New drugs

Clevidipine

Approved indication: hypertension

Cleviprex (The Medicines Company)

glass vials containing 25 mg/50 mL and 50 mg/100 mL

Australian Medicines Handbook section 6.3.5

Occasionally, patients present with a hypertensive crisis which requires their blood pressure to be rapidly reduced. Controlling hypertension is also vital in patients having cardiac surgery.

Clevidipine is a short-acting intravenous dihydropyridine calcium channel blocker. In perioperative patients, the blood pressure is reduced by up to 5% within 2–4 minutes of starting an infusion. Clevidipine is rapidly metabolised and has a terminal half-life of 15 minutes. Its effect on blood pressure is gone within 5–15 minutes of stopping the infusion.

Six different doses of clevidipine were tried in a placebo-controlled study of 91 patients who had undergone cardiac surgery. The proportion of patients whose blood pressure reduced in response to clevidipine increased with the dose. Despite blood pressure falling by at least 10% there was no significant change in heart rate although beta blocker use was not controlled for.[1]

The ESCAPE trials enrolled patients having cardiac surgery. In ESCAPE-1, 152 hypertensive patients were randomised to receive clevidipine or a placebo infusion before surgery. The target blood pressure was reached in a median of six minutes with clevidipine. Treatment only failed in 7.5% of the patients given clevidipine compared with 82.7% of the placebo group.[2] ESCAPE-2 assessed the effect of clevidipine on postoperative hypertension. After surgery 110 patients were given clevidipine or a placebo. Only 8.2% failed to respond to the drug compared with 79.6% of the placebo group. The median time to reach the target blood pressure with clevidipine was 5.3 minutes.[3]

The ECLIPSE trials were safety studies, but also reported on blood pressure control. They compared clevidipine with nicardipine, sodium nitroprusside and glyceryl trinitrate in 1512 hypertensive patients having cardiac surgery. Clevidipine was significantly more effective than sodium nitroprusside and glyceryl trinitrate at keeping the blood pressure within a target range. There was not a significant difference between clevidipine and nicardipine for the specified range.[4]

Clevidipine has also been used to control acute severe hypertension. In an open-label trial, 131 people who presented with a systolic blood pressure above 180 mmHg or a diastolic blood pressure above 115 mmHg were given an infusion of clevidipine for at least 18 hours. The dose was titrated to keep the blood pressure within a target range. That range was reached within 30 minutes by 88.9% of the patients. Most patients were able to switch to oral therapy within six hours of stopping clevidipine.[5]

Patients who are not given oral antihypertensives need monitoring, after prolonged infusions, for at least eight hours after the infusion stops. This is because of the risk of rebound hypertension. More common adverse effects of clevidipine in severe hypertension are headache, nausea and vomiting.

Some of the adverse effects of clevidipine can be anticipated from its action. These include hypotension, tachycardia and a negative inotropic effect which can exacerbate heart failure. In perioperative use there are reports of atrial fibrillation.[2,3] In ESCAPE-1, 9.4% of the patients developed acute renal failure compared with 2% of the placebo group.[2] In the ECLIPSE trials, the overall incidence of death, myocardial infarction, stroke or renal dysfunction at 30 days was similar for clevidipine and its comparators.[4]

Clevidipine is presented as an emulsion containing phospholipids. It is contraindicated in patients who are allergic to egg and soy products. Severe aortic stenosis is also a contraindication.

Clevidipine is likely to be more expensive than the drugs currently used to reduce blood pressure urgently, and it may be no safer overall. Although there were fewer deaths than with sodium nitroprusside, clevidipine did not reduce the overall rate of death, myocardial infarction, stroke or renal dysfunction significantly more than its comparators.[4]

T T manufacturer provided additional useful information

REFERENCES *A

1. Bailey JM, Lu W, Levy JH, Ramsay JG, Shore-Lesserson L, Prielipp RC, et al. Clevidipine in adult cardiac surgical patients: a dose-finding study. Anesthesiology 2002;96:1086-94.
2. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. Anesth Analg 2007;105:918-25.

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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3. Singla N, Warltier DC, Gandhi SD, Lumb PD, Sladen RN, Aronson S, et al; ESCAPE-2 Study Group. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg 2008;107:59-67.
4. Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, Lumb PD, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg 2008;107:1110-21.
5. Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. Ann Emerg Med 2009;53:329-38.

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)