NEW DRUGS

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Cinnarizine/dimenhydrinate

Approved indication: vertigo

Cizinate (Southern Cross)
20 mg/40 mg tablets

Vertigo has a variety of causes. These may be peripheral, such as labyrinthitis, or central, such as cerebellar ischaemia, or a mixture of the two. The treatment of vertigo should be aimed at the cause, but a variety of drugs has been used to relieve the symptom. These include antihistamines, anticholinergics and antiemetics.

The combination product contains two antihistamines. Cinnarizine inhibits histamine H_1 and H_4 receptors and dopamine D_2 receptors. It can also block calcium channels. Dimenhydrinate is a salt of diphenhydramine and chlorotheophylline. It inhibits histamine H_1 receptors and muscarinic acetylcholine receptors and can enter the brain. The combination of cinnarizine and dimenhydrinate will therefore have peripheral and central effects.

After oral administration, diphenhydramine is released from dimenhydrinate. Diphenhydramine and cinnarizine are rapidly absorbed with peak plasma concentrations being reached in 2–4 hours. They are metabolised mainly by cytochrome P450 (CYP) 2D6 in the liver. There may be a potential to interact with other drugs metabolised by CYP2D6, such as antidepressants and beta blockers. The half-lives of the drugs vary with the age of the patient but are around 4–6 hours. Cinnarizine and its metabolites are mainly excreted in the faeces, while diphenhydramine and its metabolites are mainly excreted in the urine. The combination is therefore contraindicated in patients with severe hepatic or renal impairment.

The combination of cinnarizine and dimenhydrinate has been used in Europe for many years, so there are several studies of its efficacy. An analysis of five of the double-blind, randomised trials involved 635 patients with an average age of 53 years. Most of them had experienced vertigo for more than one year. A total of 196 patients took the combination, while the others took either cinnarizine, dimenhydrinate or betahistine. The drugs were taken three times a day for four weeks. According to a symptom rating scale (range 0–40), the patients' symptoms decreased by more than 70% with the combination. This decrease was greater than the decrease seen with the components given alone (see Table). More than 68% of the patients felt much improved or very much improved after taking the combination compared with 33% of the betahistine group and 35% of the placebo group.[1]

A more recent double-blind trial compared the combination to betahistine in 306 patients with peripheral vestibular vertigo. Approximately 55% of the patients had a Ménière-like symptom complex, but patients with confirmed Ménière's disease were excluded. A 12-item scale was used to calculate a mean vertigo score. After four weeks this composite score had declined by 67.5% in the patients taking the combination and by 59.5% in those taking betahistine. Approximately 71% of the 152 patients randomised to the combination felt much improved or very much improved compared with 63% of the betahistine group.[2]

In the analysis of five trials, the most frequent adverse effects seen with the combination of cinnarizine and dimenhydrinate were fatigue, somnolence, dry mouth, headache and abdominal pain. The sedative effects may be increased by other drugs, including alcohol, which depress the central nervous system. As the combination has some anticholinergic effects, it is contraindicated in patients with angle-closure glaucoma or urinary retention. Convulsions, raised intracranial pressure and

Table **Efficacy of cinnarizine/dimenhydrinate for vertigo**[1]

	Number of patients (intention to treat)	Mean reduction in vertigo score after four weeks (range 0–40)
Cinnarizine 20 mg/dimenhydrinate 40 mg	196	13.6
Cinnarizine 20 mg	60	11.5
Cinnarizine 50 mg	98	7.8
Dimenhydrinate 40 mg	59	11.4
Dimenhydrinate 100 mg	97	7.3
Betahistine 12 mg	40	5.7
Placebo	51	6.4

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

alcohol abuse are also contraindications. Cinnarizine has been associated with extrapyramidal effects including tardive dyskinesia. As these effects may be irreversible, the combination should only be used for short-term management.

Combining cinnarizine with dimenhydrinate has a greater effect on vertigo than either drug alone, but the difference may be small. For example, in the five-trial analysis there was a difference of approximately two points between the combination and cinnarizine 20 mg on the 40-point vertigo score (see Table).[1] However, cinnarizine is not available on its own in Australia. Although there is European experience with the combination, it is only indicated in Australia for adults who have not responded to other treatments. In view of the uncertainty about long-term safety, treatment should not usually exceed four weeks.

T manufacturer provided the product information

REFERENCES

1. Schremmer D, Bognar-Steinberg I, Baumann W, Pytel J; for the Clinical Investigators. Efficacy and tolerability of a fixed combination of cinnarizine and dimenhydrinate in treatment of vertigo: analysis of data from five randomised, double-blind clinical studies. Clin Drug Investig 1999;18:355-68. https://doi.org/10.2165/00044011-199918050-00003
2. Scholtz AW, Hahn A, Stefflova B, Medzhidieva D, Ryazantsev SV, Paschinin A, et al. Efficacy and safety of a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg vs betahistine dihydrochloride 16 mg in patients with peripheral vestibular vertigo: a prospective, multinational, multicenter, double-blind, randomized, non-inferiority clinical trial. Clin Drug Investig 2019;39:1045-56. https://doi.org/10.1007/s40261-019-00858-6

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.