 30% from baseline in the ADHD-RS-IV for which there was a statistically significant improvement. As well as looking a functional gains through parental report for which there was no statistically significant difference between placebo and Guanfacine in the 2 key secondary domains of functioning – learning and school domain and family domain as measured on Weiss Functional Impairment Rating Scale –Parent report (WFIRS-P) at 13 weeks[6].

Open trial of 25 children with mean age of 9.03 years with a diagnosis of pervasive developmental disorder DSMIV who had failed treatment with methylphenidate in a multisite 8 week placebo-controlled trial. Primary measure was parent-rated hyperactivity subscale of the Aberrant Behavior Checklist (ABC) for both teacher and parent ratings. Dosing ranged from 1mg to 3mg/ daily using the immediate release preparation so dosing was in two to three divided doses. 39% improvement over baseline in the parent reported ABC hyperactivity subscale and this is compared to similar study using risperidone for more serious behavioural problems. Main adverse effect was sedation in 28% and irritability (moody, tearful and easily frustrated) in 28%

"Improvements in impulsivity, hyperactivity and inattention by the increase in noradrenaline release in the synapse"

of the population and 3 patients withdrew due to irritability. Effects on blood pressure and pulse were modest and appeared to diminish over time[7].

The Pediatric Psychopharmacology Autism network study in use of guanfacine ER in 62 subjects (85% boys) aged 5-14 years over an 8 week trial in 5 USA sites. Aberrant behaviour checklist –hyperactivity scale was the primary outcome measure. Statistically significant results in the hyperactivity subscale of the ABC scale and also hyperactivity scale in the ADHD rating scale in favour of guanfacine[8].

Why it might be used

- Guanfacine may be used instead of clonidine to ensure better control over the day as well as being less sedating.
- As adjuvant medication for psychostimulants to ensure proper sleep at night when doses are given earlier in the day and also extending the hyperactivity control without affecting the sleep.

Benefits

Single daily dose
Can be used with or without psychostimulants
Only licensed for patients 6-17, what happens to adult stabilised on it?

Problems

Cost
Until listed on PBS there could be considerable expense in using the medication.

To be taken with water, milk or other liquid at the same time each day either day or night, should not be chewed, crushed or broken and not to be taken with a high fat meal.

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Further information:
Consumer medicine information https://www.nps.org.au/medical-info/medicine-finder/intuniv-modified-release-tablets