Guanfacine hydrochloride

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Approved indication: attention deficit hyperactivity disorder

Intuniv (Shire)

1 mg, 2 mg, 3 mg and 4 mg modified-release tablets

Australian Medicines Handbook section 18.5

Drugs are only one part of the management of attention deficit hyperactive disorder (ADHD) in children and adolescents.[1] If drug treatment is necessary, psychostimulants such as dexamfetamine and methylphenidate are considered. Atomoxetine is another option and sometimes clonidine is used. Like clonidine, guanfacine hydrochloride is an agonist of the alpha$_2$ adrenergic receptor. Its effects in ADHD are uncertain, but guanfacine does not stimulate the central nervous system.

The new product is a modified-release formulation with peak plasma concentrations reached five hours after the dose is taken. It has a half-life of 18 hours and is suitable for once-daily dosing (morning or evening). The target dose is guided by the child's weight. Most of the dose is metabolised and excreted in the urine with 30% excreted as unchanged drug. The metabolism involves cytochrome P450 3A, so there is a potential for interactions with drugs such as ketoconazole and rifampicin. Guanfacine should not be taken with grapefruit juice. It should also not be taken with high-fat food because this significantly increases absorption. The tablets must not be chewed or crushed.

There have been several placebo-controlled studies of guanfacine in children aged 6–17 years. These trials have usually included a dose optimisation phase as the dose of guanfacine needs to be adjusted according to response and adverse effects. Responses were assessed with tools such as the ADHD Rating Scale IV. Some of the studies included patients taking atomoxetine or psychostimulants, but there were no comparative studies when guanfacine was evaluated in Australia.

A review of 10 studies published up to 2013 concluded that the efficacy of guanfacine was significantly better than placebo. However, in some of the studies a benefit was not seen in adolescents (13–17 years).[2]

In a more recent phase III trial, 338 patients were randomised to take guanfacine, atomoxetine or placebo. They had ADHD of at least moderate severity (mean baseline ADHD Rating Scale scores 43–44). The double-blind phase of the trial was 10 weeks for children (6–12 years) and 13 weeks for adolescents (13–17 years). At the end of the trial the scores had reduced by an average of 23.9 with guanfacine, 18.6 with atomoxetine and by 15 with placebo. Approximately 68% of the guanfacine group were judged to have improved compared with 56% of the atomoxetine group and 44% of the placebo group.[3]

An eight-week trial compared guanfacine monotherapy, methylphenidate monotherapy, and the two drugs together. This trial randomised 212 children and adolescents with baseline scores of 35–37 on the ADHD Rating Scale. These scores reduced by 16.7 with guanfacine, 15.8 with methylphenidate and by 18.3 with the combination. According to a Clinical Global Impression rating scale, 69% of the patients taking guanfacine were very much improved compared with 81% for methylphenidate and 91% for combined treatment.[4]

A randomised-withdrawal study assessed the longer term efficacy of guanfacine in 526 patients. Those who responded (68.6%) to open-label treatment entered a 26-week double-blind phase. At week 13 they were randomised to continue treatment or to be switched to placebo. The primary end point of the study was the proportion of patients whose ADHD Rating Scale scores increased by at least 50%. This treatment failure occurred in 64.9% of those switched to placebo and 49.3% of those who continued guanfacine.[5]

Some of the participants in the phase III trials[3,5] took guanfacine in an open-label extension study. These 214 patients were treated for up to two years. The mean score on the ADHD Rating Scale was 36.7 at baseline and had declined by 19.8 points at the end of the study.[6]

In the review of placebo-controlled trials, 12% of the patients taking guanfacine discontinued it because of adverse events, compared with 4% of the placebo group. Somnolence, sedation and fatigue were common reasons for discontinuing.[2] Caution is therefore needed if the patient is also taking drugs that depress the central nervous system, such as sedating antihistamines. Alcohol should be avoided. Other very common adverse effects include headache and abdominal pain. In combination with methylphenidate, guanfacine increases irritability and insomnia.[4]

Like clonidine, guanfacine can lower blood pressure. Hypotension and bradycardia are common adverse effects. When treatment is stopped, pulse and blood pressure can increase and hypertensive encephalopathy has been reported. It is therefore recommended that guanfacine is gradually discontinued rather than stopped abruptly.

Regular measurement of height and weight is recommended during treatment. However, the body mass index of most patients will remain in the same category while taking guanfacine.[6]

NEW DRUGS

A meta-analysis of seven studies found that 59% of patients will benefit from guanfacine, while 33.3% will respond to placebo.[7] Although a small difference in the scores on a rating scale can be statistically significant, there is debate about what is the minimum important clinical difference. Guanfacine is therefore reserved for children and adolescents 6–17 years old who cannot take or who have had an inadequate response to stimulants or atomoxetine.

T manufacturer provided the AusPAR

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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